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Philippe Gautret, Philippe Parola, Davidson H. Hamer, Emilie Javelle: Conceptualization, Methodology, Software, Supervision, Writing- Reviewing and Editing.

Pierre Dudouet, Carsten Schade Larsen, Frank von Sonnenburg, Marta Díaz-Menéndez, Elena Trigo, Federico Gobbi: Data curation, Investigation, Writing- Original draft preparation.

Martin P. Grobusch, Denis Malvy, Vanessa Field, Inés Oliveira Souto, Hilmir Àsgeirsson: Writing- Reviewing and Editing, Validation.

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Chikungunya resurgence in the Maldives and risk for importation via tourists to Europe in 2019-2020: a GeoSentinel case series.

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Key words: outbreak; travel; tourism; GeoSentinel; arbovirus; vector-borne disease

Abbreviations:

Ae. Aedes

CHIKV: chikungunya virus

ECDC: European Center for Disease Control

EIA: enzyme immunoassay

ELISA: enzyme-linked-immuno-sorbent-assay

IFAT: immunofluorescent antibody test

NA: not available

RT-PCR: reverse transcription polymerase chain reaction

Abstract

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Background: Chikungunya virus (CHIKV) is an arthropod-borne virus mainly transmitted in tropical areas by *Aedes* spp. mosquitoes. It has been responsible for small-to-large outbreaks in temperate areas including southern Europe and North America. Past outbreaks in 2006 on the islands of Maldives, as well as on other islands in the Indian Ocean and in Southeast Asia, demonstrated for the first time the capacity of CHIKV to disseminate through travel and transcontinental commerce, and revealed the major socio-economic impact of CHIKV epidemics. Recently, CHIKV has been circulating in highly touristic areas including the Maldives, where 1,736 cases were notified by the Health Protection Agency during 2019.

Case series: Among EuroTravNet/GeoSentinel patient records, eight CHIKV-confirmed cases imported the Maldives to France, Germany, Denmark, Italy and Spain were identified between February 2019 and February 2020; exceeding the total number of CHIKV infections travel-acquired in Maldives reported to this surveillance network during the previous 10 years.

Conclusions: The prevention and control of CHIKV introduction into naïve areas colonised by competent vectors is crucial. CHIKV outbreaks must be detected and reported in a timely manner. This must lead to adapted health information for international travellers and to prompt management of suspected imported cases. Conversely, travellers make for excellent sentinels and increased reports of imported cases might reflect a change in the level of endemicity or even herald an outbreak. Feedback to the local health authorities and matching this with local epidemiological surveillance data may lead to health benefits for the local population.

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Introduction

Chikungunya virus (CHIKV) is transmitted by *Aedes* spp. mosquito bites and was historically confined to Africa and Asia [1]. Since 2006, chikungunya has emerged on a global scale, with outbreaks occurring in the Indian Ocean, Oceania, Southern Europe and, from 2013, in the Americas [2]. Travellers are a formidable 'vehicle' for the global spread and propagation of viral infections as illustrated by the ongoing coronavirus pandemic. Their advice toward health risks in endemic or epidemic countries visited, as part of a pre-travel consultation, could be improved [3]. A lack of awareness may extend the time between the start of a viraemic illness, with risk of transmission to local mosquitoes, and the first notification and investigation of cases. Moreover, travel-acquired CHIKV infection may result in long-term sequelae, such as incapacitating arthralgias [4].

In the Maldives, chikungunya was first reported in 2006 with a total of 11,879 suspected and confirmed cases. This outbreak eventually affected more than 60% of the archipelago inhabitants by April 2007 [5]. In subsequent years, and until 2019, CHIKV circulation was rarely documented in the Maldives. Only five imported chikungunya cases were reported to EuroTravNet/GeoSentinel networks over the period 2009-2018. In 2019, the Maldives' local health authorities registered a total of 1,736 confirmed cases, of which 277 cases were recorded in just one month (December 2019). Tourists to the Maldives at that time would have been at higher risk of CHIKV infection [6].

The French GeoSentinel Marseille site reported a CHIKV confirmed infection acquired in Maldives in December 2019 [7]; five additional cases imported to Denmark, Germany, and Spain in 2019 were retrospectively identified in the EuroTravNet/GeoSentinel Surveillance Network's database. Other 2 cases were reported in Italy in the first months of 2020. We present the characteristics of these eight cases and discuss aspects of this re-emergence of CHIKV in touristic areas of the Maldives.

Case series of eight European travellers returning from the Maldives with CHIKV infection in 2019-2020.

