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DOI: https://doi.org/10.1093/jtm/taad008

Journal of Travel Medicine

International Society of Travel Medicine
Established 1991
Promoting healthy travel worldwide

Journal of Travel Medicine, 2023, 1–8
https://doi.org/10.1093/jtm/taad008
Review

Review

Chikungunya: risks for travellers

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†In Memoriam: Professor Fabrice Simon died on 29 April 2022.

Submitted 30 September 2022; Revised 10 January 2023; Accepted 11 January 2023

Abstract

Rationale for review: Chikungunya outbreaks continue to occur, with changing epidemiology. Awareness about chikungunya is low both among the at-risk travellers and healthcare professionals, which can result in underdiagnosis and underreporting. This review aims to improve awareness among healthcare professionals regarding the risks of chikungunya for travellers.

Key findings: Chikungunya virus transmission to humans occurs mainly via daytime-active mosquitoes, *Aedes aegypti* and *Aedes albopictus*. The areas where these mosquitoes live is continuously expanding, partly due to climate changes. Chikungunya is characterized by an acute onset of fever with joint pain. These symptoms generally resolve within 1–3 weeks, but at least one-third of the patients suffer from debilitating rheumatologic symptoms for months to years. Large outbreaks in changing regions of the world since the turn of the 21st century (e.g. Caribbean, La Réunion; currently Brazil, India) have resulted in growing numbers of travellers importing chikungunya, mainly to Europe and North America. Viremic travellers with chikungunya infection have seeded chikungunya clusters (France, United States of America) and outbreaks (Italy in 2007 and 2017) in non-endemic countries where *Ae. albopictus* mosquitoes are present. Community preventive measures are important to prevent disease transmission by mosquitoes. Individual preventive options are limited to personal protection measures against mosquito bites, particularly the daytime-active mosquitos that transmit the chikungunya virus. Candidate vaccines are on the horizon and regulatory authorities will need to assess environmental and host risk factors for persistent sequelae, such as obesity, age (over 40 years) and history of arthritis or inflammatory rheumatologic disease to determine which populations should be targeted for these chikungunya vaccines.

Conclusions/recommendations: Travellers planning to visit destinations with active CHIKV circulation should be advised about the risk for chikungunya, prevention strategies, the disease manifestations, possible chronic rheumatologic sequelae and, if symptomatic, seek medical evaluation and report potential exposures.

Key words: Aedes, management, prevention, infection, transmission, epidemiology, Arbovirus

Introduction

Chikungunya virus transmission to humans occurs mainly via daytime-active mosquitoes, *Aedes aegypti* and *Aedes albopictus*. The areas where these mosquitoes live are continuously expanding, partly due to climate changes. Large outbreaks in shifting regions of the world (e.g. Caribbean, La Réunion; currently Brazil, India) since the turn of the 21st century have resulted in growing numbers of travellers with imported chikungunya, mainly to Europe and North America. Chikungunya is characterized by an acute onset of fever with joint pain. Symptoms usually resolve within 1–3 weeks, but at least one-third of the patients continue to experience debilitating rheumatologic symptoms for months and sometimes years. Travel-related viremic cases of chikungunya have also generated autochthonous clusters (France, United States of America) and outbreaks (Italy in 2007 and 2017) in non-endemic countries where *Ae. albopictus* mosquitoes are present.

Prior to the COVID-19 pandemic, the volume of international tourist arrivals had been increasing steadily, reaching more than 1.5 billion in 2019[1] suggesting that a sizable number of travellers are potentially at risk for chikungunya virus infection. Nevertheless, awareness about chikungunya is low, both among the at-risk travellers and healthcare professionals, and this can result in underreporting. Thus, awareness must be improved, particularly for those at higher risk. This narrative review aims to describe the recent epidemiology of chikungunya and its clinical course and to raise awareness about the risk of chikungunya for travellers.

