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Original Article

Chikungunya in Zhejiang Province, Southeast China

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ABSTRACT

Background: Chikungunya is emerging and reemerging word-widely in the past decades. It is non-endemic in Zhejiang Province, Southeast China. Aedes albopictus, one of major vectors of chikungunya, is widely-distribution in Zhejiang, and autochthonous transmission is possible after introducing chikungunya virus.
Methods: Retrospectively collected the epidemiological, clinical and genetic data of chikungunya and conducted the descriptive analysis and gene sequence analysis.
Results: From 2008 to 2022, 29 chikungunya cases, including 26 overseas imported and 3 local cases, were reported and no cases died of chikungunya. More than half of the imported cases (53.85%) were from Southeast Asia. Seasonal peak of the imported cases was noted between August and September, and 42.31% cases onset in those 2 months. Eight prefecture-level cities and 16 counties reported cases during the study period, with Jinghua (27.59%) and Hangzhou (24.14%) reporting the largest number of cases. The 3 local cases were all reported in Qujiang, Quzhou in 2017. For imported cases, the male-female gender ratio was 2.71:1, 20–30 years old cases (46.15%) and commercial service (42.31%) accounted for the highest proportion. Clinically, fever (100%), fatigue (94.44%), arthralgia (79.17%), headache (71.43%) and erythra (65.22%) were the most common reported symptoms. Eight whole-genome sequences were obtained and belonged to East/Central/South African (ECSA) or Asian genotype.
Conclusions: With the change of immigration policy, the surveillance of chikungunya should be strengthened and the ability of the case discovery and diagnosis should be improved in Zhejiang in the post-COVID-19 era.

1. Introduction

Chikungunya fever is a mosquito-borne viral disease caused by chikungunya virus (CHIKV). The major vectors are *Aedes aegypti* and *Aedes albopictus,* which also transmit dengue virus. CHIKV is a ~11.8 kb long single-stranded, positive-sense RNA virus and belongs to the family *Togaviridae*, genus *Alphavirus*. It contains 4 nonstructural proteins, namely nsP1, nsP2, nsP3, and nsP4, encoded at the 5′ end of the genome, and 5 structural proteins encoded at the 3′ end of the genome, including 3 glycosylated proteins, namely E1, E2, E3, a small 64 amino-acids glycoprotein 6K, and one non-glycosylated nucleocapsid protein C (CP) [1]. Chikungunya was firstly used to name a dengue-like disease with obvious joint pain in Southern Tanganyika during later 1952 and early 1953. It means “that which bends up” or “walking bent” in local language, which references to the curved posture of patients because of the severe joint pains. The virus responsible for this disease was firstly isolated in 1957. Three different CHIKV genotypes had been identified, named as East/Central/South African (ECSA), West African and Asian. In an outbreak with high epidemic magnitude in coastal areas of Orissa, Eastern India, in 2010, the Indian Ocean Lineage (IOL) group within ECSA genotype was isolated. The urban outbreak of CHIKV was first identified in Thailand in 1967, then in India in the 1970s. After 2004, chikungunya outbreak accelerated its frequency and expanded its geographical range. The first outbreak in European and the Americas was identified in 2007 and 2013, respectively. By now, CHIKV had been confirmed in over 110 countries in Asia, Africa, Europe and the

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Americas, and always co-circulates with other arboviruses, such as dengue virus, zika virus, and yellow fever virus. A meta-study conducted by Li et al. [2] indicated that the overall seroprevalence of CHIKV was 25% (95% CI: 22–29). Among all World Health Organization (WHO) regions, the rate was highest in the South-East Asian (42%, 95% CI: 17–67), lowest in the Eastern Mediterranean Region (2%, 95% CI: 0–5). And the top 5 countries/areas with highest infection rates were Cameroon (68%, 95% CI: 25–100), Comoros (63%, 95% CI: 58–68), Haiti (58%, 95% CI: 56–59), Thailand (49%, 95% CI: 6–92), and Indonesia (39%, 95% CI: 32–45). There were no significant differences in seroprevalences between developed and developing countries, as well as between urban and rural areas.