The patients' median age was 44 years (range: 30-80 years) with a male-to-female ratio of 5:3. Seven individuals were tourists, whereas one visited relatives and friends. Only one patient reported a pre-travel consultation with his general practitioner. The mean duration of stay in the Maldives was 11 days (range: 7-15 days), and the mean delay between arrival in Maldives and symptom onset was 11 days (range: 5-20 days). Six patients developed symptoms during their travels; while the other two patients became symptomatic after return. Acute unspecific symptoms included fever in all patients (8/8), arthralgia and headache (8/8), diffuse rash (4/8), lymphadenitis (1/8), edema (1/8) and joint swelling (1/8). Two patients required hospitalisation (Table). Interestingly, the French case had a positive chikungunya RT-PCR [9] and travelled with two other individuals who reported similar symptoms and were serologically confirmed in another lab to have chikungunya.

Table. Overview of eight confirmed chikungunya cases among travellers returning from the Maldives, by date of onset, February 2019 to February 2020 (ages are rounded by five for anonymization, NA data not available).

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Case	Reporting country	Place of exposure	Period of exposure	Age	Sex	Date of onset	Clinical acute symptoms	Pre-travel encounter	Outcomes	Recovery status	CHIKV positive diagnosis	Alterative diagnoses tests
1	Denmark	Maldives main island including the capital, Malé	10/02/19-24/02/19	35	M	23/02/19	Fever /acute diarrhea/ headache/ rash/ arthralgia/ myalgia	No	Arthralgia persistent for 10 months. Prednisolone for 3 months	Yes	RT-PCR on plasma targeted structural polyprotein E1. Serology IgM 1 :1.280 and IgG = 1 :2.560 (indirect immunofluorescence)	Negative HIV-test, negative dengue RDT (Ag+Ab), negative dengue PCR
2	Germany	Maldives	09/06/19-21/06/19	30	F	19/06/19	Fever/sweat/chills/ acute diarrhea/ headache	NA	NA	NA	Positive IgM and IgG antibodies (Euroimune EIA)	Negative dengue and Zika serology
3	Germany	Maldives	26/06/19-09/07/19	30	M	05/07/19	Fever/ arthralgia/ myalgia	No	NA	NA	Positive IgM and IgG antibodies (Euroimune	Dengue IgG

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											EIA)	positive. Dengue IgM and NS1 Ag negative. Negative Zika serology
4	Germany	Maldives	01/04/19-15/04/19	45	M	22/04/19	Fever/ arthritis	Yes (GP)	NA	NA	Positive IgM and IgG antibodies (Euroimune EIA)	Negative dengue and Zika serology
5	Spain	Maldives	10/04/19-21/04/19	40	M	20/04/19	Fever/ sweat/ chills/ headache	NA	NA	NA	Positive IgM antibody 1.77 (IFAT, Euroimmun)	Dengue: IgG positive and IgM negative.

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6	France	Dhangethi, Malé	07/12/19-15/12/19	35	M	13/12/19	Fever/ headache/ diffuse rash/ cervical lymph nodes	No	Recovered	Yes	RT-PCR on plasma	Negative dengue and Zika RT-PCR and serology, negative malaria blood smear microscopy
7	Italy	Maldives, Thinadhoo island	12/01/20-26/01/20	80	F	27/01/20	Fever / arthralgia/ myalgia	No	Arthralgia and myalgia persistent for 5 months	Improvement, but persistent arthalgia	RT-PCR on plasma	NA
8	Italy	Maldives, Thinadhoo island	22/02/20-29/02/20	30	F	27/02/20	Fever/ nausea/ arthralgia/ myalgia /rash	No	Arthralgia persistent for 4	Improvement, but persistent	Positive IgG and IgM (IFAT serology)	NA

