Epidemiological Features, Clinical Symptoms and Environmental Risk Factors for Notifiable Japanese Encephalitis in Taiwan from 2008 to 2020

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Abstract

Background: Japanese encephalitis is a zoonotic parasitic disease caused by the Japanese encephalitis virus, and may cause fever, nausea, headache, or meningitis. This study aimed to investigate the epidemiological features, epidemic trends, and correlations between the number of confirmed Japanese encephalitis cases in Taiwan from 2008 to 2020 in gender, age, season, and residential area; clinical symptoms of cases, high-risk areas of disease and hypothesized the environmental and climate factors also might affect the disease in Taiwan.

Objective: This study aims to comprehensively investigate the epidemiological, clinical, and environmental characteristics of Japanese Encephalitis (JE) in Taiwan using population surveillance data gathered over a 13-year period.

Methods: This study reviewed publicly available annual summary data on reported Japanese encephalitis cases in the Taiwan Centers for Diseases Control (TCDC) between 2008 and 2020.

Results: This study collected 309 confirmed domestic and four patients with imported Japanese encephalitis. There was an increasing trend in the incidence of Japanese encephalitis, 0.69–1.57 cases per 1,000,000 people, peaking in 2018. Case fatality rate is 8.3%. Comparing sex, age, season, and place of residence, the incidence rate was highest in male, 40–59 years-old patients, summer, and the Eastern region, with 1.89, 3.27, 1.25, and 12.2 cases per million population, respectively. The average coverage rate of Japanese encephalitis vaccine for children in Taiwan is 94.9%. Additionally, the major clinical manifestations of the case include fever, unconsciousness, headache, stiff necks, psychological symptoms, vomiting, and meningitis. The major occurrence place of Japanese encephalitis included paddy fields, pig farms, pigeon farms, poultry farms, and pond. For air pollution factors, linear regression analysis showed that SO2 (ppb) concentration was positively associated with Japanese encephalitis cases (? = 2.184, p = 0.020), but CO (ppb) concentration was negatively (? = -0.157, p = 0.014). For climate factors, relative humidity (%) was positively associated with Japanese encephalitis cases (? = 0.380, p = 0.021).

Conclusions: This study is the first to report confirmed cases of Japanese encephalitis from the surveillance data of the TCDC between 2008 and 2020. It identified that residence, season, and age were risk factors for Japanese encephalitis in Taiwan. Air pollution and climatic factors indeed influence the rise in Japanese encephalitis cases. This study confirmed that Japanese encephalitis remains a prevalent infectious disease in Taiwan, with its epidemic gradually increasing in severity. These findings empower clinicians and healthcare providers to make informed decisions, guiding their care and resource allocation for patients with Japanese encephalitis, a disease that significantly impacts the health and well-being of the Taiwanese population.

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ABSTRACT

Background

Japanese encephalitis is a zoonotic parasitic disease caused by the Japanese encephalitis virus, and may cause fever, nausea, headache, or meningitis. This study aimed to investigate the epidemiological features, epidemic trends, and correlations between the number of confirmed Japanese encephalitis cases in Taiwan from 2008 to 2020 in gender, age, season, and residential area; clinical symptoms of cases, high-risk areas of disease and hypothesized the environmental and climate factors also might affect the disease in Taiwan.

Methods

This study reviewed publicly available annual summary data on reported Japanese encephalitis cases in the Taiwan Centers for Diseases Control (TCDC) between 2008 and 2020.

Results

This study collected 309 confirmed domestic and four patients with imported Japanese encephalitis. There was an increasing trend in the incidence of Japanese encephalitis, 0.69–1.57 cases per 1,000,000 people, peaking in 2018. Case fatality rate is 8.3%. Comparing sex, age, season, and place of residence, the incidence rate was highest in male, 40–59 years-old patients, summer, and the Eastern region, with 1.89, 3.27, 1.25, and 12.2 cases per million population, respectively. The average coverage rate of Japanese encephalitis vaccine for children in Taiwan is 94.9%. Additionally, the major clinical manifestations of the case include fever, unconsciousness, headache, stiff necks, psychological symptoms, vomiting, and meningitis. The major occurrence place of Japanese encephalitis included paddy fields, pig farms, pigeon farms, poultry farms, and pond. For air pollution factors, linear regression analysis showed that SO_2 (ppb) concentration was positively associated with Japanese encephalitis cases ($\beta = 2.184$, $p = 0.020$), but CO (ppb) concentration was negatively ($\beta = -0.157$, $p = 0.014$). For climate factors, relative humidity (%) was positively associated with Japanese encephalitis cases ($\beta = 0.380$, $p = 0.021$).

Conclusions

This study is the first to report confirmed cases of Japanese encephalitis from the surveillance data of the TCDC between 2008 and 2020. It identified that residence, season, and age were risk factors for Japanese encephalitis in Taiwan. Air pollution and climatic factors indeed influence the rise in Japanese encephalitis cases. This study confirmed that Japanese encephalitis remains a prevalent infectious disease in Taiwan, with its epidemic gradually increasing in severity. These findings empower clinicians and healthcare providers to make informed decisions, guiding their care and resource allocation for patients with Japanese encephalitis, a disease that significantly impacts the health and well-being of the Taiwanese population.

Key words: Epidemiology; Japanese encephalitis virus; Domestic; Environmental factor; Retrospective study

1. Introduction

The Japanese encephalitis virus (JEV) is a significant public health concern in Asia, causing an estimated 68,000 clinical cases annually, primarily in East Asia and Southeast Asia [1]. Although symptomatic Japanese encephalitis (JE) occurs infrequently, it has a serious case-fatality rate, with up to 30% of encephalitis cases resulting in death. Encephalitis survivors have a high likelihood of developing permanent neurological or psychiatric sequelae, with an estimated occurrence rate of 30% to 50% of cases. The endemic transmission of Japanese encephalitis virus (JEV) poses a health threat to over 3 billion people in a substantial portion of the World Health Organization (WHO) South-East Asia and Western Pacific regions [1]. The disease currently lacks a specific antiviral treatment, necessitating supportive care measures like managing symptoms and providing respiratory and nutritional support to help patients overcome the infection [2]. Vaccination stands as the effective strategy to prevent the disease, with WHO recommending the integration of JE vaccination into national immunization programs in all regions where the disease poses a significant public health threat [1, 3].

Japanese encephalitis (JE) is a mosquito-borne viral infection caused by the Japanese encephalitis virus (JEV), a member of the Flaviviridae family closely related to dengue, yellow fever, and West Nile viruses [4]. JEV is primarily transmitted from animals to humans through the bite of infected mosquitoes, particularly Culex mosquitoes, especially Culex tritaeniorhynchus (Cx. tritaeniorhynchus), with pigs and ardeid birds serving as the main amplifying hosts [5, 6]. The clinical presentation of JE in humans varies widely, encompassing a spectrum ranging from mild or asymptomatic infection to severe encephalitis. This severe form of the disease is characterized by significant mortality, with a high death rate among infected individuals. Additionally, survivors of severe JE often experience sequelae within the central nervous system [7].

JE poses a significant public health threat, particularly in Asian countries, especially in South Asia, Southeast Asia, and East Asia [8, 9]. Several countries in these regions have successfully implemented various intervention measures to reduce JE morbidity, including early diagnosis, prompt treatment, national immunization programs, and effective vector control strategies [10, 11]. Despite these efforts, over 3 billion people still reside in JE-endemic countries, with an estimated 67,900 cases occurring annually [8]. The severity of JE is evident in its high mortality rate, with approximately 20–30% of cases resulting in fatalities. Additionally, 30–50% of JE survivors experience significant long-term neurological sequelae [9, 12]. Previous studies have also highlighted the ongoing public health concern posed by JE in Taiwan[13].