Chikungunya virus and transmission

Since its first detection in 1953 in Tanzania, chikungunya virus (CHIKV) has been responsible for periodic outbreaks. CHIKV is an arthropod-borne virus (arbovirus). In the last decade, CHIKV has caused outbreaks in several tropical African countries and islands and reached the Americas via the Caribbean region.[2–5] In late 2013, the first locally acquired cases were reported in the Caribbean, and by October 2020, CHIKV had spread to 45 countries and territories on all continents, except Antarctica.[6–8]

CHIKV, the alphavirus that causes chikungunya, is differentiated into three genetically distinct lineages: West African (WA), East-Central-South African (ECSA) and Asian.[9] A new sub-lineage arose from an A226V amino-acid change in the ECSA E1 glycoprotein during the 2005–2006 Indian Ocean outbreaks (Indian Ocean lineage: IOL), which was associated with enhanced viral multiplication in *Ae. albopictus* mosquitoes and dissemination.[10] A novel American sub-lineage arose from the 2013 introduction of the Asian lineage to the Caribbean (Asian/American).[11]

The virus exists in a sylvatic cycle between forest-dwelling mosquitoes and nonhuman primates. Transmission to humans occurs in a rural and urban cycle mainly via the daytime-active mosquitoes, *Ae. aegypti* and *Ae. albopictus* in tropical and subtropical settings.[7,12] The life span of *Ae. albopictus* is estimated to be around 1 month but varies according to different characteristics, such as gender, temperature, susceptibility to insecticides. One comparative study of deltamethrin-susceptible and resistant strains of *Ae. albopictus* found that the average survival time of female deltamethrin-susceptible and resistant mosquitoes was 41 and 23 days, respectively, compared with 26 and 17 days, respectively, for male mosquitoes.[13] Individuals bitten by infected mosquitoes can be viremic for 5–7 days, with a viral level sufficient to infect feeding mosquitoes that transmit the virus to other humans when feeding. Transmission is dependent on numerous factors, including environmental (e.g. rainfall, altitude), ecological (e.g. presence of competent mosquitoes, presence of sylvatic cycle) and social (e.g. population mobility between rural and urban settings, lifestyle, including travel).

Several studies have modelled the increase of arboviral infections in areas where competent mosquitoes could thrive due to projected changes in climatic conditions.[14–22] These models predict northern expansion into continental USA to include parts of Southern Canada and eastern expansion to include most of Europe by 2050. Results from one study using a mechanistic phenology model suggest that, from 1950 to 2000, the world became 1.5% more suitable per decade for the development of *Ae. aegypti* and predicted that the rate will accelerate to 3.2–4.4% per decade by 2050.[22]

Epidemiology of chikungunya as an imported disease

The risk of chikungunya infection is highest for travellers going to countries experiencing ongoing chikungunya outbreaks in the Americas, parts of Africa and Asia, and the transmission patterns shift frequently over time. CHIKV, along with dengue virus (DENV) and, more recently, Zika virus (ZIKV) are among the most frequently diagnosed viral infections in travellers.[23–25] Although DENV and ZIKV are flaviviruses, unlike CHIKV which is an alphavirus, all three are transmitted by the same *Aedes* mosquito species vectors. Travellers from 'no risk' areas are vulnerable when travelling to areas with virus circulation, particularly during an outbreak, because most of them are immunologically naïve.

Infected travellers who return home to areas where CHIKV-competent mosquitoes are present could give rise to local clusters or outbreaks. However, in temperate climates, these mosquitoes are generally only active during the summer. Chikungunya has been a notifiable disease in Europe since 2006, and in the USA since 2015.[26] It is also a notifiable disease in some other countries including Australia, New Zealand, India, and Japan. The chikungunya outbreak in late 2013 in the Caribbean was reported to be responsible for the number of chikungunya cases reported in the USA and Europe in 2014, with nearly 2800 cases of travel-related chikungunya in the US states (not including locally-acquired or travel-associated cases in US Territories) and nearly 900 in Europe (Figure 1).[27–30] A close temporal correlation was found during 8 consecutive years between imported cases of chikungunya and the corresponding outbreaks that occurred in Martinique and Guadeloupe, two French overseas territories in the Caribbean that are very popular among French tourists. Of the 68 cases of chikungunya infections reported in France between 2009 and 2016, 59% were in patients that had been exposed in Guadeloupe or Martinique.[27] The occurrence of cases in returning travellers follows the same time patterns as the outbreaks in these areas. Although low, the number of locally acquired chikungunya cases is higher in Europe than in the US states and in 2016 and 2017, locally acquired chikungunya