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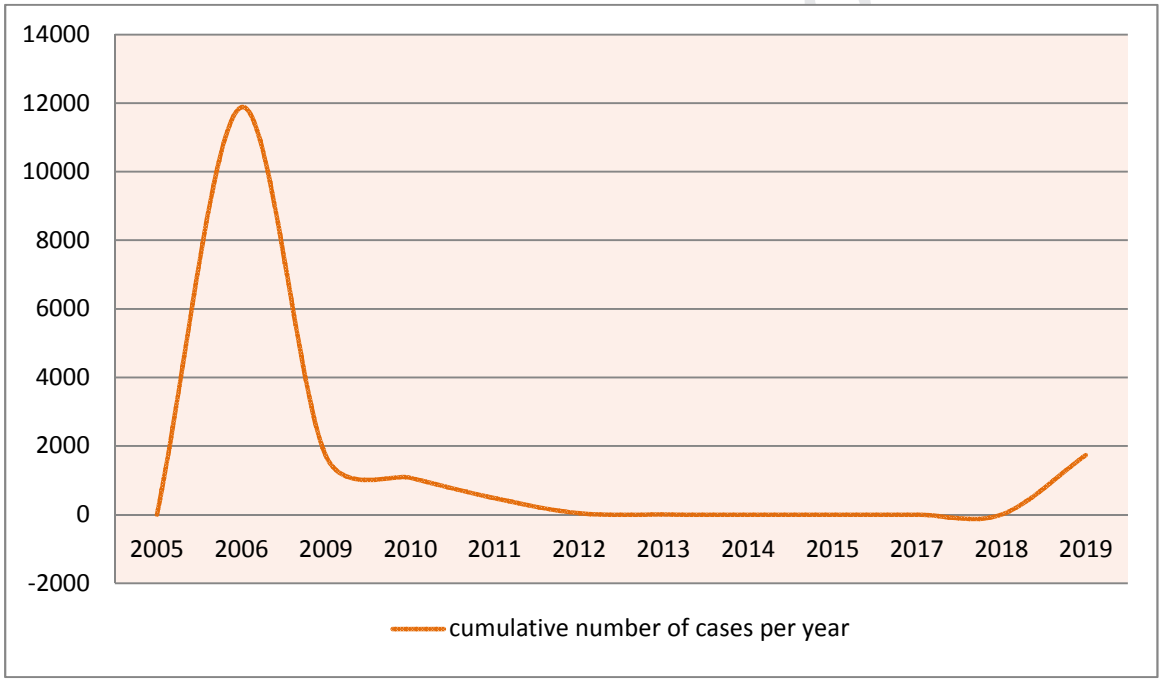
									months. Prednisolone ongoing treatment	arthalgia		

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Discussion

According to the data from the Ministry of Health and the Maldivian's Health Protection Agency [10,11] and the European Centre for Disease Prevention and Control (ECDC) [12,13], no autochthonous case of CHIKV was registered in the Maldives from 2013 to 2019 (**Figure**).

Figure: Cumulative number of confirmed and suspected chikungunya virus infection cases by year, built according to data provided by the Health Protection Agency and the Health Ministry of Maldives and ECDC at their official websites [10-13].



From 2009 to December 2018, only three cases acquired by visitors to the Maldives were reported in the literature or in the ProMED International Society of Infectious Diseases database, one from France [14] and two from Germany [15], all in 2009. Since 2019, concomitantly with a dengue outbreak, the Maldives health authorities have reported an epidemic of CHIKV, with 1,736 cases reported as of the 31st December 2019 [6].As experienced in the United States Virgin Islands in 2014, current and possibly recurrent chikungunya outbreaks in the Maldives could have major human and economic impact [16].

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Several factors may have contributed to this re-emergence including waning anti-CHIKV herd immunity in the local population over time, a recent re-introduction of the virus due to the flux of tourists or migrant workers, notably in areas less reached in 2006, and changes in viral strains and vector density [17].

For the first time in 2006, a large part of the atoll was involved in a CHIKV outbreak, but unevenly so. Incidence was highest in the following atolls: Raa, Malé, Meemu and Lhaviyani. Interestingly, the French case in this report took a diving trip, which disembarked in only two locations, Dhenghethi Island and Malé, the capital, at the end of their trip. He arrived in Dhengheti (Alif Dhaal atoll) on 9 December and Malé on 12 December, 2019; date of symptom onset was 13 December, 2019. According to the patient's history and considering the 4 to 7-day incubation period of CHIKV [1], Dhengethi Island was the most likely location of exposure. However, during former epidemics, this highly touristic place was considered to be low risk for CHIKV transmission compared to Malé and other atolls. This highlights the importance of mapping exposures of cases and determining places of transmission contemporary to an epidemic, with the aim of improving case detection and implementing targeted vector-control measures that limit CHIKV dissemination [18]. From a clinical point of view during the first CHIKV outbreak in the Maldives, patients reported fever during 1-6 days as a primary symptom of illness, and other symptoms included joint pain, arthritis, arthralgia, headache, rash and sore throat, but lymph nodes were not noticed [5]. No clinical description from the recent epidemic are available yet, however, lymphadenitis presented by the French case in this series have been mostly reported during infection with the Asian chikungunya lineage. Basically, we do not know exactly the origin of the viruses responsible for the 2006 and the 2019 chikungunya Maldivian outbreaks. Whether it is the same strains or not remains to be determined.

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Unusually strong rainfall in the second half of 2006 in the Maldives probably led to suitable conditions for expansion of mosquito populations and different CHIKV strains could have been introduced from neighboring areas enduring epidemics at that time. Curiously, in 2007, *Aedes aegypti* was identified as the predominant vector of CHIKV in Malé, whereas *Ae. albopictus* was identified as the main vector found on other islands. Importantly, *Ae. albopictus* was the main vector for the new variant from the East/Central and South African (ECSA) CHIKV lineage which emerged in the Indian Ocean in 2006. A study analyzing the evolutionary relationships of CHIKV in South and Southeast Asian regions after 2005 found that the Sri Lankan and Singapore CHIKV strains, including one strain imported from the Maldives in 2006, were evolutionarily more closely related to the Indian isolates of the ECSA lineage than to the Indian Ocean Islands (IOL)-ESCA strains [19].