Other than arthralgia, chikungunya is always indistinguishable with dengue in clinical. After infection, most people will recover in few days, some even have no notable symptoms and the estimated proportion of silent infection was 40%. But some will experience long-term disabilities, mainly arthralgia. A meta-analysis including 24 studies indicated that the pooled prevalence rates for the long-term disabilities of CHIKV disease patients were found 39.70% for follow up time between 6 and 12 months, 35.85% for follow up time between 12 and 18 months and 28.20% for greater than 18 months, respectively [3]. Female, ≥40 years old, diabetes, hypertension, severity of pain at acute stage (self-assessment numerically scale ≥ 7) were recognized as the risk factors for the long-term disabilities. As an emerging arbovirus infection, chikungunya fever constitutes a serious public health problem. The study evaluated the global burden caused by CHIKV between 2010 and 2019 indicated that it caused the average yearly loss of over 106,000 disability-adjusted life years (DALYs) during this period [4]. Long-term rheumatic sequelae provided the largest DALY component, while acute symptoms and early death accounted for relatively less of the overall burden. CHIKV caused substantially more burden in the Americas than in any other region of WHO. It was believed that the disproportionate higher disease burden in the Americas was attributed to the limited active surveillance reporting in other regions and the lack of immunity in populations of the Americas. The economic burden study of the chikungunya outbreak in the U.S. Virgin between 2014 and 2015 showed that the average number of missed day from work in the 12 months following onset was 9 days, resulting an estimated cost of $15.5 million; the estimated direct healthcare costs for the first 2 months and 3–12 months following the outbreak were $2.9 million and $0.6 million, respectively; and the total estimated cost associated with the outbreak ranged from $14.8 to $33.4 million (approximately 1% of gross domestic product) [5]. CHIKV is not endemic in mainland China, but since 2008, imported chikungunya cases were reported constantly [6]. The first autochthonous transmission of CHIKV in China was reported by Guangdong Province in 2010 [7]. Zhejiang is one of the most densely populated and affluent province in southeast of China. As the highly human mobility, Zhejiang is vulnerabled to the traveled-related communicably disease. This study depicted the epidemiology and clinical characteristics of chikungunya in Zhejiang province, and tried to provide guiding information for the disease control and prevention in the post COVID-19 era.

2. Materials and methods

2.1. Study design and data collection

This was a 15-year population-based surveillance study of chikungunya. All the cases would be recorded in the National Notifiable Disease Surveillance System (NNDSS) after diagnosis by clinician. A survey, including demographic profile (name, age, gender, occupation and address), epidemiological history and clinical presentation, would be conducted immediately by staff from the Center for Disease Control and Prevention. Imported/indigenous cases were defined according to the epidemiological history. Cases would be recognized as imported if he/she got infected in regions other than Zhejiang Province. The case that had no travel history in CHIKV-endemic region or the region with autochthonous transmission of CHIKV in the past 12 days before the onset would be classified as the indigenous case. Chikungunya cases were diagnosed according to the diagnostic and treatment scheme for chikungunya fever before August 2018 and diagnosis for chikungunya fever (WS/T 590-2018) after August 2018. The map of Zhejiang province was freely downloaded from National Earth System Science Data Sharing Infrastructure (http://www.geodata.cn/). All the strains with complete genome sequences of CHIKV were download from the National Center for Biotechnology Information (NCBI; www.ncbi.nlm.nih.gov/). “Chikungunya” and “Zhejiang” were used as keywords to get all the potential strains isolated in Zhejiang Province. The information of the strain, including date of isolation and the infectious origin, was obtained through consulting the uploader or the comment in NCBI. Basic Local Alignment Search Tool (BLAST; https://blast.ncbi.nlm.nih.gov/Blast.cgi) was used to identify the strains with highest similarity to that isolated in Zhejiang. Strains with complete genome sequence and isolated from different locations, time, of different genotypes were randomly downloaded from NCBI.

2.2. Statistical analysis

WPS Office software was used for the data management. SPSS17.0 software was employed for the statistical analysis. Quantitative data was presented as median and interquartile range (IQR). Qualitative data was described as percentage. ArcGIS (version 10.0.0) software

was used for the geographical-distribution-plotting. Sequences were aligned with MAFFT 6.843 with L-INS-i. A rectangular evolutionary tree was established with Maximum-likelihood method in MEGA 7.0.25. NC004162 was used as the reference sequence to identify the mutation of amino acid in the E1–E3 gene.