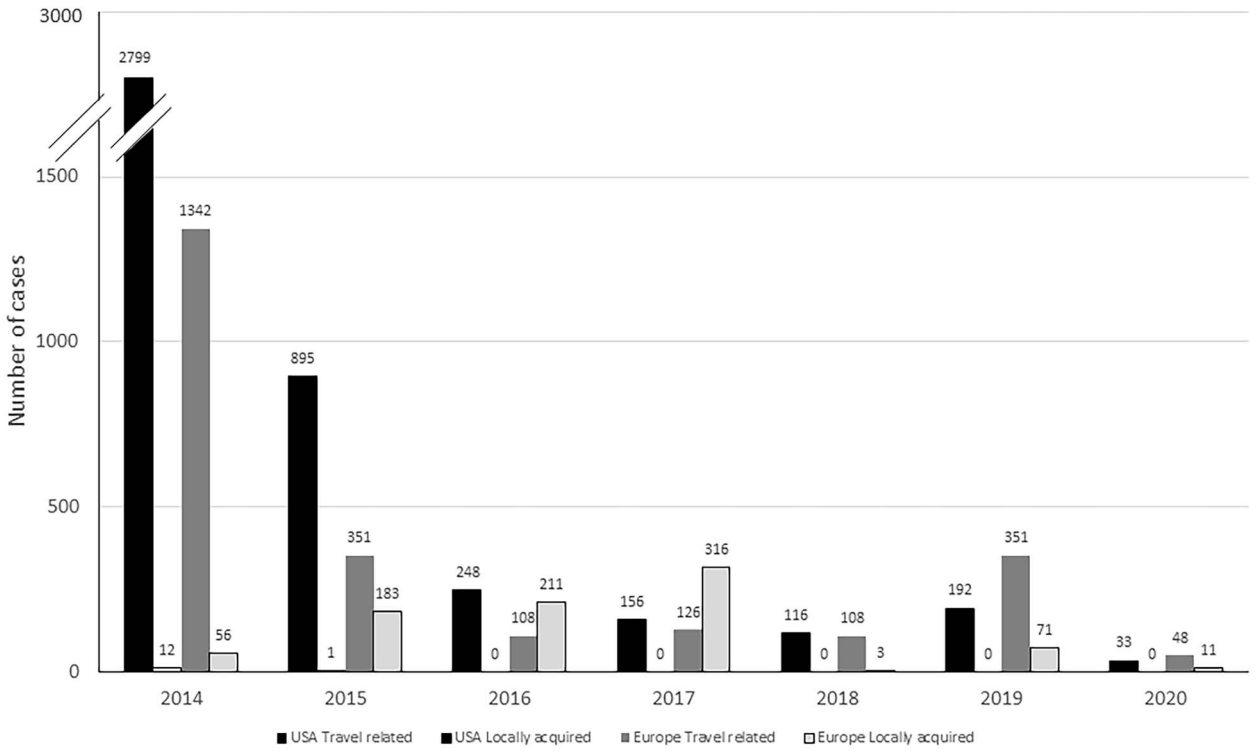

Figure 1. Travel related and locally acquired CHIKV infections in the US states (not including US Territories) and Europe[27–30]

cases in Europe exceeded travel-related cases, due to outbreaks in the Lazio (Anzio, Latina and Roma) and Calabria (Guardavalle Marina) regions in Italy (Figure 1).

TESSy is an online system set up by ECDC for the collection, analysis and dissemination of data on communicable diseases in the European Union (EU). Member States validate and upload their data. For each disease under surveillance, the TESSy database has a description of the key attributes of the national surveillance systems for that disease, but these criteria vary between countries. Thirteen EU countries reported 2616 travel-related chikungunya cases between 2012 and 2018.[26] Three successive epidemiologic periods were observed during this period; with the highest number of cases (75%) occurring in 2014–2015, when most cases were associated with the Caribbean and South America. The highest infection rates among travellers were observed during the same phase. In 2019, 516 cases (82% laboratory-confirmed) were reported in 15 European countries, with 21% reported in France, 18% in UK and 17% in Germany.[28] Among the 397 travel-related cases, 36 countries of probable exposure to infection were identified, but nearly 80% of the travellers had been to Asia, mainly Thailand, India and Myanmar.