Nestled at 23°4' north latitude and 121°0' east longitude, Taiwan enjoys a subtropical climate with average monthly temperatures ranging from a comfortable 16°C to 29°C. Average monthly relative humidity hovers between 75% and 90%. Despite its status as a developed nation with a per capita gross domestic product (GDP) of US$35,244 [14], Taiwan continues to grapple with the challenges posed by Japanese encephalitis (JE). Despite occasional imported cases of Japanese Encephalitis (JE) in recent years [15], local infections persist in Taiwan, indicating limitations in the effectiveness of preventive measures in controlling or eradicating the disease. The number of Japanese Encephalitis cases in Taiwan ranges from sporadic confirmed cases to cluster epidemics, with the middle-aged population exhibiting the highest rate of Japanese encephalitis virus. Addressing the disease burden caused by JEV is imperative, and effective public health measures should be adopted in Taiwan. Although some studies provided epidemiological data on Japanese Encephalitis (JE) in Taiwan, their study did not delve into the clinical symptoms of JE patients over the past decade nor investigate the potential association between climate and air pollution factors and the number of cases [16]**.** This study aims to comprehensively investigate the epidemiological, clinical, and environmental characteristics of Japanese Encephalitis (JE) in Taiwan using population surveillance data gathered over a 13-year period.

2. Methods

2.1. ***Ethical Policy***

Studies utilizing freely available information from the public domain and analyzing open datasets with properly anonymized data do not require ethical approval. The authors are confident in the added value of this study, which aligns with the public use of government reports[17-19].

2.2. ***Study Area***

Taiwan is an island in East Asia located between 21°45’ N and 25°56’ N. The Tropic of Cancer (23.5° N) passes through Chiayi City, situated in south-central Taiwan, dividing the entire island into two climate zones. Taiwan has a total land area of 35,980 km^2 and a population of approximately 23 million people, resulting in an average population density of 635 individuals per km^2. The northern part of Taiwan belongs to the subtropical climate zone, whereas the southern part belongs to the tropical climate zone. Consequently, the weather in Taiwan is relatively warm, with high humidity occurring throughout the year [20, 21]**.**

2.3. ***Case Definitions***

A clinical case was defined as an individual of any age experiencing an acute onset of fever accompanied by a change in mental status and/or new onset of seizures (excluding simple febrile seizures) at any time of the year **[9, 13]**. A confirmed case was defined as a clinical case with positive laboratory test results, including the presence of IgM antibodies specific to the JE virus in a single sample of cerebrospinal fluid (CSF) or serum; a four-fold increase in IgG antibodies; the detection of JE virus antigens in tissue via immunohistochemistry; or the detection of the JE virus genome in serum, plasma, blood, CSF, or tissue samples. Additionally, cases meeting the clinical case definition and epidemiologically linked to a confirmed case were also considered confirmed [22, 23].

2.4. ***Surveillance for Japanese Encephalitis Infection***

JE has been categorized as a notifiable infectious disease since 1955. Physicians are required to report all cases that meet the case definition of JE, collect samples, and send them to the TCDC within one week of the case being reported for examination [22]. We collected data from all JE-confirmed cases reported to the Taiwan CDC from January 2008 to December 2020. The reported information included patient age, sex, area of residence, geographic location, seasonal variation of exposure, and date of JE onset.

2.5. *Laboratory tests*

In 1998, the Taiwan CDC developed an E/M-specific capture IgM and IgG enzyme-linked immunosorbent assay (E/M-specific IgM/IgG ELISA) for Japanese encephalitis (JE) and dengue fever (DF) **[13, 24, 25]**. Hemagglutination inhibition (HI) and E/M-specific IgM/IgG ELISA are both employed as screening tools for detecting antibodies against Japanese encephalitis (JE) and dengue fever (DF) [26-28]**.** This study employed a previously described differential testing algorithm [28]. Briefly, samples positive on the JE ELISA underwent further testing using the DF ELISA. The combined results from both assays informed the final interpretation. Positive JE ELISA and negative DF ELISA indicated the presence of JEV antibodies only, while positive results in both tests suggested a false-positive JE result. Long-term evaluation demonstrated high sensitivity and specificity of the E/M-specific IgM/IgG ELISA, effectively differentiating JEV infections from dengue virus infections [28]**.** Since 2001, real-time polymerase chain reaction (PCR) analysis of acute-phase serum samples collected within seven days of symptom onset and cerebrospinal fluid (CSF) from individuals diagnosed with Japanese encephalitis (JE) has been employed for diagnostic purposes [29]. Nevertheless, enzyme-linked immunosorbent assay (ELISA) remains the primary diagnostic testing method, with the E/M-specific IgM/IgG ELISA being the most widely utilized ELISA method.

The JE laboratory has confirmed that clinical cases meeting one of the following specific laboratory criteria should be defined as confirmed cases of JE: (1) an HI titer of the convalescent serum of 1:160 and at least a 4-fold increase between the HI titers of convalescent and acute sera [26, 27]. (2) an HI titer of 1:320 derived from a single serum sample [26, 27]. (3) an IgM-positive serum sample, as determined by an ELISA test, or a fourfold increase in IgG levels between paired serum samples [27]. (4) a sample exhibiting a positive real-time polymerase chain reaction (PCR) reaction [27]. (5) a sample that has been found to be positive for indirect immunofluorescence antibody staining following the isolation of the virus from cerebrospinal fluid (CSF) **[29, 32]**. (6) virus isolation can be accomplished through cell culture techniques using either the mosquito C6/36 cell line or plaque assays with the BHK-21 cell line. [28]. (7) an alternative approach is the extraction of viral RNA from JEV-infected culture medium using the QIAamp Viral RNA Mini Kit (Qiagen, Germantown, MD) [15].

2.6. Surveillance of Environmental Factors

The data set comprised monthly air pollutant data from 2008 to 2020, obtained from the air quality monitoring network of the Environmental Protection Agency. The pollutants analyzed included total suspended particulates (TSP), particulate matter (PM) 2.5 and 10 (PM2.5 and PM10), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), ozone (O_3), dust fall volume, and lead concentration [30]. Furthermore, monthly weather data from the Meteorological Bureau of the Ministry of Communications for the same period were analyzed. The meteorological variables included temperature, rainfall, relative humidity, atmospheric pressure, the number of days with precipitation, and the duration of sunshine [31]. Statistical analyses and correlation tests were employed to assess the temporal and spatial trends in air pollutants and meteorological factors, as well as their potential association with Japanese encephalitis case numbers.

2.7. *Data Analysis*

This study presents a retrospective historical analysis of all cases of Japanese encephalitis diagnosed in Japan since 2008, including both domestic and imported cases. We confirmed the number of individuals diagnosed with Japanese encephalitis from 2008 to 2020 and examined the epidemiological characteristics of these cases, including sex, age, time of diagnosis, and area of residence. Disparities and outcomes were analyzed. Our analysis then focused on the variables of sex, age, time of diagnosis, changes in living area, trends and related outcomes for cases of Japanese encephalitis from 2011 to 2020. Descriptive data are presented as means and summaries where appropriate. Categorical variables were compared using chi-squared tests. Odds ratios (ORs) were calculated using logistic regression, with 95% confidence intervals estimated using parameter estimation. All statistical analyses were performed using SPSS (IBM SPSS version 21; Asia Analytics Taiwan Ltd., Taipei, Taiwan). All statistical tests were two-tailed, with an α value of 0.05. A p-value less than 0.05 was considered statistically significant.