3. Results

3.1. Epidemiologic characteristic

A total of 29 cases, including 26 imported and 3 indigenous infections, were reported in Zhejiang during 2008–2022. No cases died of CHIKV. All the imported cases were infected abroad, with 53.85% from Southeast Asia, 38.46% from South Asia and 7.69% from sub-Saharan Africa. Thailand (23.08%), Myanmar (19.23%), Bangladesh (19.23%) and India (11.54%) were the top 4 countries exporting the most chikungunya cases to Zhejiang in this period. The first ever recorded chikungunya case in Zhejiang was reported in 2008. Since then, cases were reported with interval of several years. After 2016, cases were confirmed every year between 2016 and 2020, with the annual case number peaked in 2019 (Fig. 1). Yet, no cases were diagnosed in 2021 or 2022. More than three quarters of imported cases (88.46%) had onset between April and September, and the seasonal peak was noted in August and September (Fig. 1). The first and the only autochthonous transmission of CHIKV was reported in 2017. A total of 3 indigenous cases were reported and all had onset in August. Other than Lishui, Shaoxing, and Taizhou, all the prefecture-level cities in Zhejiang reported chikungunya cases between 2008 and 2022. Jinhua (27.59%) and Hangzhou (24.14%) were the top 2 cities confirmed the most cases. Sixteen out of 91 counties reported case in this period and the total case number ranged from 1 to 6 (Fig. 2). All the 3 indigenous cases were reported in Qujiang. The 3 counties identified the most cases were Yiwu (6), Qujiang (4) and Tongxiang (3). The male-female gender ratio for the imported case was 2.71:1. The age ranged from 20 to 74 years old, with median of 30 (26, 48.5) years old, and about half (46.15%) were at the age of 20–30 years old (Fig. 3). More than one–third of imported cases (38.46%) were foreigner. Business service (42.31%), Housework or unemployment (26.92%) were the most frequently reported occupations for imported cases. For the 3 indigenous cases, 2 were female, the age were 22, 28, and 54 years old, respectively, and the occupation were worker, teacher and farmer, respectively.

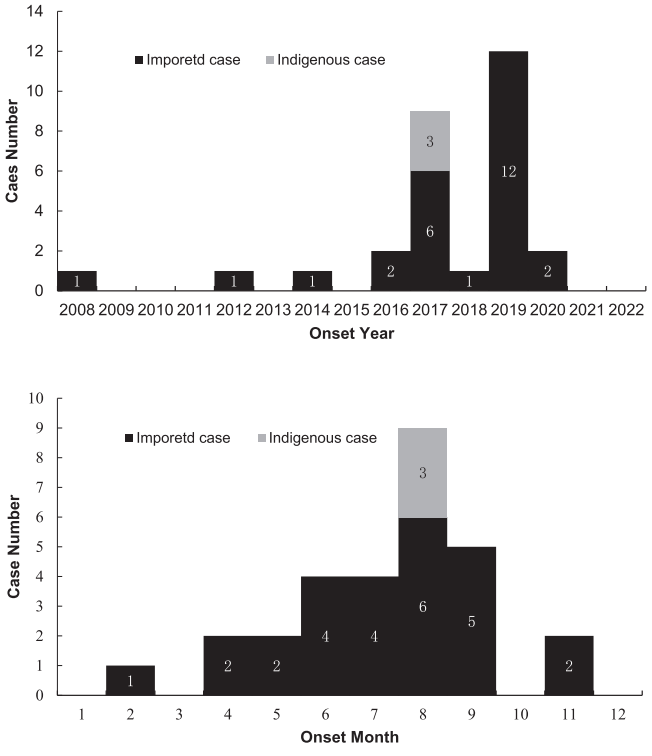

Fig. 1. The temporal distribution of chikungunya fever in Zhejiang province during 2008–2022.

3.2. Clinical characteristic

The onset and confirmed date for all the cases were available. The date of first visit to hospital was reported by 26 cases. The time intervals between onset and first visit ranged from 0 to 3 days, with the median of 1.00 (0.00, 2.00) days. The intervals between first visit and confirmation were at the range of 0 to 31 days and the median was 0.00 (0.00, 2.00) days. The intervals between onset and confirmation ranged from 0 to 82 days, and the median was 2.00 (1.00, 4.50) days. Clinically, chikungunya fever was characterized with fever (100%), fatigue (94.44%), arthralgia (79.17%), headache (71.43%), and erythra (65.22%) (Fig.4). For the 28 cases with fever, 25 cases reported the maximum body temperatures, and they ranged from 38.2°C to 40°C, with 92% cases ≥38.5°C, 64% cases ≥39.0°C, and 62% cases ≥39.5°C. For the cases with arthralgia, knee (73.33%) was most frequently involved, followed by ankle (53.33%), wrist (46.67%) and finger (35.71%). For the cases with erythra, rashes were mostly on the extremities (75%), and the ratios that had rashes on trunk and face were both 66.67%. For the cases reporting their diagnosis on admission, more than half (58.33%) were diagnosed as probable/confirmed chikungunya fever, and one third were diagnosed as probable dengue.

3.3. Phylogeny and amnion acid mutation of CHIKV

Eight strains isolated in Zhejiang with complete genome sequence were obtained in PubMed, and 3 of them were from indigenous cases (Fig. 5). The strain of KC488650 was isolated from a Philippine seaman.