Similar to the French experience where chikungunya cases followed the same time pattern as the outbreaks in Guadeloupe and Martinique,[27] the number of CHIK and Zika virus infections in Spain increased after their introduction and spread in the Americas.[30] In Spain, 22 655 records from a collaborative network were analysed for arbovirus infections from January 2009 to December 2018.[30] Among 861 infections found, 280 (32.5%) were CHIK. In Switzerland, a peak of 78 imported cases of chikungunya was reported in 2014.[31] The highest rates were seen for those aged 25–64 years, but this could be due to the demographics of travellers, rather than being a risk factor. Local transmission has been reported in the USA, France and Italy.[28,32]

In the USA, chikungunya was only occasionally identified in travellers before the dramatic increase of imported cases in 2014, both in the states as well as US Territories.[29] From 2006 to 2013, an average of 28 cases were identified annually (range 5–65) in travellers from affected areas in Asia, Africa or the Indian Ocean.[33] Since 2014, chikungunya cases have been reported in American travellers returning from affected areas in the Americas and local transmission has been reported in Florida, Texas, Puerto Rico and the US Virgin Islands.[29] In Australia and Japan, where chikungunya became a notifiable disease since 2006, no locally acquired cases have been reported, only travel-related cases that reflected an increasing range of exposure countries.[34,35] A separate review recently summarized imported chikungunya cases published in literature.[36]

Travellers who make frequent or recurrent trips or who have longer stays in destinations with ongoing virus circulation are expected to have a greater risk based on their increased duration of exposure.[37] One review of 8 studies reported that military personnel had a low risk for CHIKV infections in endemic settings but had a similarly high risk as that for local inhabitants, during chikungunya outbreaks.[38]

Population movements, due to war, or natural disasters such as flooding, hurricanes and earthquakes, can also facilitate the spread of CHIKV in endemic areas or during outbreaks.[39,40] These populations are often housed in temporary, over-crowded accommodation under conditions of poor hygiene. For example, in 2016, an earthquake in Ecuador resulted in significant

mortality and morbidity, infrastructure damage, including health infrastructure and psychological trauma.[39] The first ZIKV outbreak occurred at that time with co-circulating DENV and CHIKV.[40] Health authorities are responsible for taking measures to minimize the risk of infection in areas at risk, but when health resources are stretched due to a natural disaster or large epidemics, such as the current COVID-19 pandemic, vector control programs may collapse. The disruptions due to the SARS-CoV-2 pandemic likely played a role in the 2022 dengue outbreak in Cuba.[41]

Chikungunya disease

Between 3.8 and 27.7% of CHIKV infections are asymptomatic although, compared with other arboviral infections, more individuals with CHIKV infections appear to develop clinical symptoms.[42,43] Some of the symptoms, e.g. fever, myalgia and exanthema, are also seen with DENV and ZIKV infections.[23,44–46]

Following transmission, CHIKV replicates initially in the skin, primarily in dermal fibroblasts, then enters the lymph nodes and blood system and is disseminated to all organs.[47] Replication of CHIKV in peripheral tissues results in high viremia, with up to $>10^9$ virus particles/mL facilitating transmission via mosquito bloodmeals.[48] The incubation time can range from 1 to 12 days but is typically 3–7 days.[43,49]

Most of the common symptoms of chikungunya infection resemble those of other arbovirus infections but joint involvement is a key feature of chikungunya, charactierized by an acute onset of fever with joint pain that can be debilitating. The joint pain can last from a few days up to months and even years. Thus, the course of chikungunya is described to have an acute phase followed by a post-acute phase (between 1 and 3 months) and a chronic phase (after 3 months).[50] Alphaviruses, including chikungunya, O'nyong'nyong, Sindbis, Barmah Forest, Ross River and Mayaro viruses, are associated with acute and chronic rheumatic symptoms,[51] but the aetiology of persistent joint pain is still poorly understood.[47] Recent evidence suggests that the virus does not persist in synovial fluid during chronic chikungunya infection implying an autoimmune mechanism.[51] Other common symptoms include muscle pain, joint swelling, nausea, fatigue and exanthema.

