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ORIGINAL ARTICLE

Epidemiological Characteristics of Zika Virus Infections Imported into Taiwan between 2016 and 2021

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Background: Zika virus is a mosquito-borne virus that has resurfaced. It has been confirmed to cause microcephaly and Guillain–Barré syndrome. The number of Zika virus infections in South America has increased considerably since 2015. **Aim:** This study confirmed the epidemiological characteristics of the cases of Zika virus infections imported into Taiwan. **Methods:** Patients with travel history to areas at risk of Zika virus infections and had their blood, urine, or saliva samples tested positive for Zika virus through reverse transcription polymerase chain reaction by the Taiwan Centers for Disease Control were included in this study. **Results:** Taiwan reported its first case of Zika virus infection in January 2016, and it has reported 26 cases as of December 2021. Most of the patients were men (76.9%, 20/26), aged 20–59 years (73.1%, 19/26), and lived in Northern Taiwan (73.1%, 19/26). Most of the cases were reported in summer and autumn (76.9%, 20/26). The 26 patients included one 4-year-old girl and three teenage boys aged 15–19 years; 22 patients were from Southeast Asia, three patients were from the Americas, and one patient was from Africa. **Conclusion:** This study is the first to report on the epidemiological characteristics of Zika virus infections imported into Taiwan between 2016 and 2021. These findings can aid policymakers and clinical experts in developing prevention and control measures targeting Zika virus infections, which cause severe illness and imposes a considerable burden on the population.

Key words: Epidemiology, Zika virus, zoonosis, imported, retrospective

INTRODUCTION

Zika virus was first isolated in Uganda, Africa in 1947.[1] Its effects on public health were limited until the occurrence of the 2007 Yap Islands Zika virus outbreak in Oceania.[2] Zika virus was subsequently detected in French Polynesia in 2015 and in other Pacific islands.[3] The spread of Zika virus to the Americas has been occurring on a large scale since 2015. The World Health Organization (WHO) confirmed the first local Zika virus infection in Northeast Brazil in May 2015, which was the first case of Zika virus infection in the Americas. In January 2016, the outbreak spread to various Central and South American countries and territories, and local Zika virus infections were reported in Brazil, Columbia, El Salvador, Guatemala, Mexico, Paraguay, Suriname, Venezuela, Honduras, Panama, Martinique, French Guiana, Puerto Rico, and Haiti.[4] Zika virus infections spread rapidly during the 2015–2016 outbreak, and more than 80 countries across the Americas, Oceania, Southeast Asia, and Africa were affected. The WHO declared Zika virus as a public health emergency of international concern in February 2016.[5] The spread of Zika virus has gradually slowed down since 2017; however, the

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virus is still spreading, and it could cause outbreaks in specific regions.[6] The WHO is urging countries to establish long-term response preparedness for Zika virus infections.

Zika virus is a type of *Flavivirus* (*Flavivirus*, *Flaviviridae*),[7] and it is an enveloped, icosahedral, positive-sense single-stranded ribonucleic acid virus comprising approximately 10,794 bases. Zika fever is a vector-borne disease transmitted by the *Aedes* genus.[8] Researchers have isolated Zika virus from *Cercopithecus aethiops* and *Erythrocebus patas*, and current direct evidence strongly suggests that the transmission of Zika virus is a cycle formed by vector mosquitoes of the *Aedes* genus and primates.[7,8] However, further research is required to understand the transmission of Zika virus because it has also been isolated from zebras, elephants, buffaloes, and rodents. The 2013 outbreak in Polynesia confirmed that humans are one of the reservoirs of Zika virus.[4]

Similar to patients with other *Flavivirus* infections, only a proportion of patients infected with Zika virus exhibit noticeable symptoms. On average, 20% of all patients with Zika virus infections exhibit clinical symptoms, which typically include fever, skin rash, arthralgia, arthritis, and nonpurulent/hyperemic conjunctivitis.[9] An increasing number of studies have demonstrated that these neurological abnormalities are correlated with Zika virus infections, and women who are infected with Zika virus during their pregnancy have an increased risk of giving birth to newborns with neurological abnormalities such as microcephaly.[10]