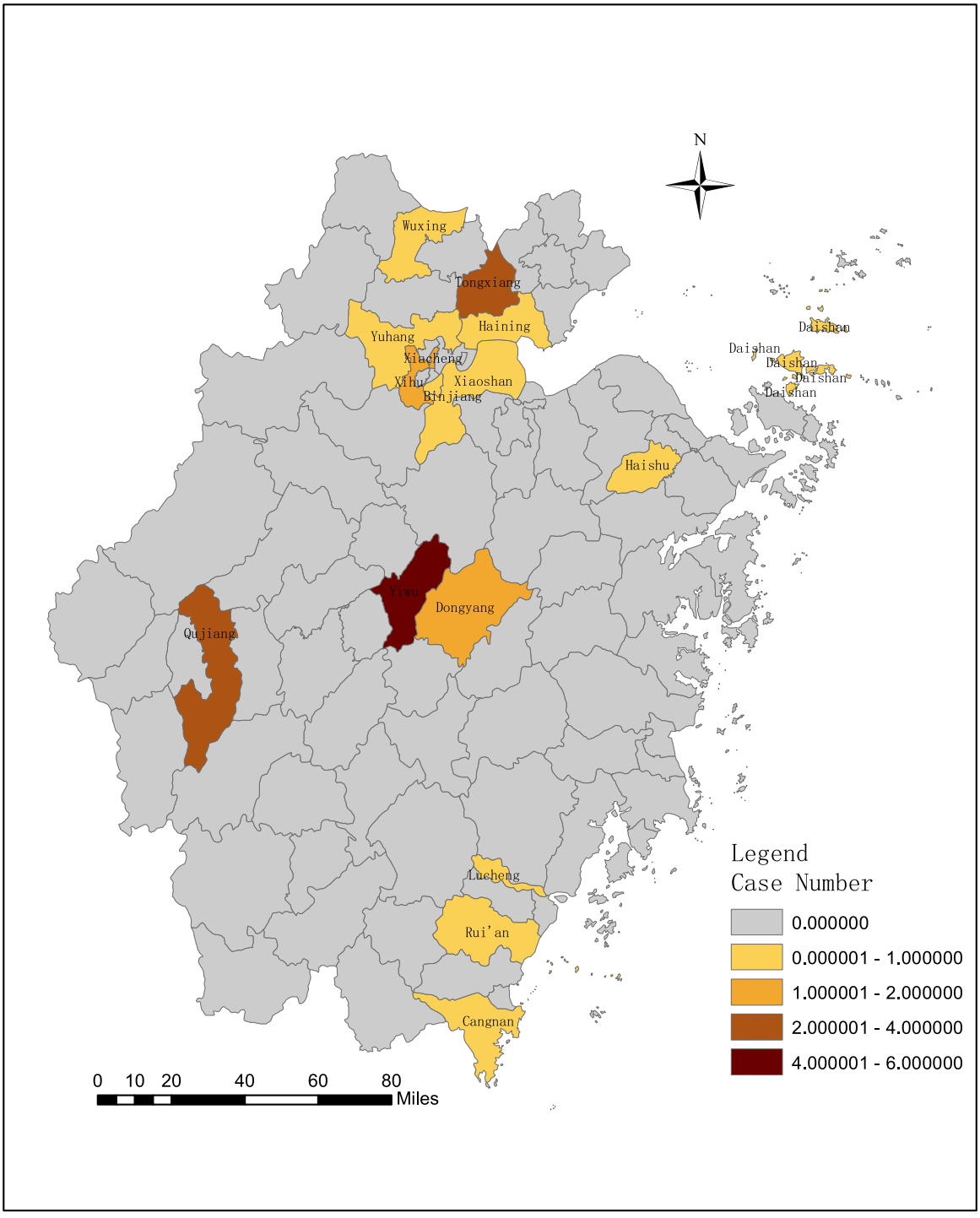

Fig. 2. The geographical distribution of chikungunya fever in Zhejiang province during 2008–2022. (http://www.geodata.cn/data/datadetails.html?dataguid=258898130861140&docid=6835).