3. Results

The flowchart of this study is shown in Figure 1. There were 313 confirmed cases of local and imported infection, 309 confirmed local cases (98.7%), 195 male patients (62.3%), 182 cases aged 40-59 years (58.1%), 245 cases in summer (78.3%) and 145 cases in the southern region (46.3%). There were four confirmed cases of imported infection (1.3%) (Table 1). There was no statistically significant difference between the number of confirmed cases in 2008 and 2020 and the relationship between different identities (local or imported), sex, age group, season and place of residence (all $p>0.05$) (Table 1). There was a statistically significant difference between the number of confirmed cases in 2008 and 2020 and the relationship between different seasons and place of residence (all $p<0.05$) (Table 1).

The main clinical symptoms of Japanese encephalitis were fever (32.3%), unconsciousness (18.7%), headache (15.7%), stiff neck (7.3%), psychiatric symptoms (6.8%) and vomiting (5.7%), as shown in Table 2.

There were 24 deaths from Japanese encephalitis, of which 15 were male (62.5%) and 9 were aged 50-60 years (37.5%). The mortality rate (per 1,000,000) ranged from 0.04 to 0.17 between 2008 and 2020 (Table 3).

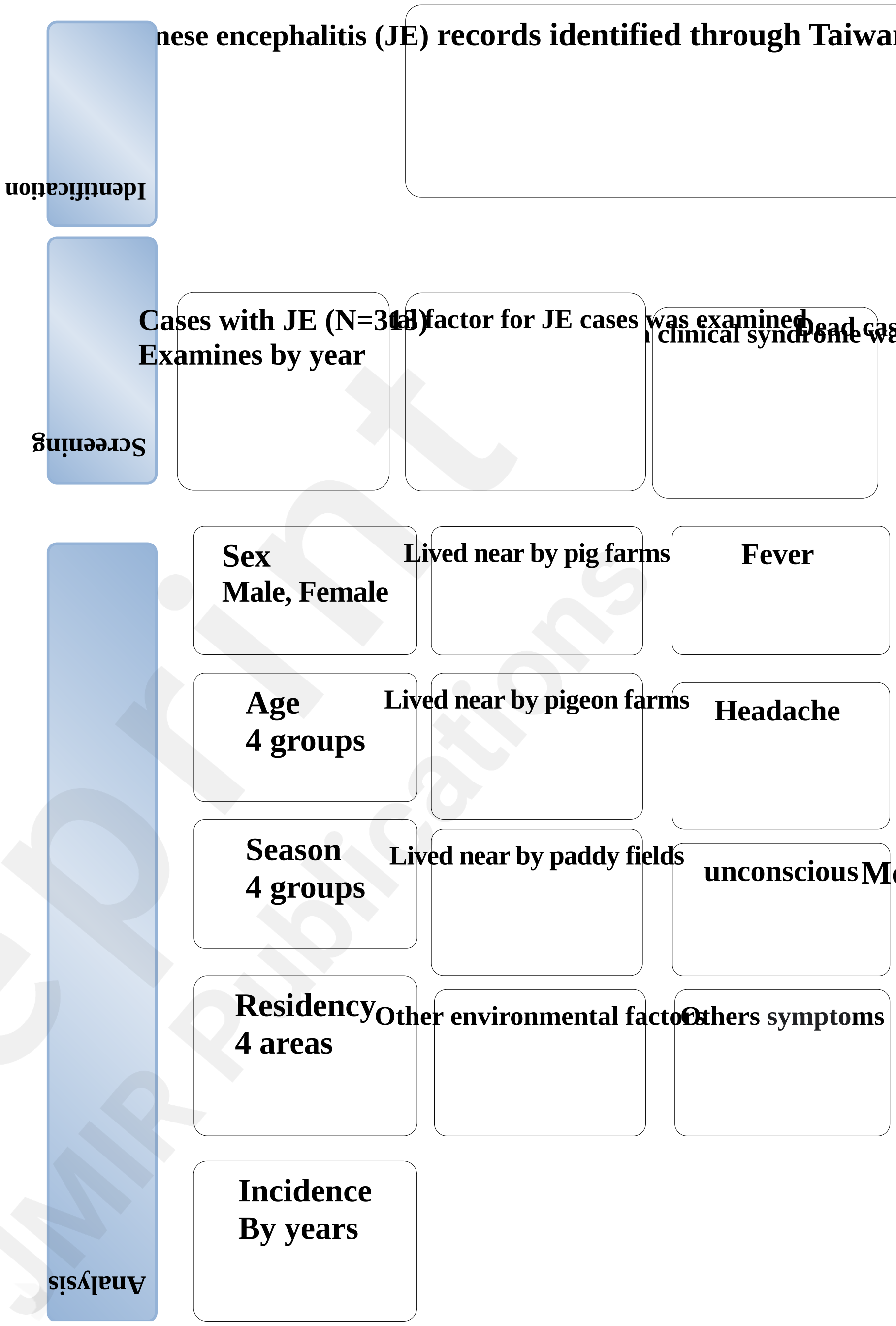


Figure 1. Flowchart of the study sample selection from the Taiwan Centers for Disease Control Datab

Table 1. Epidemiological features of Japanese encephalitis cases in Taiwan from 2008 to 2020

Variable	Total	2008 N=17	2009 N=18	2010 N=33	2011 N=22	2012 N=32	2013 N=16	2014 N=18	2015 N=30	2016 N=23	2017N =25	2018 N=37	2019 N=21	2020 N=21	*p*
Individual															
Domestic	309	17	17	32	22	32	16	18	30	23	25	37	19	21	-
Imported	4	0	1	1	0	0	0	0	0	0	0	0	2	0	
Sex															
Male	195	12	13	22	14	17	12	12	19	12	15	20	13	14	.903
Female	118	5	5	11	8	15	4	6	11	11	10	17	8	7	
Age group															
< 20	10	3	1	1	1	0	1	0	0	1	0	1	0	1	
20-39	68	5	3	11	8	9	5	3	7	2	4	6	3	2	.259
40-59	182	9	9	16	9	17	9	10	20	16	14	24	14	15	
≧60	53	0	5	5	4	6	1	5	3	4	7	6	4	3	
Season															
Spring	40	1	2	2	0	10	2	0	0	2	3	10	7	1	
Summer	245	15	14	29	20	19	14	15	28	14	19	25	13	20	< .001
Fall	28	1	2	2	2	3	0	3	2	7	3	2	1	0	

Winter	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	
Residency															**.008**
Northern	**78**	**2**	**5**	**10**	**9**	**4**	**5**	**2**	**7**	**4**	**8**	**10**	**5**	**7**	
Central	**65**	**4**	**2**	**6**	**5**	**5**	**3**	**5**	**4**	**5**	**5**	**9**	**5**	**7**	
Southern	**145**	**9**	**4**	**14**	**4**	**21**	**8**	**11**	**18**	**11**	**10**	**17**	**11**	**7**	
Eastern	**25**	**2**	**7**	**3**	**4**	**2**	**0**	**0**	**1**	**3**	**2**	**1**	**0**	**0**	

Table 2. Clinical symptoms of Japanese encephalitis cases in Taiwan from 2008 to 2020

Variable	Year													
	Total	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Fever	280	16	18	30	18	26	15	14	28	21	21	33	20	20
Headache	136	13	5	19	13	15	8	7	9	9	8	14	6	10
Stiff necks	63	1	6	3	6	6	3	5	3	5	7	11	3	4
Muscle cramps	35	7	2	5			3	2	6	2	3	2		3
Vomiting	49	4	2	11	4	5	3	1	2	1	3	8	4	1
Speaking difficulty	9		2		3	4								
Coma	30	4	5	12	7	2								
Unconscious	162	5	6	21	11	9	11	9	13	17	14	20	12	14
Encephalitis	3				1	2								
Paralysis	1				1									
Psychological symptoms	59					9		5	11	5	5	15	6	3
Paralyzed limbs	3					3								
Diarrhea	2					2								