Located at 23°4′N and 121°0′E, Taiwan has a subtropical climate with an average monthly temperature ranging from 16°C to 29°C and an average monthly relative humidity ranging from 75% to 90%. It is a developed country with a gross domestic product per capita of US$ 34,485.[11] The first imported case of Zika virus infection in Taiwan occurred in January 2016.[12] Taiwan does not have any local cases of Zika virus infections, indicating that the effectiveness of implementing preventive measures that limit or eradicate Zika virus may be limited. Zika virus infections in Taiwan are sporadic. However, few Taiwan-based studies have employed big data analytics to explore epidemiological information pertaining to the risk of diseases related to Zika virus infections. Therefore, this study retrieved and analyzed data from the Taiwan National Infectious Disease Statistics System (TNIDSS) to explore the epidemiological characteristics, differences, and trends of the Zika virus infections that were imported into Taiwan between 2016 and 2021, including the sex, age, and residence of the involved patients and the seasonality of the imported cases.

MATERIALS AND METHODS

Ethical compliance

The present study was approved by the Research Ethics Committee of Asia Eastern University of Science and Technology (IRB No. 202304EM004), and was conducted in accordance with Declaration of Helsinki. The patient consent was waived by the IRB. The authors are confident that the present study adds value and conforms to the standards for the public use of government reports.[13-16]

Definition of reported case and confirmed case[17]

Clinical conditions

1. Skin rash or fever accompanied by any of the following symptoms: Arthralgia, arthritis, or nonpurulent/hyperemic conjunctivitis. The symptoms cannot be explained by other medical diagnoses
2. The mother of a newborn or fetus has a history of exposure to Zika virus and her newborn or fetus exhibits any of the following conditions after other etiologies have been excluded: (a) microcephaly or (b) intracranial calcification or inborn nervous system abnormalities.

Definition of history of exposure to Zika virus

Women have visited an area with a high prevalence of Zika virus infections or an area with confirmed cases of Zika virus infections during her pregnancy, or her sex partner has visited an area with a high prevalence of Zika virus infections or an area with confirmed cases of Zika virus infections during her pregnancy or up to 6 months before her pregnancy.

Definition of microcephaly

(1) An infant is defined by a specialist to have microcephaly if their head circumference is lower than the third percentile on the basis of age, sex, and the growth curve of the gestation period, and their head circumference is not proportional to their body length and weight. (2) The head circumference of a fetus is determined through ultrasonic examination to be smaller than three standard deviations.

Test conditions

A patient is defined as testing positive for Zika virus if any of the following test results are obtained:

1. Zika virus is isolated and identified from clinical specimens
2. Their clinical specimen tests positive in a molecular biology nucleic acid test
3. Their Zika virus-specific immunoglobulin A or immunoglobulin G antibodies test positive in acute or initial serum after other cross reactions of *Flavivirus* have been excluded
4. Their Zika virus-specific immunoglobulin A or immunoglobulin G antibodies test positive or multiplied by four times or more in paired sera (convalescent serum and acute serum).

Epidemiological conditions

To confirm a Zika virus infection, at least one of the following conditions must be met:

1. The assessed patient has visited an area with confirmed cases of Zika virus infections 2 weeks before they became ill
2. The assessed patient visited an area with a high prevalence of Zika virus infections 2 weeks before they became ill
3. The sexual partner of the assessed patient has visited an area with confirmed cases of Zika virus infections or a high prevalence of Zika virus infections 6 months before the patient became ill.

Definition of reporting case

A Zika virus infection report must be made if any of the following conditions are met:

a. Clinical condition (1) and any of the epidemiological conditions are met
b. Clinical condition (2) is met.[17]

Confirmed case

A confirmed case is a case that meets test conditions (1), (2), or (4).[17]

Data source

The present study retrieved data from the TNIDSS, which is a public database established and operated by the Taiwan Centers for Disease Control (TCDC).[18] The public TNIDSS database contains data on five categories of communicable diseases listed in the Communicable Disease Control Act. The TNIDSS platform provides transparent, up-to-date epidemic information. To ensure information security and privacy, this public database includes only secondary data (i.e., notification date, onset date, confirmation date, and the number of confirmed imported cases of Zika virus infections), not identifiable case details. The database does not store the medical history of patients, their signs and symptoms, or their laboratory test results.