It belonged to Asia genotype and had the highest similarity with a strain isolated in the Philippines, 2012. MT123008, MT123009, MT123010, and MG912993 were isolated from the cases of the outbreak in Qujiang in 2017, and all the 4 sequences belonged to ESCA genotype. MT123008, MT123009, and MT123010 were from the indigenous cases, and they were exactly the same in nucleotide sequence. MG912993 was isolated from the first case of the outbreak. She had a business trip in Bangladesh and got onset 4 days after returning home. MG912993 had a similarity of 99.99% with the 3 indigenous strains. And all the 4 strains (MT123008, MT123009, MT123010, and MG912993) had the highest similarity with MK468612 (99.95%–99.96%), which was isolated from an infected in Bangladesh in July 2017. OL840905, OL840906 and OL840907 were isolated in

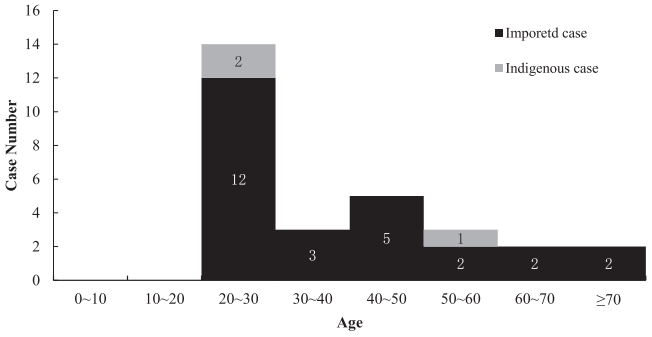

Fig. 3. The age distribution of chikungunya fever in Zhejiang province during 2008–2022.

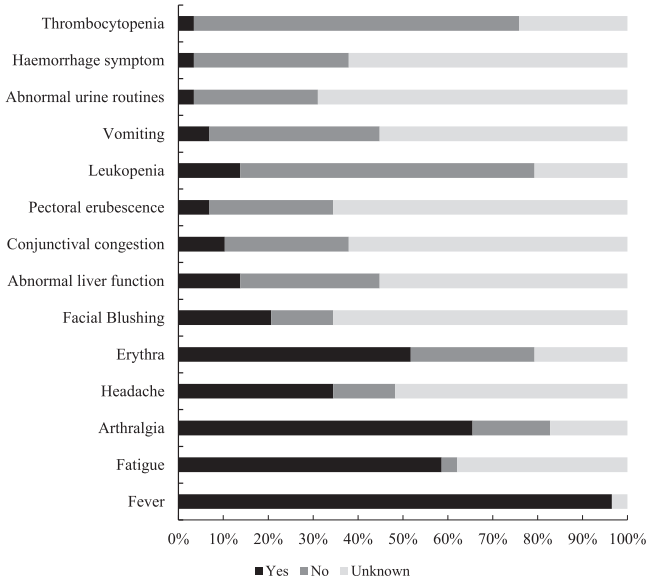

Fig. 4. The clinical spectrum of chikungunya cases in Zhejiang province from 2008 to 2022.

2019. OL840905 and OL840906 were from 2 cases with Thailand travel history, OL840907 was from a case with Myanmar travel history. Those 3 strains all belonged to ESCA, and had high similarity in nucleotide sequence with each other (99.94%–99.99%). Besides that, they were highly similarity with a strain from a newborn infected in Yunan province in 2019 (MW110475, 99.95%–99.96%) and an infected with Thailand travel history in Australia in 2019 (MN630017, 99.90%–99.93%). Compared with reference sequence of NC004162, all the 8 strains isolated in Zhejiang had amnion acid mutation (Table 1).

4. Discussion

No specific antiviral treatment and commercial vaccine are available for chikungunya till now [8]. Several candidate vaccines are under research. The supportive treatment is mainly including analgesic and antipyretic administration. Non-steroidal anti-inflammatory drugs, including aspirin, should not be used until dengue can be ruled out in order to reduce the risk of bleeding. Early identification of severe cases that require hospitalization is quite important. The keys of chikungunya prevention and control in endemic region include reducing the number of mosquito-breeding habitats, killing mosquitoes and avoiding mosquito bites. In general, the transmissions of arboviruses include the sylvatic cycle (cyclical transmission between non-human animal host and insects) and the urban cycle (cyclical transmission between human and insects). Before 1990s, it was believed that CHIKV was maintained in the sylvatic cycle in the jungle of Asia and Africa with occasional transmission into humans [8]. A series of large outbreaks, which started on the coast of Kenya in 2004 and ravaged the Comoros Islands, the island of La Réunion, and other islands in the southwest Indian Ocean in early 2005, followed by an epidemic in the Indian subcontinent in 2005-2006, declare the emergence and global expansion of CHIKV [9]. The first ever autochthonous transmission of CHIKV in European was identified in northeastern Italy in summer 2007, and at least 205 cases were reported. This is also the first autochthonous CHIKV transmission in the temperate region. The emergence of CHIKV in the Americas was announced in December 2013, when the first indigenous chikungunya cases was diagnosed in Saint Martin. Since then, chikungunya had spread to 52 countries and territories in North, Central, and South America, and caused >3.47 million suspected and confirmed cases and at least 544 deaths as 2022 [10–12]. The drivers for the globally emergence and reemergence of CHIKV were complicated: climate change, globalization which favors travel and virus imported from CHIKV endemic region, virus evolution, urbanization, insufficient mosquito control, vector adoption. Although transmission through blood transfusions and vertical transmission had been reported, the vast majority of cases were transmitted through female mosquito-biting. *Aedes aegypti* is the main vector for CHIKV. Yet *Aedes albopictus* is an increasing important vector for CHIKV transmission as its role in the emergence of chikungunya in temperate areas, where no *Aedes aegypti* is founded. The geographical distribution of *Aedes aegypti* in mainland China is limited, only in the border or coastal areas of Yunnan, Guangxi, Guangdong, and Hainan Province [13]. And the sustained vector surveillance indicated that its geographic distribution expended in Yunnan Province but contracted in Guangxi, Guangdong, and Hainan Province in recent years. No *Aedes aegypti* had been detected in Zhejiang. With the emergence and reemergence of CHIKV, the first case in Zhejiang, imported from Malaysia, was reported in 2008. Since then, chikungunya cases were identified on and off during 2009–2015, and every year during 2016–2020. The first autochthonous CHIKV transmission in Zhejiang was reported in Qujiang district, Quzhou city in 2017. One case imported from Bangladesh and 3 indigenous cases