Muscular ache	**2**					**2**								
Encephalitic stimulation symptoms	**10**							**1**	**3**	**2**	**1**	**2**		**1**
Dystonia	**16**								**4**	**4**	**2**	**1**	**2**	**3**
Meningitis symptoms	**6**													**3**
Aseptic meningitis														**3**

Table 3. The mortality rate per 1,000,000 and the characteristics of deceased cases with Japanese encephalitis from 2014 to 2020 in Taiwan

Variable	Year*										
	2008 N=2	2009 N=2	2010 N=2	2011 N=1	2013 N=1	2014 N=3	2015 N=1	2016 N=4	2017 N=3	2018 N=2	2019 N=3
Mortality Rate per 1,000,000	0.09	0.09	0.09	0.04	0.04	0.13	0.04	0.17	0.13	0.08	0.13
Sex											
Male	1	2	0	1	0	3	0	3	2	2	1
Female	1	0	2	0	1	0	1	1	1	0	2
Age group											
< 20											
20-30											
30-40			1			1					
40-50	1		1			1	1	1			
50-60		1			1	1		2	1		3
60-70	1	1							1	2	
70-80								1	1		
>=80				1							

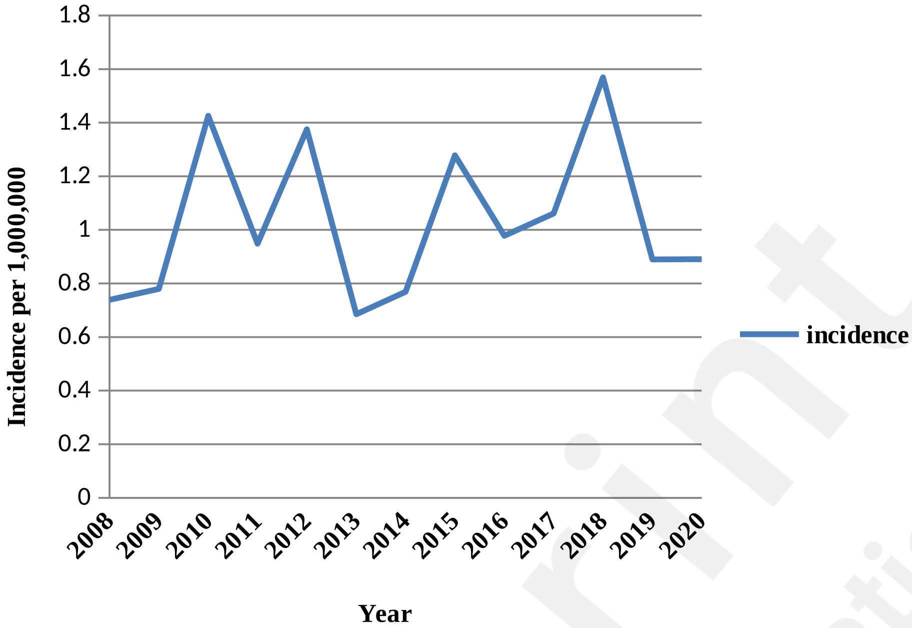
***: There were no reported deaths due to Japanese encephalitis in 2012 and 2020.**

The main environmental factors associated with Japanese encephalitis were paddy fields (27.5%), pig farms (27.1%), pigeon farms (21.5%), poultry farms (11.2%), ponds (5.0%) and domestic pets (3.1%), as indicated in Table 4.

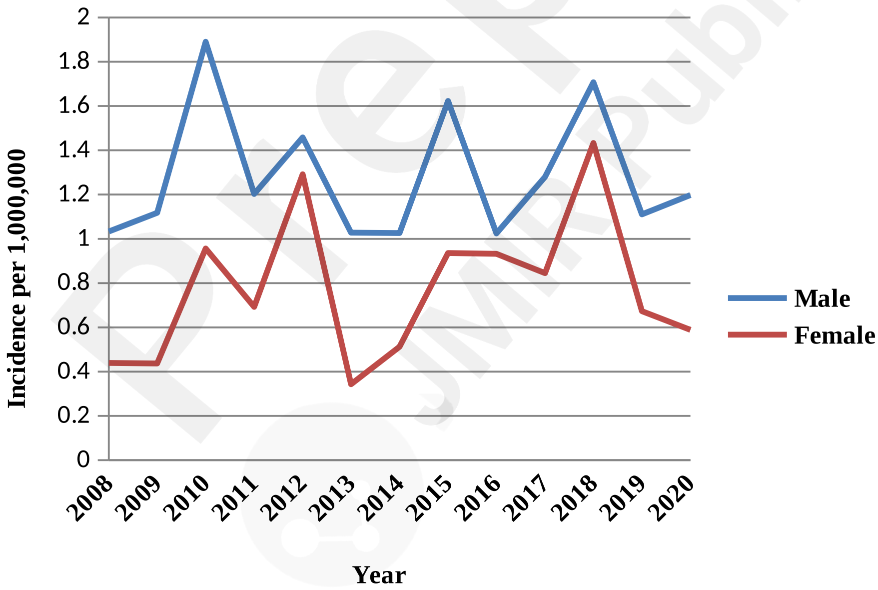
Linear regression analysis showed that SO_2 concentration was associated with Japanese encephalitis (β = 2.184, standard error = 0.922, p = 0.020) (Table 6). Linear regression analysis also showed that O_3 concentration and Japanese encephalitis cases were associated (β = -0.157, standard error = 0.063, p = 0.014) (Table 5). Linear regression analysis showed that climatic factors were associated with Japanese encephalitis cases (R^2 = 0.344, F = 11.980, p <0.001) (Table 6).

The incidence of confirmed cases of Japanese encephalitis per million population was 0.69-1.57 (Figure 2A) and 1.02-1.89 in males during 2008-2020 (Figure 2B). The incidence of confirmed cases of Japanese encephalitis per million in the 40-59 age group was 1.25-3.27 during 2008-2020 (Figure 2C), 0.55-1.25 in summer (Figure 2D), and 0-12.2 in the northern region (Figure 2E). The national coverage of Japanese encephalitis vaccine in Taiwan is shown in Figure 3.

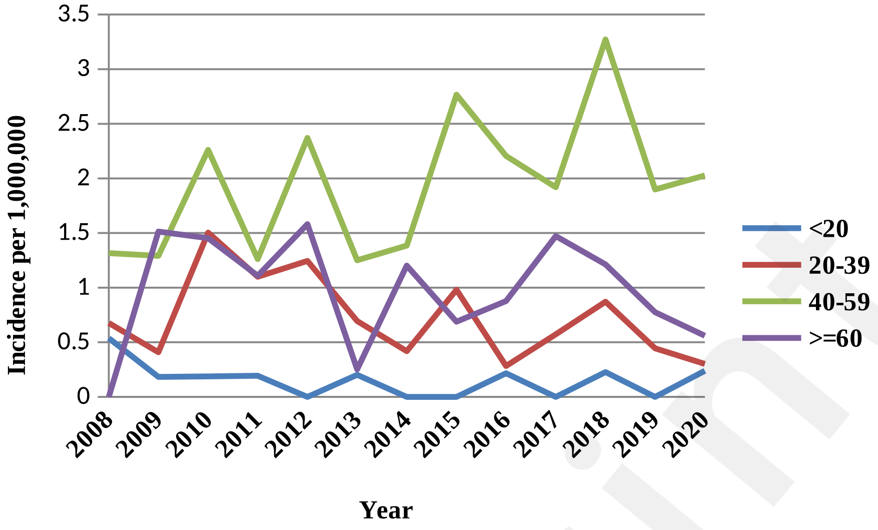
(A)