Neurological and ocular complications are uncommon but have been reported in several outbreaks, and CHIKV has been isolated from cerebrospinal fluid.[7,52,53] A systematic review reported 130 cases of possible neurological chikungunya, 9 being considered as probable, 55 as plausible and 51 as disputable.[54] The most frequent neurologic manifestations of chikungunya were encephalitis, optic neuropathy, neuro-retinitis and Guillain–Barré syndrome. Ocular complications have also included uveitis, scleritis, keratitis and myositis.[52] Direct viral involvement was demonstrated in infants and elderly patients in whom complications and neurologic sequelae were more frequent.

Although the typical chikungunya symptoms usually resolve in 1–3 weeks, some patients experience persistent rheumatologic symptom for months to years. In a cohort of French military police based on Reunion Island during the 2005–2006 outbreak, 6 months after CHIKV infection over 90% of those with the most symptomatic cases reported chronic rheumatic symptoms, and 50% still reported chronic rheumatic symptoms 30 months later.[55,56] Six years after infection, 48% (39/81) continued to report moderate to intense rheumatic pain.[57] In addition, those who had had a CHIKV infection, compared with those who had not been infected, reported more nonspecific morbidity (e.g. headaches and fatigue) and an important psychological impact (e.g. frequent depressive moods and social disabilities), leading to a significant impairment of their quality of life (measured using the SF-36 tool) and higher healthcare use.[55,58]

In another cohort study of 159 patients who had been referred to a rheumatologist for persistent rheumatic or musculoskeletal pain following CHIKV infection during the 2005–2006 outbreak on the Reunion Island, 94 (59%) reported rheumatologic complaints (rheumatoid arthritis in 40, spondylarthritis in 33 and undifferentiated polyarthritis in 21) 6 years after infection.[59] Persisting arthralgia and arthritis were the most frequent reported sequelae followed by alopecia and depression in a systematic review of 37 studies with follow-up ranging from 1.5 to 72 months.[60] Although older individuals and those with underlying joint conditions were more likely to develop chronic symptoms, the French military police were relatively young, with a median age of 44 years.[57,60] However, information on the prevalence of long-term sequelae remains limited to observational studies which lack comparator groups. A 1-year follow-up analysis of 165 patients with acute CHIKV infection and 167 controls in the US Virgin islands found an almost 3-fold increased risk for persistent arthralgia in patients 6 and 12 months after illness onset.[61] At 12 months, patients were significantly ($P < 0.01$) more likely than controls to report difficulty performing daily activities. The unadjusted persistent arthralgia estimates at 6 (44%) and 12 (33%) months from that study are consistent with the pooled estimate from a meta-analysis (40%, 95% CI: 31–49%).[62]

Reports varied regarding CHIKV infection during pregnancy. The 2006 La Réunion island CHIKV outbreak had no observable effect on pregnancy outcomes.[63] Among 1400 pregnant women (628 uninfected, 658 infected during pregnancy, 27 infected before pregnancy and 87 infected on unknown dates), CHIKV infections occurred during the first trimester for 15%, the second for 59% and the third for 26%. Outcomes (caesarean deliveries, obstetric haemorrhaging, preterm births, stillbirths after 22 weeks, birth weight, congenital malformations and newborn admissions) were similar between the groups. Only hospitalization rates during pregnancy differed between infected and uninfected women (40 vs. 29%).