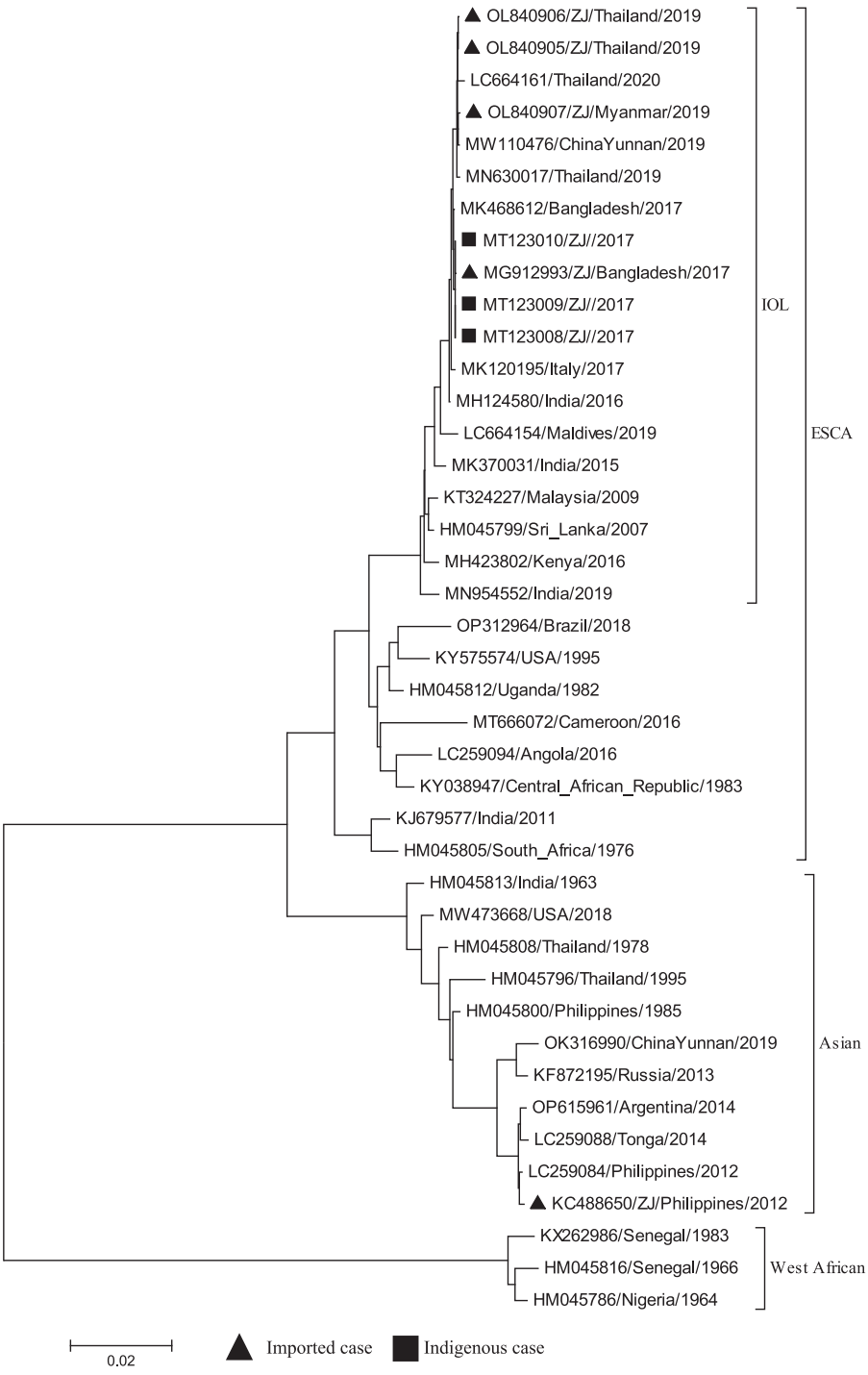

Fig. 5. Phylogenetic tree of chikungunya strains based on complete genome sequence.