1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Incidence per 1,000,000
2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020
Year
incidence

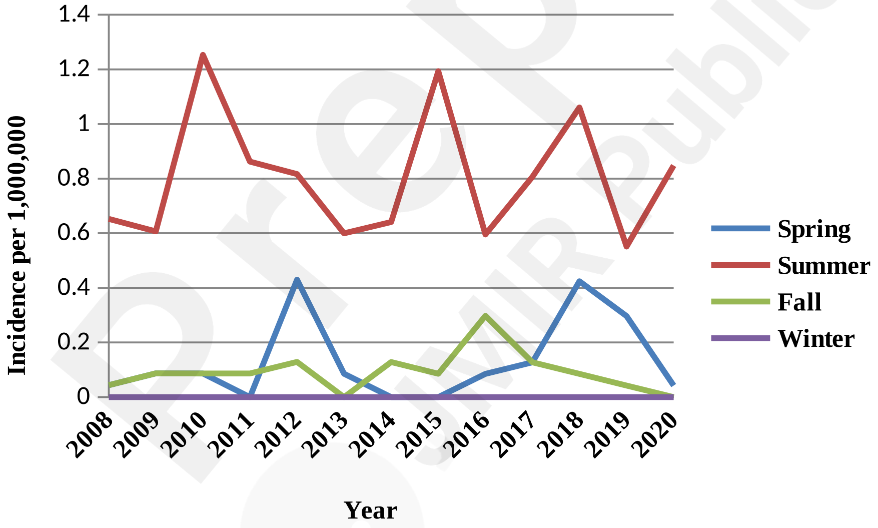
(B)


2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Incidence per 1,000,000
2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020
Year
Male
Female

(C)


Incidence per 1,000,000
3.5
3
2.5
2
1.5
1
0.5
0
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
Year
<20
20-39
40-59
>=60

(D)


Incidence per 1,000,000
1.4
1.2
1
0.8
0.6
0.4
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2008
2009
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2012
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Year
Spring
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Fall
Winter

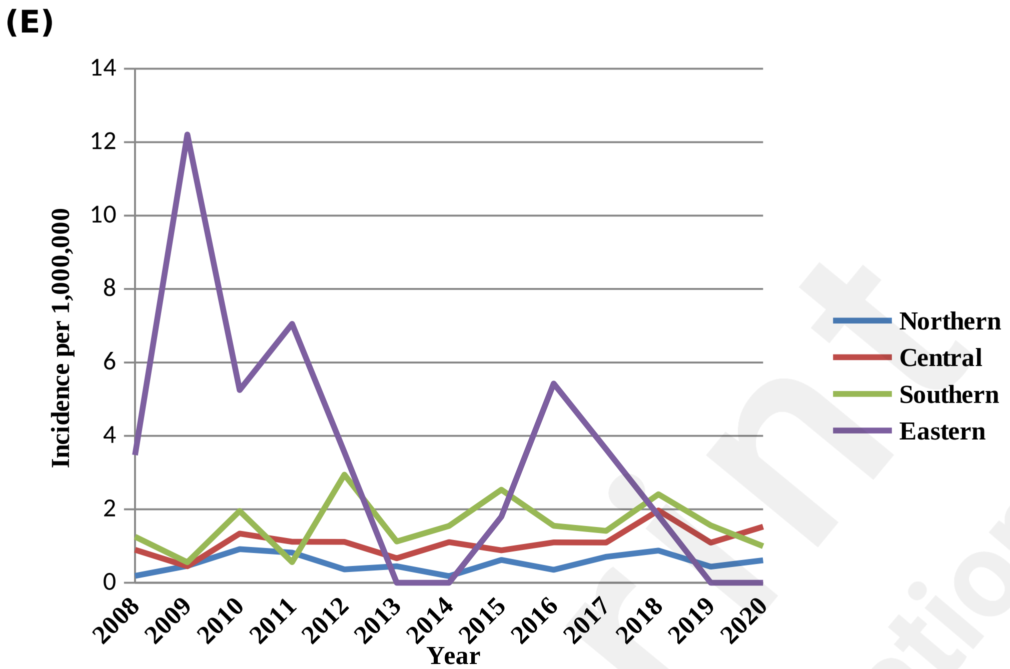

Figure 2. Incidence of confirmed JEV among patients in Taiwan according to (A) population, (B) gender, (C) age, (D) season and (E) region of residence by year from 2008 to 2020

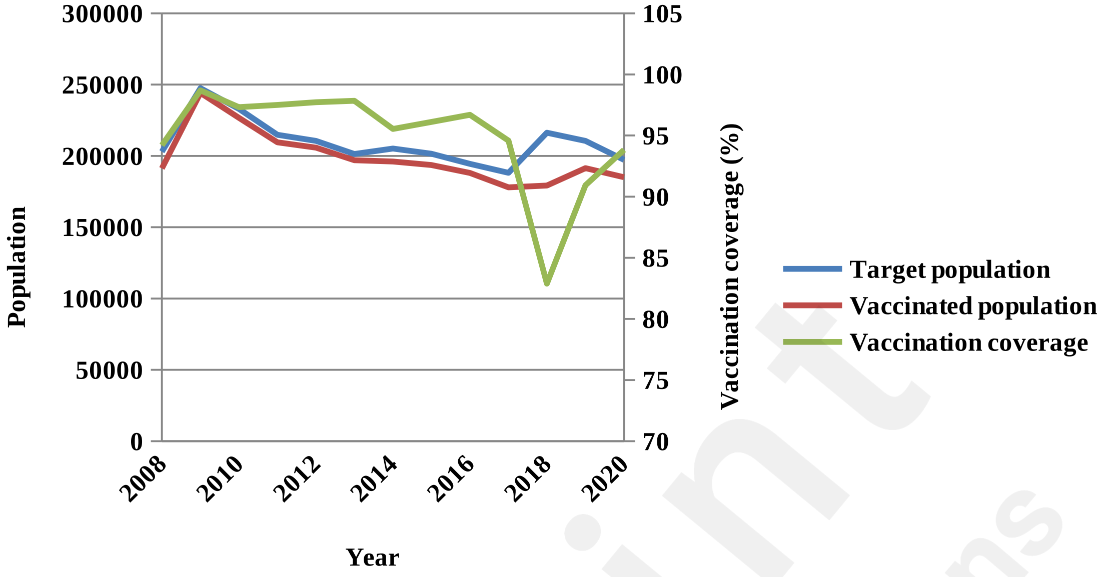

Figure 3. National immunization coverage for Japanese encephalitis in Taiwan from 2008 to 2020

Table 4. Environmental factors associated with Japanese encephalitis cases in Taiwan between 2008 and 2020.

Variable (lived nearby)	Year													
	Total	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Pig farms	158	4	6	8	10	23	10	11	13	11	13	25	13	11
Pigeon farms	125	7	4	14	2	17	5	7	9	11	10	19	8	12
Paddy fields	160	9	6	17	9	16	9	11	14	11	8	26	14	10
Egret nests	6	1		1		4								
Henhouses	2	1	1											
Pond	29	2	2	3	1	7	3	2	3	1	1	3	1	
Clam breeding farms	1		1											
Poultry farms	65			9	6	11	3		5	6	5	12	4	4
Goat farms	4			2		1					1			
Owned pets	18			1	5	5	3		2	1				1
Farmlands	6				3	3								
Orchards	8				3	5								

4.