Data analysis

The present study adopted a retrospective descriptive design to examine all imported cases of Zika virus infections since 2016. We confirmed the number of people diagnosed as having Zika virus infections between 2016 and 2021 and examined the distribution of their epidemiological characteristics (i.e., sex, age, time of diagnosis, and living area), differences, and results. Next, we focused on sex, age, time of diagnosis, changes in living area, trends, and related results in our analysis of the cases of Zika virus infections that were confirmed between 2016 and 2021. Descriptive data are presented as means and total, where appropriate. Categorical variables were compared by performing Chi-square tests. All statistical analyses were performed using SPSS (IBM SPSS version 21; Asia Analytics Taiwan, Taipei, Taiwan). All statistical tests were two-sided, with an $\alpha = 0.05$; a value of $P < 0.05$ was regarded as a statistically significant result.

RESULTS

Twenty-six eligible patients were identified from the CDC database of Taiwan, and their data for January 2016 to December 2021 were retrieved. A detailed flowchart of the sample selection process is presented in Figure 1. The retrieved data comprised information regarding infection risk factors (sex, age, season in which an infection was reported, and area of residence), and the corresponding case numbers were also obtained [Table 1].

Statistical data from the National Tourism Bureau, Ministry of Transportation and Communication, were used to estimate the number of travelers who visited countries with a high risk of Zika virus infection, and the estimations were used as the denominator to calculate the number of Zika virus infection cases linked to each country. The annual rate of imported Zika virus infections changed significantly during the study period, decreasing by 20%. The mean annual incidence of imported Zika virus infections was 0.61/1,000,000 people [range 0–1.45; Figure 2]. The rate of imported Zika virus infections is the highest in 2020 compared to the other years.

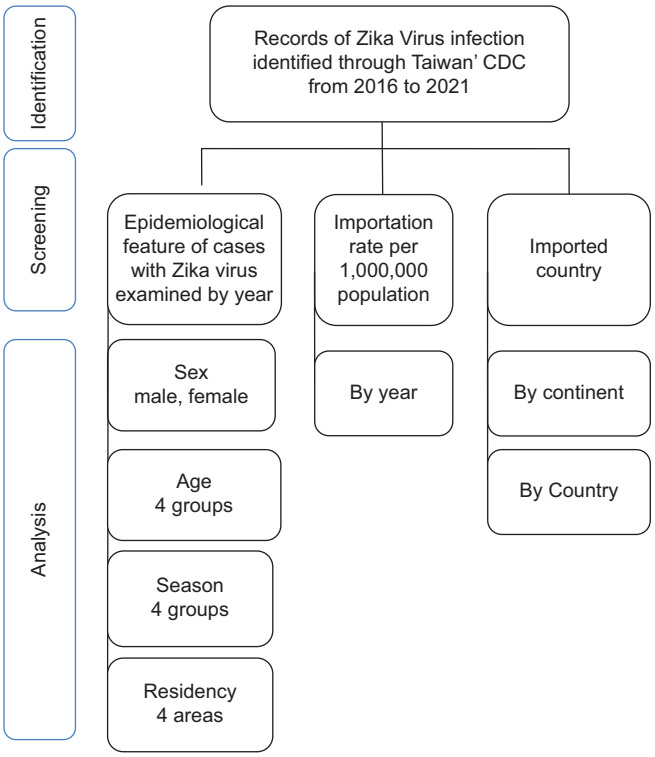

Figure 1: Process for selecting study sample based on data (January 2016 to December 2021) from Taiwan Centers for Disease Control Database

Table 1: Epidemiological features of cases of Zika virus infection reported in Taiwan from 2016 to 2021

Variable	Year*						*P*
	Overall (*n*=26), *n* (%)	2016 (*n*=13), *n* (%)	2017 (*n*=4), *n* (%)	2018 (*n*=3), *n* (%)	2019 (*n*=4), *n* (%)	2020 (*n*=2), *n* (%)	
Identify							
Domestic	0	-	-	-	-	-	-
Imported	26 (100)	13 (100)	4 (100)	3 (100)	4 (100)	2 (100)	
Gender							
Male	20 (76.9)	9 (69.2)	4 (100)	2 (66.7)	3 (75)	2 (100)	0.789
Female	6 (23.1)	4 (30.8)	0	1 (33.3)	1 (25)	0	
Age							
<20	4 (15.4)	0	1 (25)	0	3 (75)	0	0.203
20–39	12 (46.2)	7 (53.8)	3 (75)	1 (33.3)	0	1 (50)	
40–59	7 (26.9)	4 (30.8)	0	1 (33.3)	1 (25)	1 (50)	
≥60	3 (11.5)	2 (15.4)	0	1 (33.3)	0	0	
Season							
Spring	3 (11.5)	1 (7.7)	1 (25)	0	0	1 (50)	0.689
Summer	9 (34.6)	4 (30.8)	2 (50)	1 (33.3)	2 (50)	0	
Fall	11 (42.3)	7 (53.8)	1 (25)	2 (66.7)	1 (25)	0	
Winter	3 (11.5)	1 (7.7)	0	0	1 (25)	1 (50)	
Residency							
Northern	15 (57.7)	6 (46.2)	3 (75)	2 (66.7)	3 (75)	1 (50)	0.818
Central	7 (26.9)	5 (38.5)	0	1 (33.3)	1 (25)	0	
Southern	4 (15.4)	2 (15.4)	1 (25)	0	0	1 (50)	
Eastern	0	0	0	0	0	0	