were confirmed in this outbreak, and this is also the second autochthonous transmission of CHIKV in mainland China [14]. Two cases were reported in 2020, but no cases were reported in 2021 and 2022. It was partly attributed to the control and prevention strategy conducted during COVID-19 pandemic. For the imported cases in Zhejiang, Southeast Asia was the major source of infection. And it was also the most frequently reported source of infection for the imported cases in mainland China, Japan and Prague, Czech Republic [7,15–17]. For the imported chikungunya case in Spain, South America, Central America and Caribbean were the 2 most frequently mentioned regions where they were infected [18]. The difference in the distribution of infection source might be related to the differences in the preference of travel destination for the people in different region. A study conducted in the United States indicated a statistically significant positive association between passenger flows via airline travel from countries experiencing chikungunya epidemics and the number of imported chikungunya cases at

Table 1
The amnion acid mutation of strains isolated in Zhejiang, with NC004162 as reference.

GenBank	Gene Segment	Amnion acid mutation
KC488650	E1	72 N→S; 98 A→T; 145 T→A; 255 A→S; 269 V→M; 304 P→S
KC488650, MG912993, MT123008, MT123009, MT123010, OL840905, OL840906, OL840907	E1	211 K→E
MG912993, MT123008, MT123009, MT123010, OL840905, OL840906, OL840907	E1	284 D→E; 317I→V
KC488650	E2	2T→I; 5N→H; 118S→G; 146 Q→R; 149K→R; 157V→A; 205G→D; 248L→F; 255I→V; 317V→I; 318V→R; 371V→L; 375T→S; 384M→V
KC488650, MG912993, MT123008, MT123009, MT123010, OL840905, OL840906, OL840907	E2	57G→K; 74I→M; 160N→T; 181L→M; 211I→T; 267M→R; 299S→N; 344A→T
MG912993, MT123008, MT123009, MT123010, OL840905, OL840906, OL840907	E2	164A→T; 194S→G; 205G→S; 264V→A; 312T→M; 386V→A
KC488650, MG912993, MT123008, MT123009, MT123010, OL840905, OL840906, OL840907	E3	23I→T
KC488650	E3	33E→K; 44R→S; 60H→R

A, Alanine; C, Cysteine; D, Aspartic acid; E, Glutamic acid; F, Phenylalanine; G, Glycine; H, Histidine; I, Isoleucine; K, Lysine; L, Leucine; M, Methionine; N, Asparagine; P, Proline; Q, Glutamine; R, Arginine; S, Serine; T, Threonine; V, Valine; W, Tryptophan; Y, Tyrosine.

the state level. As the number of arriving airline passengers increased by 10%, the estimated number of imported cases increased by 5.2% [19].

For imported chikungunya cases, male greatly outnumbered female in Zhejiang, with the male-female gender ratio of 2.71:1. But the surveillance conducted in Taiwan of China, Paris of France and Spain founded that there were significant more female in imported chikungunya cases, and the male-female gender ratio ranged from 0.41:1 to 0.55:1 [18,20,21]. For the imported cases in Japan and Iran, female was slightly more than male, and the gender ratios were 0.90:1 and 0.92:1, respectively [17,22]. More male cases were confirmed in Prague, Czech Republic (gender ratio: 1.14:1) and mainland China (gender ratio: 1.54:1), while the gender ratio was still lower than that in Zhejiang [7,16]. Research was needed to explore the potential reason for the overwhelming more male imported cases in Zhejiang. Besides that, the imported chikungunya case in Zhejiang were always reported as 20–50 years old, business service/ housework or unemployment, and about half of the cases were 20–30 years old. Most of the cases would seek medical advice after onset. Clinically, fever, fatigue, arthralgia, headache, erythra and facial blushing were the most frequently complained symptoms complained by the chikungunya case in Zhejiang. For the cases reporting their maximum body temperature, more than 90% were ≥38.5°C, and about two thirds were ≥39°C. The study conducted in hospitalized febrile infants younger than 3 months of age in French Guiana indicated that infants who presented irritability, high fever and skin rash were more likely to have chikungunya infection [23]. Clinically, chikungunya is always undistinguished with dengue and zika virus disease, and one third of cases in Zhejiang were hospitalized as suspect dengue. For cases with acute fever, rash, myalgia, or arthralgia and recent travel within the previous 2 weeks to an endemic area, all those 3 infections should be considered. Laboratory tests are particularly important for the diagnostic, but cross-reactivity among *Flaviviruses* need be attentioned. The ratio of asymptomatic infection for CHIKV (about 30%) was lowest among those 3 viruses, and the ratio for zika and dengue were 80% and 60%–80%, respectively [24,25]. According to the review conducted by Jose Dario Martinez [24], symptomatic CHIKV infection was characteristic with high fever (≥39°C), arthritis and lymphocytopenia, dengue could be differentiated with high fever (≥39°C), neutropenia and thrombocytopenia, and symptomatic Zika virus infection was characteristic with mild fever and rash. Besides that, long-lasting, chronic articular manifestations that may persist for months to years is a hallmark sign for chikungunya.