Table 5. Association between air pollution factors and Japanese encephalitis cases was examined through multiple linear regression analysis

Variables	Non-standardization coefficient B value	Non-standardization coefficient Standard error	p
TSP (μg/□^{3})	-0.028	0.055	0.613
PM 2.5 (μg/□^{3})	0.022	0.177	0.900
PM 10 (μg/□^{3})	0.007	0.124	0.954
SO_2 (ppb)	2.184	0.922	0.020
CO (ppm)	-17.244	19.092	0.369
NO_2 (ppb)	-0.342	0.564	0.546
O_3 (ppb)	-0.157	0.063	0.014
Dustfall volume (tonne/km^2/month)	0.029	0.509	0.955
Lead (μg/□^{3})	43.751	72.026	0.545

TSP: total suspended particulate

R^2 = 0.417; F= 6.824 (*P* value < 0.001); df = (9, 86)

N=96

Table 6. Relationship between climate factors and Japanese encephalitis cases was analyzed using multiple linear regression analysis

Variables	Non-standardization coefficient B value	Non-standardization coefficient Standard error	p
Temperature (°C)	-0.025	0.192	0.897
Precipitation (mm)	-0.004	0.004	0.299
Relative humidity (%)	0.380	0.163	0.021
Mean Pressure (hPa)	-0.247	0.155	0.115
Number of Days with Precipitation >=0.1mm (day)	-0.017	0.199	0.931
Sunshine Duration (hr)	0.029	0.016	0.075

R^2 = 0.344; F=11.980 (*P* value < 0.001); df = (6, 137)

N=144

5. Discussion

Japanese encephalitis (JE) is the most prevalent cause of viral encephalitis in Asia, with transmission occurring through mosquito bites. It is endemic in most of South and Southeast Asia, but the number of cases can vary significantly between regions [32]. The discipline of epidemiology employs demographic methods to characterize the distribution of a particular organism and to analyze data in order to determine the factors influencing that distribution [33]. Epidemiology also encompasses the investigation of the distribution of diseases and the factors that influence the occurrence of disease in populations over time and space. Additionally, it examines the epidemiological characteristics associated with disease transmission, presentation, and outcome. This discipline has consistently been influenced by policy interventions and disease prevention measures [34]. From 2008 to 2020, a total of 313 cases of Japanese encephalitis were confirmed in Taiwan. Of these cases, 1.3% were imported, while 98.7% were indigenous, indicating that Japanese encephalitis is endemic in Taiwan. The high incidence rate among men is consistent with previous studies [35-37]. It can be postulated that the underlying cause may be differences in personal hygiene habits. Furthermore, most cases occur in individuals aged 40 to 59 years. Patients in this age group exhibited a higher incidence compared to those younger than 20 years (1.94 versus 0.73), which is consistent with previous studies [13, 38, 39]. The government of Taiwan can utilize the similarities and differences in epidemiological characteristics as a foundation for developing and implementing its epidemic prevention policy or strategy.

Among all epidemiological characteristics, seasonal variation is the most susceptible to the distribution of all confirmed cases. In essence, seasonal variation is sufficient to affect the significant increase or decrease of confirmed cases, thereby indicating that the disease in South Asia, Southeast Asian countries, or even Taiwan is endemic [40]. Outbreaks of the disease in question typically occur during the summer months in Taiwan, in accordance with the findings of previous studies [41-44]. According to the Central Weather Administration of Taiwan, the average summer temperature in Taiwan is 26.4 degrees Celsius [45]. Consequently, the findings indicate that temperature is a pivotal factor influencing the vector competence and survival of infected mosquitoes. Moreover, southern Taiwan is situated in rural and suburban areas. A previous study indicated that in rural and suburban areas, traditional rice farming and intensive pig breeding provide an ideal environment for both mosquito development and the transmission of JEV among humans. Our findings align with those of previous studies [46-48]. In other words, there are always traces of the Japanese encephalitis virus in Taiwan that present a threat to public health and increase the clinical medical burden. At this juncture, it is imperative to address these significant challenges head-on, employing strategies to prevent and control them. It is imperative that the Taiwanese government's health department proactively propose local prevention strategies and implement effective surveillance operations to control the epidemic and reduce the number of cases, thereby eliminating the health threat.

JEV is spread by mosquitoes within an enzootic cycle that includes reservoirs among pigs and birds, with humans serving as unintentional dead-end hosts. In the past decade, both serological and genetic evidence from previous studies suggests the presence of JEV in the local fauna [49]. As in the previous study, workplaces of cases in Taiwan are commonly found in pig farms, pigeon farms, and paddy fields [50, 51]. This study recommends that Taiwan's government health departments should increase publicity about measures to prevent Japanese encephalitis by raising pigs and pigeons in rural areas.

A previous study demonstrated that while the impacts of the COVID-19 lockdown on various sectors, including the economy, research, travel, education, and sports, were clear, the effects on the occurrence of vector-borne diseases (VBDs) were less apparent [52]. The number of cases reported was compared with the number of cases predicted for each year from 2015 to 2020 for the VBDs (Japanese encephalitis) under study to infer whether the COVID-19 lockdown had any impact on their prevalence in Taiwan. The actual number of cases was 21 both before and after the lockdown (2019 and 2020). The predicted number of cases for 2020, based on the trend of the previous five years (2015-2019), was also close to the actual number of cases. This suggests that the Japanese encephalitis virus has been consistently present in the local area of Taiwan for a long time. During the COVID-19 period, the number of Japanese encephalitis cases did not fluctuate significantly. The analysis suggests that the lockdown did not have a significant impact on the incidence of VBDs such as

Japanese encephalitis.

In the majority of cases, patients infected with Japanese encephalitis do not exhibit any clinical symptoms [53]. The infection commences with a non-specific febrile illness, with an incubation period of 5–15 days in humans. Non-specific symptoms, such as diarrhea, coryza, and rigors, typically manifest 3–4 days prior to the onset of JE, which is characterized by the development of clouding of consciousness, headache, vomiting, and, in some cases, seizures [54]. Consequently, the clinical symptoms observed in Japanese encephalitis cases in Taiwan are consistent with those previously documented in other studies [55-57]. It is challenging to differentiate between Japanese encephalitis virus and other pathogens that can cause encephalitis and meningitis, including enterovirus, mumps virus, mycoplasma, herpes virus, and other viruses. This necessitates the use of viral culture or serological examination [58]. Therefore, this study proposes that the current understanding of JE serum complex flavivirus cross-reactivity, which may result in variable clinical outcomes, could inform future preventive and therapeutic interventions.

During the investigation period of this study, Taiwan exhibited a consistently low incidence rate of JE and its associated mortality from 2008 to 2020. The average incidence and mortality rates were 1.03 cases per 1,000,000 and 0.09 cases per 1,000,000, respectively. A total of ten cases of JE were reported in children. Consequently, the study indicates that the JE vaccination offered a moderate level of protection among children in JE-endemic Taiwan, a finding consistent with previous studies [59]. The implementation of the JE immunization program has been a pivotal factor in controlling the spread of JE. It is necessary to sustain a high vaccination coverage rate for JE and reinforce the disease surveillance system to ensure the efficacious control and eventual eradication of JE [60].

The prospective effects of climate change on public health are a rapidly expanding field of investigation. This encompasses the immediate consequences of more intense heat waves and declining food security, in addition to the indirect influences on the prevalence of infectious diseases [61-65]. Research has demonstrated that the proximity of collection sites to human dwellings (AOR=2.02, p=0.009) and a relative humidity exceeding 80% (AOR=2.40, p=0.001) are significant independent risk factors for the transmission of JE viruses [66]. This finding is consistent with the present study. The results of this study indicate a positive correlation between relative humidity and Japanese encephalitis cases (B = 0.380, p = 0.021) through multiple linear regression analysis. The findings of this study indicate that climate change is a significant factor influencing the incidence of infectious diseases. It is therefore recommended that public health and epidemic prevention experts give this issue their attention, with the implementation of early planning measures to reduce the risk of disease.