However, the risk of mother-to-child chikungunya virus transmission was nearly 50% when mothers were viremic in the week just preceding delivery.[64,65] The newborns may develop sepsis, hemodynamic instability, acute encephalopathy, seizures, cerebral haemorrhage and cerebral palsy. Half of the children may exhibit diminished neurocognitive performance at 2 years of age. The largest series of congenital chikungunya included 19 cases of vertical transmission out of 30 women with intrapartum viremia (vertical transmission rate 48.7%).[66] The cases were exclusively observed in near-term deliveries in the context of intrapartum viremia and caesarean section showed no protective effect on transmission. All infected neonates were asymptomatic at birth, and the median onset of neonatal disease was 4 days (range 3–7 days). Pain, prostration and fever were present in 100% of cases and thrombocytopenia in 89%.

Table 1. Summary of phase 3 randomized placebo-controlled clinical trials of chikungunya candidate vaccines registered on ClinicalTrials.gov[73]

NCT number	Vaccine type (number of doses)	Location/population	Actual/expected primary completion date (status)	Primary outcomes
NCT04546724	Live attenuated (1)	US/Healthy adults aged ≥18 years	May 2021 (completed)	Safety and immunogenicity 28 days post-vaccination
NCT04786444	Live attenuated (1)	US/Healthy adults aged 18–45 years	July 2021 (completed)	GMT of CHIKV-specific antibodies
NCT04650399	Live attenuated (1)	Brazil/Healthy adolescents aged 12–17 years	May 2022 (recruiting)	Safety and immunogenicity 28 days post-vaccination
NCT05072080	VLP (1)	US/Healthy adolescents and adults aged 12–64 years	June 2022 (recruiting)	Safety and immunogenicity 22 days post-vaccination
NCT05349617	VLP (1)	US/Adults aged ≥65 years with stable health	March 2023 (not yet recruiting)	Safety and immunogenicity 22 days post-vaccination
NCT04566484[a]	Whole virus inactivated, adjuvanted (2)	Panama, Colombia, and Thailand/Healthy adolescents and adults aged 12–65 years	December 2022 (recruiting)	Safety and immunogenicity 28 days post-vaccination
NCT04838444 (subset of NCT04546724)	Live attenuated (1)	US/Healthy adults aged ≥18 years	December 2025 (enrolling by invitation)	Seroprotection 5 years post-vaccination

[a]Phase 2/3 study.

Severe illness was observed in ten cases (52.6%) and mainly consisted of encephalopathy with pathologic MRI findings (brain swelling, cerebral haemorrhages) which was observed in nine neonates, including four who evolved towards persistent disabilities.

The mortality rate was reported to be about 0.1% during outbreaks in the Reunion and the Andaman Nicobar Islands in 2006.[41] During outbreaks in Europe, the mortality rate was reported to be 0.25%, although during the Italian outbreak in 2007, the reported mortality rate was 0.5%.[7,67] The delay between disease onset and death ranged from 2 to 150 days and the median age of those who died was 67 years.[68] Older age, primary neurological, cardiovascular or respiratory comorbidities and presence of diabetes or hypertension were reported to contribute to death.

Prevention and treatment of chikungunya

Public awareness about CHIKV and its transmission mode is relatively low.[69] A recent systematic review of individual and community measures for prevention and control of CHIKV infections identified six categories: behavioural protective measures, insecticide use, public education, control of blood and blood products, biological vector control and quarantine of infected individuals.[70] Nevertheless, the impact of these measures have rarely been assessed.

Personal protective measures include wearing long sleeves and pants, clothes impregnated with insect repellent, use of repellent sprays, and limiting activities that increase mosquito exposure.[12,71,72] Community measures include the removal of standing water, which eliminates potential breeding places, and the use of larvicides in ponds and irrigation channels.

Results from studies in Thailand and Cambodia suggest that long-term immunity may be induced by natural infection, but this warrants further investigation.[73,74] There are currently no licensed vaccines available although several promising vaccine candidates are in development. There are three vaccines being assessed in seven phase 3 clinical trials (Table 1).[75]

Frequent business and professional travellers are more likely to receive advice on how to avoid mosquito bites in the setting of their occupational health consultations, but rates of pre-travel counselling are low. Despite having good knowledge about malaria, its prevention and effective prophylaxis, airline cabin crew and pilots have low compliance rate with measures to prevent mosquito bites.[76,77] Although these studies focused on malaria which has night-biting mosquito vectors, they may be relevant for CHIKV prevention given their transmission via mosquito vectors.