Virus evolution and importation of novel virus strain are the important drivers for the emergence and reemergence of chikungunya [26]. IOL CHIKV, which carrying an alanine-to-valine mutation at position 226 within the E1 glycoprotein (E1-A226V), was responsible for a series of outbreaks in Kenya, the Indian ocean, the Indian subcontinent and Southeast Asia in the previous decade [26,27]. The adaptive mutation E1-A226V was proved to enhance CHIKV replication in *Aedes albopictus*, which render the wide spread of CHIKV in the region abundant with this mosquito. However, the IOL CHIKV of the outbreaks during 2016–2020 in India, Pakistan, Bangladesh, the Maldives, Myanmar, Thailand, and Kenya lacked E1-A226V but carried a lysine to-glutamic acid mutation at position 211 within the E1 glycoprotein (E1-K211E) and a valine-to-alanine mutation at position 264 within the E2 glycoprotein (E2-V264A). Further study suggested that the sub-lineage E1-K211E/E2-V264 was diverged from ancestral IOLs in India around 2008, and caused sporadic outbreaks in India during 2010–2015 and in Kenya in 2016. After acquisition an isoleucine-to-valine mutation at position 317 within E1 (E1-I317V), it conducted the massive expansion in several regions during 2014–2020, including the Indian subcontinent, Eastern Africa, and Southeast Asia. The IOL CHIKV with double mutants

of E1-K211E and E2-V264 had remarkably higher fitness for *Aedes aegypti*, as indicated by significant increase in virus infectivity, dissemination and transmission [28]. E1-I317 V possibly played a role in conferring competence to *Aedes albopictus* [9]. Additional adaptive mutations that facilitate transmission by *Aedes albopictus* had been identified in E1 (A98T, K211E) and E2 (D60G, R198Q, G205S, L210Q, I211T, K233E, K252Q) [8,9]. E1-A98T and E1-K211E form a heterodimer within E1 on the surface of the viral particle and drive receptor interaction and entry. E2-L210Q is responsible for increased CHIKV dissemination in *Aedes albopictus* by increasing infectivity for epithelial cells lining the mosquito midgut [8,9]. The strain isolated from the imported case in 2012, Zhejiang, is Asian genotype and has the mutants of E1-A98T, E1-K211E and E2-I211T. All the 7 strains from cases in 2017 and 2019 belong to IOL group within ECSA genotype, and all have no E1-A226V but with E1-K211E, E1-I317V, E2-G205S, E2-I211T and E2- V264A.

5. Conclusion

The annual case number during 2015–2019 was increased as a whole in Zhejiang Province, but drastically decreased between 2020 and 2022, which was largely attributed to the series of control measures implied during COVID-19 pandemic. Asia, more specifically, Southeast and South Asia, was the major source of the imported chikungunya case in the Province. IOL CHIKV is the most common strain. All the IOL CHIKV lack E1-A226V but have E1-K211E, E1-I317V, E2-G205S, E2-I211T and E2-V264A. With the recovery of international communication, surveillance, entry inspection and quarantine, clinical professional education should be strengthened in the post-COVID-19-era. Besides that, health education and vector control should also be reinforced.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

J.R., Conceptualization and design, Data Curation, Analysis, Investigation, Methodology, Validation, Writing—Original Draft Preparation; F.L., Conceptualization and design, Investigation; Y.L., Data Curation, Investigation; J.S., Conceptualization and design, Investigation, Writing—review & editing.

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Data available statement

Research data are not shared.

Ethics statement

Not applicable.

Informed consent

Not applicable.

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