Air pollution represents one of the most significant challenges of our era, affecting not only climate change but also public and individual health through increased morbidity and mortality [67]. A multitude of pollutants are significant contributors to human disease. A previous study indicated that a comparison of the combined anthropogenic and environmental risk factors of major mosquito-borne diseases, specifically Japanese encephalitis in Thailand, revealed that higher SO_2 surface concentrations were negatively associated with disease case counts [68]. However, the results of the linear regression analysis indicated that there was a positive association between SO_2 concentration and Japanese encephalitis (B = 2.184, p = 0.020). The concentration of O_3 was found to be negatively correlated with Japanese encephalitis (B = -0.157, p = 0.014). To the best of our knowledge, this is the first study to demonstrate that the number of cases of Japanese encephalitis increased as the concentration of the air pollutant SO_2 increased, and that there was a positive correlation. The study suggests that the high concentration of SO_2 in summer, which is a season prone to Japanese encephalitis virus, may be a contributing factor. It was hypothesized that there was a correlation between these air pollutants and the disease. Consequently, this study proposes that Taiwan's official policy should implement a rigorous monitoring program to assess local climate factors and air pollution concentration changes. In the event of minor fluctuations or significant fluctuations in environmental data, it is imperative that the media and the public be promptly informed. This will enable individuals to take prompt action to mitigate environmental pressures and the threat to public health.

One limitation of the present study is that the data provided by TNIDSS lack information about the genotypes or strains of the Japanese encephalitis virus isolated.

Consequently, the type of Japanese encephalitis virus strain that spread to Taiwan and the affinity between virus strains in Taiwan and other countries were not analyzed in this study. Nevertheless, the advantage of this study was the access to the diverse data provided by Taiwan's public sector on its online platform (including the initial version of the platform) and the evaluation of the impact of the COVID-19 pandemic on the epidemiological features of typhoid and paratyphoid. The information from existing public network platforms in Taiwan is both timely and accurate. Moreover, the platform retains data for an extended period, thereby facilitating the analysis of epidemiological data on infectious diseases by researchers and institutions.

This study is the first to report on the epidemiological characteristics, clinical symptomatology, climatic factors, and air pollutants associated with Japanese encephalitis cases in Taiwan between 2008 and 2020. In 2018, the incidence rate of Japanese encephalitis was the highest (1.57 per million people). In recent years, the risk of local cases has increased at a rapid pace, resulting in a significant burden of disease, public health challenges, and epidemic prevention. The distribution of Japanese encephalitis in Taiwan is regional in nature. The risk of Japanese encephalitis among patients residing in different areas increases with age. The clinical manifestations of Japanese encephalitis are variable, and the primary areas of endemicity are pig farms, pigeon farms, and paddy fields. The Japanese encephalitis vaccine coverage rate in Taiwan is high, with an average of 94.9%. The concentration of certain environmental factors (SO_2 and O_3) may influence the increase or decrease in Japanese encephalitis cases. This information will be of use to policy-makers and clinical experts in directing prevention and control activities for wildlife and livestock infected with the Japanese encephalitis virus, which causes a severe illness and a significant burden to Taiwan. The identification of crucial data will facilitate future surveillance and research activities in Taiwan.

Figure legend

Figure 1. Flowchart of the study sample selection from the Taiwan Centers for Disease Control Database in Taiwan from January 2008 to December 2020.

Figure 2. Incidence of confirmed JEV among patients in Taiwan according to (A) population, (B) gender, (C) age, (D) season and (E) region of residence by year from 2008 to 2020

Figure 3. National immunization coverage for Japanese encephalitis in Taiwan from 2008 to 2020

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Supplementary Files

Figures

Flowchart of the study sample selection from the Taiwan Centers for Disease Control Database in Taiwan from January 2008 to December 2020.

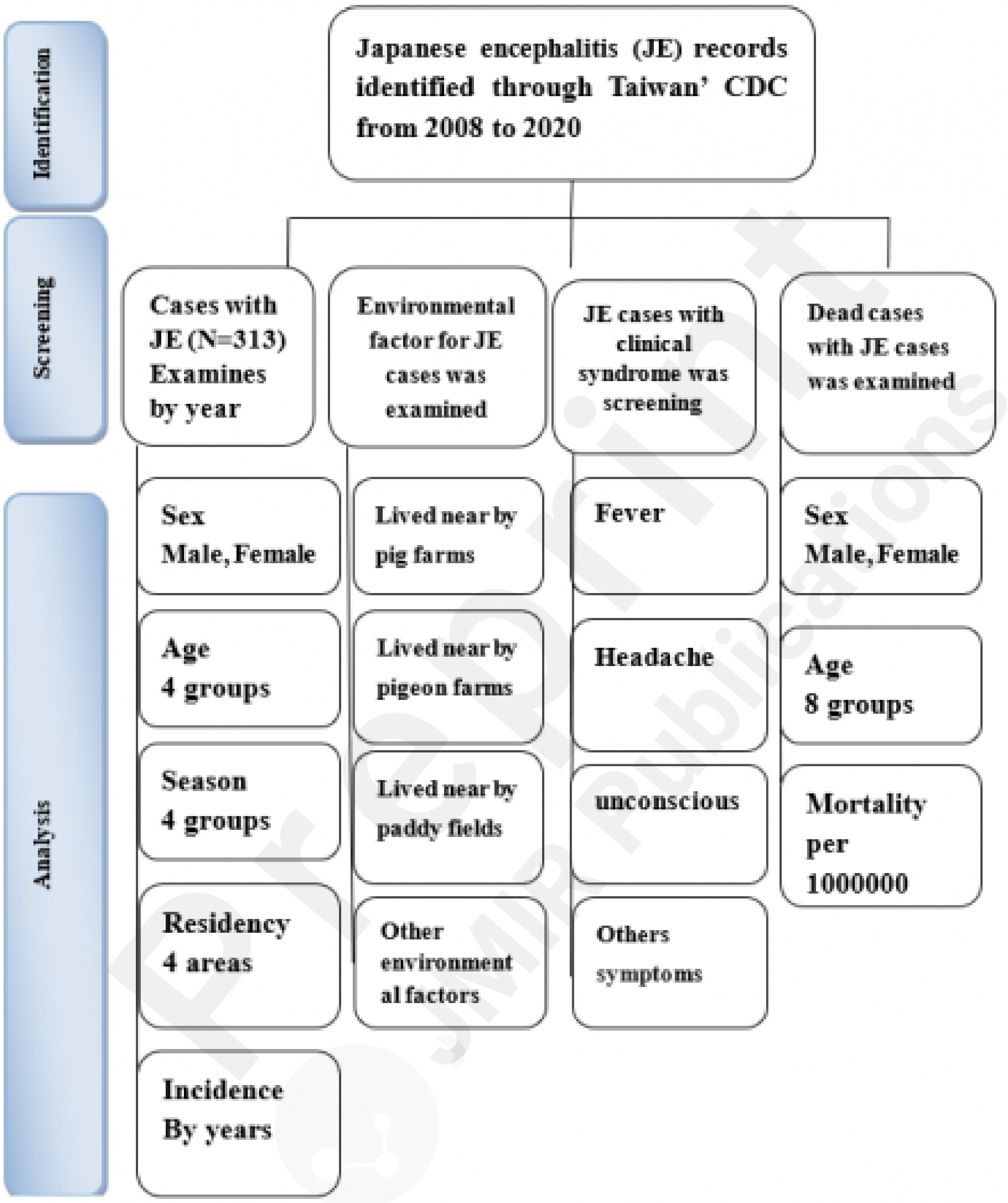

Figure 1. Flowchart of the study sample selection from the Taiwan Centers for Disease Control Database in Taiwan from January 2008 to December 2020.