Information could be provided during a pre-travel consultation with a healthcare professional, but many travellers do not attend a pre-travel consultation. Furthermore, one study found that 50% of attendees at a travel clinic may not have attended the travel clinic visit if they had known that the yellow fever 10-year booster was no longer needed.[78] Potentially airline companies could provide information on their websites and in their inflight magazines, but surveys have reported sparse information related to infection prevention, and none on how to avoid mosquito bites.[79,80] In addition, the information is generally difficult to find on tourism websites and very few provide a link to health authority websites that provide information for travellers. Travellers can access information about chikungunya outbreaks on various international websites such as World Health Organization and the American and European Centers for Disease Control and Prevention.

When travellers develop symptoms while travelling, health care may be challenging to access and suboptimal in quality, particularly in resource-limited settings.[81] Initiatives using smart phone telemedicine apps have shown usefulness, obviating the need for referral to a local doctor in 90% of travellers using the app, with symptomatic treatment as the main

therapy prescribed.[82] When travellers develop symptoms after returning home, healthcare providers may not consider chikungunya as a potential diagnosis unless a travel history is obtained, since many symptoms are non-specific.[23] Nonetheless, symptoms such as chronic arthralgia are specific to chikungunya.[27,83] Thus, it is important to raise awareness among healthcare professionals, particularly general practitioners and rheumatologists.

Many compounds have shown efficacy against CHIKV *in vitro* and some in vivo studies are in progress, but to date, there are no specific licensed therapeutics against CHIKV.[84] The current therapeutic objectives for patients with chikungunya are to relieve pain, reduce inflammation and limit joint stiffness with the use of analgesics, anti-inflammatory drugs (at least two weeks and up to 1 month after onset) and maintain hydration and general rest. Physiotherapy is often necessary to restore lost muscle tone and physical fitness due to the illness. Several clinical guidelines[85–91] have been developed for acute or chronic chikungunya and recommend the use of common analgesics or weak opioids during the acute phase and non-steroidal anti-inflammatory drugs (NSAIDs) with or without adjuvant drugs during the subacute phase. During the chronic phase analgesics, weak opioids, NSAIDS and low dose oral steroids are recommended. Disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, with or without sulfasalazine or hydroxychloroquine, in addition to steroids, are recommended in patients with chronic chikungunya with inflammatory disease. Biologics can be used in patients who are refractory to steroids and DMARDs.

Conclusions

The spread of *Ae. albopictus* in US states and Europe has increased the risk of autochthonous transmission of CHIKV. Although to date most chikungunya cases in these regions have been travel-related, two important outbreaks occurred in Italy. Effective surveillance systems are therefore important in these regions. Travellers returning to non-endemic regions with CHIKV infections can cause local clusters or outbreaks if competent mosquitos are present. Travellers should be advised about the risk of CHIKV infections when they visit areas where there is active circulation. They should also be advised about the symptoms of chikungunya, the risk of chronic rheumatologic sequelae, the need to inform their healthcare professional about where they have visited when seeking treatment for potential symptoms after having returned home and the need to self-exclude from blood donation. COVID-19 has changed travel habits with important reductions both in business and tourist trips. While this led to an increase in e-meetings and virtual conferences to replace in-person attendance and travel, many have now returned to traditional in-person attendance and travel has restarted. When chikungunya vaccines become available, expert working groups could be helpful to assess the benefit–risk balance in various populations. This will require a good understanding of the current CHIKV epidemiology and susceptible mosquito spread. It is essential to increase awareness about chikungunya among healthcare professionals and also in the general public through education programs.

Acknowledgements

The authors acknowledge medical writing and editorial services from Margaret Haugh, MediCom Consult, Villeurbanne, France.

Funding

The authors received no funding for work on this manuscript.

Authors' contributions

All authors contributed equally to this review.

Conflict of interest

E.C. declared consultancies for Valneva and Takeda. T.J. declared paid lectures, consultancies and study participation for Valneva. L.C. declared honoraria and consultancies for Shoreland, Valneva, Takeda and Merck.

Data availability

No new data were generated or analysed in support of this paper.

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