*No confirmed cases were reported in 2021. -=Not applicable

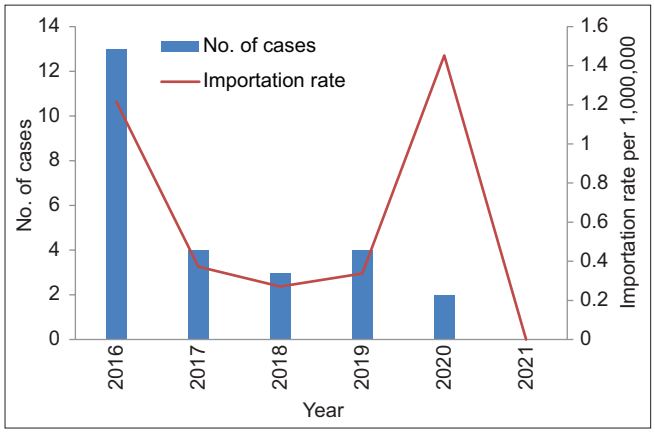

Figure 2: Rate of imported Zika virus infections and number of imported cases in Taiwan stratified by year

On the basis of the results from a survey on the cases of imported Zika virus infections reported in Taiwan between 2016 and 2021, the associations of gender with age, seasonality, and region of residence were investigated [Table 2]. Among the imported cases, 11 involved male patients, with one male patient being from the 20 to 39-year-old age group; six and three cases involving male and female patients, respectively, were reported during the summer season; 11 and 4 cases involving male and female patients, respectively, were reported in Northern Taiwan. On the basis of the results from a survey on the cases of imported Zika virus infections reported in Taiwan between 2016 and 2021, the associations of age with season and region of residence were investigated [Table 3]. In the 20–39-year-old group, three cases were reported in spring, three in summer, five in autumn, and one in winter. In the 20–39-year-old group, three cases were reported in northern Taiwan, three in central Taiwan, five in southern Taiwan, and one in Eastern Taiwan.

For the 26 imported cases, the top five countries that contributed the highest number of imported infections were Vietnam (23.1%, 6/26), Thailand (23.1%, 6/26), Myanmar (11.5%, 3/26), Malaysia (11.5%, 3/26), and the Philippines [7.7%, 2/26; Figure 3].

DISCUSSION

International travel has contributed to the spread of diseases, and the number of travelers with mosquito-borne

Table 2: Associations of gender with age, season, and region of residence based on a survey of cases of Zika virus infections imported into Taiwan between 2016 and 2021

Variable	Gender*		*P*
	Male (*n*=20), *n* (%)	Female (*n*=6), *n* (%)	
Age			
<20	3 (15)	1 (16.7)	0.073
20–39	11 (55)	1 (16.7)	
40–59	3 (15)	4 (66.7)	
≥60	3 (15)	0	
Season			
Spring	3 (15)	0	0.486
Summer	6 (30)	3 (50)	
Fall	8 (40)	3 (50)	
Winter	3 (15)	0	
Residency			
Northern	11 (55)	4 (66.7)	0.810
Central	6 (30)	1 (16.7)	
Southern	3 (15)	1 (16.7)	
Eastern	0	0	

*No confirmed cases were reported in 2021

Table 3: Associations of age with season and region of residence based on a survey of cases of Zika virus infection imported into Taiwan between 2016 and 2021