Incidence of confirmed JEV among patients in Taiwan according to (A) population, (B) gender, (C) age, (D) season and (E) region of residence by year from 2008 to 2020.

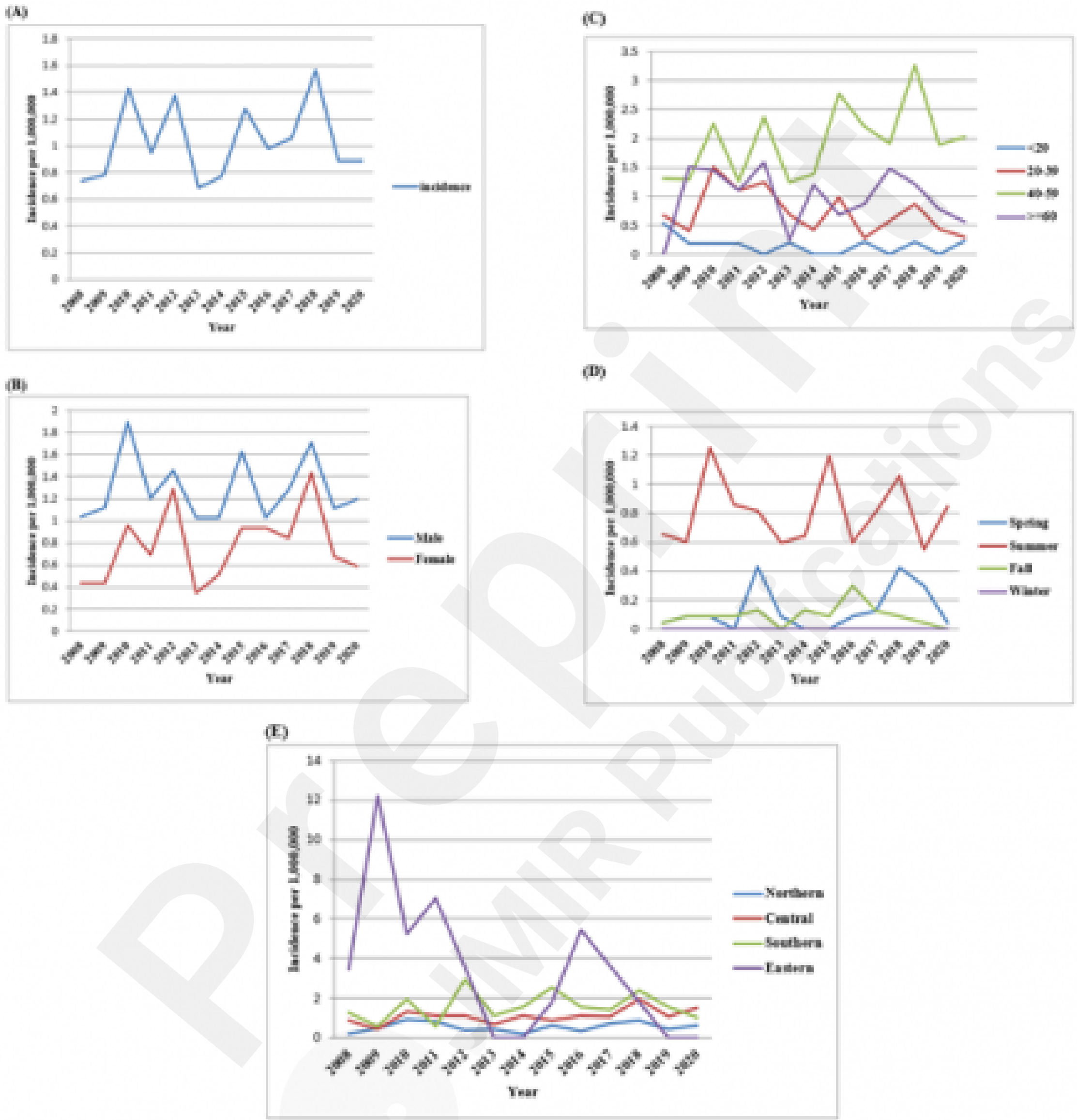

Figure 2. Incidence of confirmed JEV among patients in Taiwan according to (A) population, (B) gender, (C) age, (D) season and (E) region of residence by year from 2008 to 2020

National immunization coverage for Japanese encephalitis in Taiwan from 2008 to 2020.

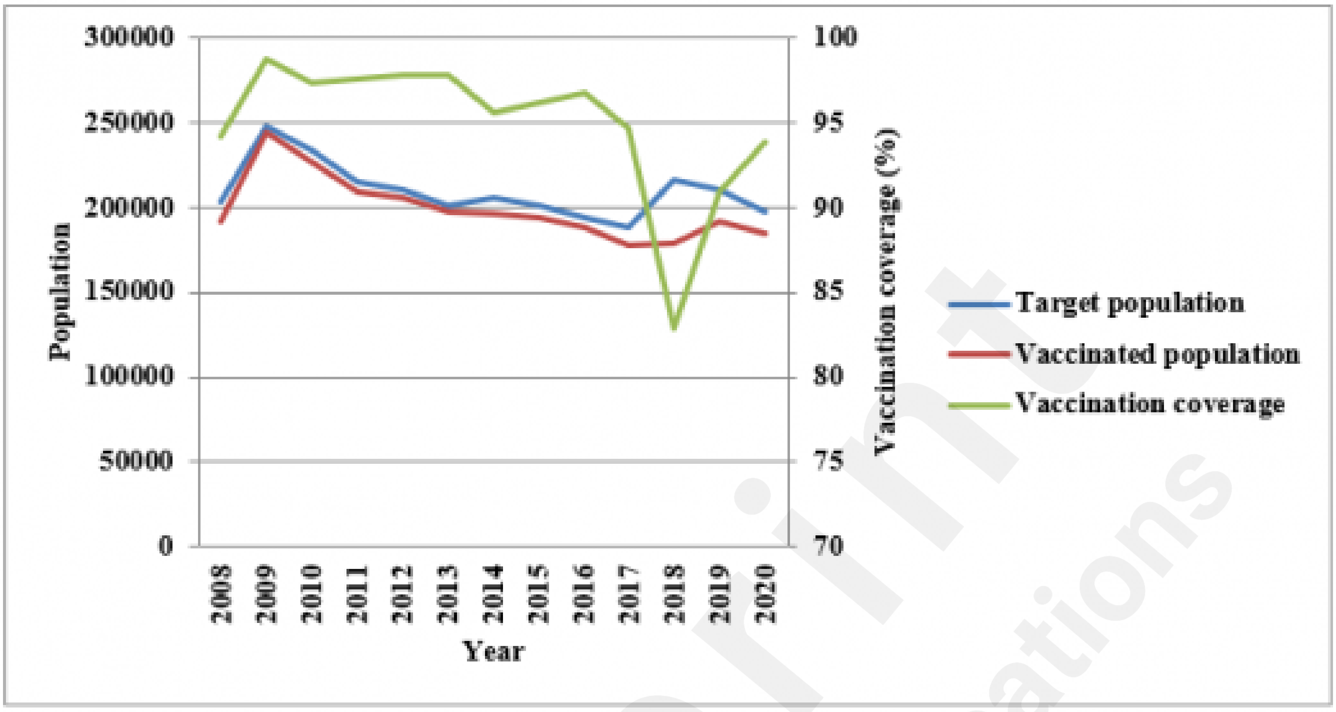

Figure 3. National immunization coverage for Japanese encephalitis in Taiwan from 2008 to 2020