Variable	Age*				*P*
	<20 (*n*=4), *n* (%)	20–39 (*n*=12), *n* (%)	40–59 (*n*=7), *n* (%)	≥60 (*n*=3), *n* (%)	
Season					
Spring	0	3 (25)	0	0	0.331
Summer	2 (50)	3 (25)	4 (57.1)	0	
Fall	1 (25)	5 (41.7)	2 (28.6)	3 (100)	
Winter	1 (25)	1 (8.3)	1 (14.3)	0	
Residency					
Northern	2 (50)	5 (41.7)	6 (85.7)	2 (66.7)	0.580
Central	1 (25)	4 (33.3)	1 (14.3)	1 (33.3)	
Southern	1 (25)	3 (25)	0	0	
Eastern	0	0	0	0	

*No confirmed cases were reported in 2021

virus infections, particularly Zika virus infections, has increased in Taiwan. However, no local infection has been reported. Therefore, performing epidemiological investigation and analysis for the imported cases in Taiwan can reduce the risk of travelers spreading diseases. The present study analyzed the cases of Zika virus infections imported into Taiwan between 2016 and 2021 to understand the long-term trends and changes relating to Zika virus infections in Taiwan. The results revealed the following findings: (1) The rate of imported cases peaked in 2020 at the apex of the epidemic curve. The reason for the high overseas importation rate in 2020 might be that due to the COVID-19 epidemic in 2020, the number of overseas tourists coming to Taiwan suddenly decreased, resulting in an increase in the importation rate. (2) The number of male patients was considerably higher than that of female patients, and this difference is still increasing. This finding is similar to that of an international study.[19] (3) Most of the patients were aged 20–39 years. This finding is similar to that of an international study.[20] (4) Most of the infections were reported in summer and autumn. This finding is similar to that of an international study.[21] And (5) geographically, the distribution of imported cases in Taiwan was uneven. Most of the cases were reported in Northern Taiwan, followed by Central and Southern Taiwan. Given the findings of the present study, policymakers and health-care planners should (1) continue to maintain the effectiveness of measures focused on Zika virus infection prevention and control, (2) strengthen health education programs for adults and provide more private counseling services, and (3) conduct prevalence surveys of high-risk groups to understand trends in Zika virus infections and the related disease burden. This study has provided epidemiological information, and it suggests that preventive policies for Zika virus infections should be formulated in Taiwan.

The WHO and the Pan American Health Organization (PAHO) have published clinical standards for the diagnosis of Zika virus infections. The WHO defined a Zika virus infection as a condition characterized by the presence of skin rash or fever accompanied by one of the following symptoms: arthralgia, arthritis, or conjunctivitis. Similarly, PAHO defined a Zika virus infection as a condition involving skin rash and at least two of the following symptoms: fever, conjunctivitis, arthralgia, muscle pain, or swelling near the joints.[22] An international study evaluated 556 children aged 2–14 years with Zika virus infections, and it discovered that children with Zika virus infections generally exhibited less severe clinical manifestations relative to adults with Zika virus infections. In fact, only 32% and 20% of the children in that study met the clinical criteria of the WHO and PAHO, respectively.[22] Children with Zika virus infections are less likely than adults with this infection to be affected by arthralgia. In fact, most children with Zika virus infections only develop skin rash or rash with leucopenia; however, these symptoms do not meet the clinical standards of the WHO and PAHO. At present, only a few cases of Zika virus infections with severe complications have been reported among children.[22] Of the 26

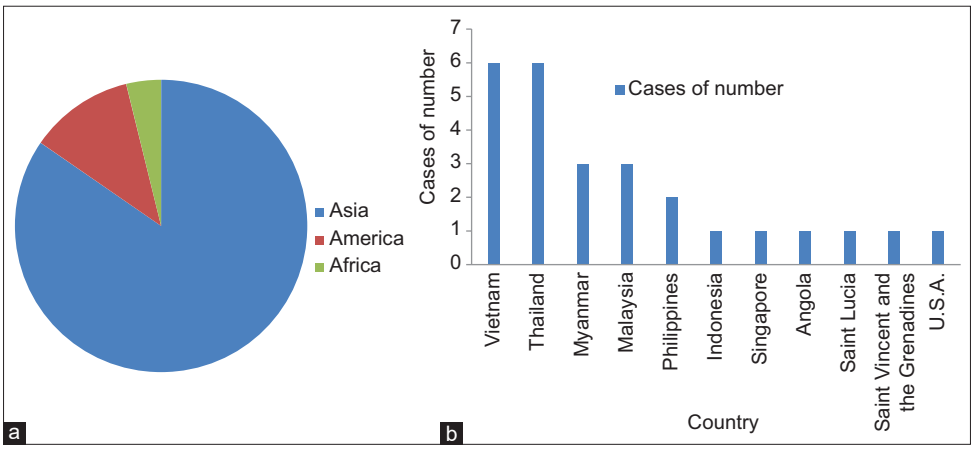

Figure 3: Reported cases of Zika virus infections imported into Taiwan from countries in Asia and other regions. (a) Cases imported from Vietnam and other countries, (b) from 2016 to 2021. Vietnam (in Asia) is the country from which the most Zika virus infection cases were imported into Taiwan

imported cases examined in the present study, four involved children. Although the present study could not determine whether these cases were caused by vertical transmission, its findings verify that children are also at risk of Zika virus infections. Therefore, the TCDC should closely monitor children entering Taiwan and screen for Zika virus infection at an early stage to reduce the health risks of this population. In addition, because the symptoms of children with Zika virus infections differ from the clinical manifestation of adults with Zika virus infections, medical professionals should clarify the epidemiological characteristics and symptoms of children with Zika virus infections. This information can help pediatricians to diagnose Zika virus infections at an early stage and provide the appropriate clinical treatment, and it also enables government health departments to closely monitor the distribution of Zika virus cases involving children such that early warning and preventive measures can be effectively implemented.

Zika virus is recognized as a major threat to global public health, and Zika virus infections have been reported in the Americas, the Caribbean, and numerous countries or regions in the Western Pacific region and South Asia between 2015 and 2016. Studies have confirmed that the risk of a Zika virus outbreak increases with vapor pressure, dengue virus outbreaks, and population density, but decreases with increased medical expenditure, a higher gross domestic product, and a higher number of travelers. A study predicted and identified Asia–Pacific countries at risk of Zika virus infections for the period from October 2016 to January 2017.[23] The same study suggested that in October 2016, the countries at high risk of Zika virus infections were clustered in South Asia and Southeast Asia (i.e., India, Sri Lanka, Vietnam, Laos, Thailand, the Philippines, Singapore, Indonesia, and Malaysia all had a risk of >80%).[23] Therefore, the present study inferred that South Asia and Australia remain at a high risk of Zika virus infections. The results of the present study are notable because they revealed that most of the cases of Zika virus infections imported into Taiwan involved travelers from Southeast Asia (84.6%, 22/26). Taiwan is a tourism hotspot in Asia that numerous travelers visit annually for business or leisure, and this substantial influx of travelers increases the risk of Zika virus infections. Therefore, the epidemic prevention agencies of Taiwan should actively monitor travelers from Southeast Asia and implement border epidemic control measures, such as isolating confirmed cases, imposing home quarantine, and implementing self-health management; these measures can effectively prevent the spread of Zika virus and protect the health of Taiwan's population. This study suggested the potential factors which lead to a major outbreak of the Zika virus within Taiwan were imported cases number and local mosquito control. Therefore, there are both importance between overseas containment measures and vector control.

The present study has three limitations. First, the infectious disease data retrieved from TCDC's internet platform only comprised basic epidemiological data about patients with Zika virus infections and did not contain any clinical data. For this reason, the present study could not identify differences or trends in patient clinical symptoms. Second, the platform did not include genetic information regarding Zika virus, details pertaining to the characteristics of the virus's antigenic structure that are prevalent in Taiwan, or information on the genetic relationships between the strains of Zika virus in Taiwan and other countries. Third, this study is a retrospective study and Taiwan CDC has not released the main purposes of imported cases entry or the information about their duration of stay. The key strength of the present study is that its findings are based on accurate, real-time data retrieved from an online public platform operated by a public agency in Taiwan. In

addition, the database contains data spanning numerous years, allowing researchers or institutions to access a wealth of data on infectious diseases.

CONCLUSION

The present study is the first to report on the epidemiological characteristics of Zika virus infections imported into Taiwan between 2016 and 2021. Because Zika virus is imported into Taiwan from overseas, screening travelers with symptoms is inadequate for monitoring Zika virus infections. Preventive measures such as revising the Zika virus monitoring model, using multimedia and accessible channels to enhance public health education programs, and implementing effective vector control can reduce the risk of Zika virus transmission. The findings of the present study can help policymakers and clinical experts to design prevention and control activities to combat Zika virus infection, which has severe health consequences and imposes a substantial burden on the Taiwanese population.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, Yu C-P , upon reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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