In 2007, the Maldivian government, with support from the World Health Organization, started a large vector-control program [5]. Since then the number of cases drastically decreased, but the surveillance was effective only until 2014. The Maldives is a large archipelago of 1,190 islands, spread out over an area of 298 square kilometers with an estimated population around 530,000 inhabitants, making long-term implementation of individual and collective vector-control strategies, and epidemiologic surveillance challenging. The situation on the Maldives might be viewed best from the ‘one-health perspective’ proposed in 2018 by Carla Mavian and colleagues [20]. Their size and the lack of resources induce more trade, facilitating the importation of vectors and introduction and establishment of viruses [21]. Frequent human migration between the Maldives and chikungunya-endemic countries, including travel to Sri Lanka and India, increase the risk of CHIKV re-introduction and spread [22]. Moreover, the unstable geological structure exposes the island chains to natural storms, hurricanes and cyclones, which can result in mass destruction and an abundant vegetation, which complicates vector-control strategies. Certain

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ecosystems could be more subject to large and recurrent arboviral outbreaks, as seen with dengue in the Fiji Islands [23]. From a historical perspective, CHIKV transmission also spontaneously ceased in some territories as for example in Bangkok; and it has been suggested that CHIKV endemicity requires very high populations of *Ae. aegypti* [24].

The year 2019 in particular brought an enhanced risk for CHIKV importation due to outbreaks reaching touristic places in Brazil, Thailand, India and Malaysia as notified by the ECDC and the GeoSentinel surveillance network [25,26]. Likewise, the Republic of Maldives is one of the most visited countries in the world with a constant growth in numbers of tourists [27]. In 2019, 1,702,887 visitors went to the Maldives according to its Ministry of Tourism, including 833,939 persons from Europe; this represents an increase of total tourist numbers of approximately 15%, as compared to 2018. From the top ten tourist countries of origin, visiting the Maldives Islands in 2019 Italians, Germans, English, Russians and French people were respectively the 3rd, 4th, 5th, 6th and 7th biggest groups [27]. Due to the lack of a denominator, incidence rates in returning travellers cannot be calculated by the GeoSentinel Network. Moreover, diagnostics are based upon local site interpretation, techniques and reporting. However, this surveillance system can monitor global trends over time and alert to warning signals such as this cluster of height imported cases from Maldives to Europe in one year, which exceeds the global record over the last 10 years.

Despite true difficulties in implementing anti-CHIKV individual and community prevention programs worldwide [28], travel medicine practitioners can play a pivotal role in raising awareness of the potential for infection and importation of CHIKV in travellers [29]. In our cases series, only one patient reported a pre-travel consultation. Being a malaria-free certified WHO country since 2015, Maldives may be wrongly considered low risk for mosquito borne illnesses. Pre-travel visits have led to a significant decrease in malaria, hepatitis A virus infection and HIV/AIDS infections among travellers [3]. To date, no such effect has been

demonstrated regarding arboviral diseases and it remains important therefore to make travellers aware of these risks and their prevention methods. Travellers must be advised to apply all-day long vector-borne preventive measures using physical and chemical barriers (use insect repellent, bed-nets, wear long-sleeved shirts and pants and stay in places with window and door screens or air conditioning). Moreover, it is important to advise travellers to present as soon as possible to a travel clinic in case of fever and/or arthralgia occurring during or after a travel to a country endemic for arboviral disease (dengue / chikungunya / Zika). It is worth stressing that Maldivian public health authorities apparently have meticulous record-keeping and efficient surveillance systems. Local epidemiological data assist in the timely adaptation of travel recommendations and the prompt detection and management of viremic cases imported into places at risk of local spread [30]. Key concepts in the control of arboviral diseases threat include pre-travel targeted advice, early detection of sentinel cases, outbreak alert leading to prompt responses, and post-travel multi-disciplinary management of cases.

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Conclusion

These eight chikungunya cases in returned travellers from the Maldives, over a period of one year 2019-2020, indicate an increased risk of acquisition of CHIKV infection at this highly touristic destination, and a risk of exportation. Health professionals and health authorities should adapt their pre-travel advice accordingly, and promptly investigate those with symptoms suggestive of CHIKV on return from Maldives, to reduce CHIKV spread in European regions at risk of local transmission, due to the presence of *Aedes albopictus* mosquitoes. If the current situation in the Maldives evolves into a second large CHIKV outbreak, parameters (including host immunity, virus strains and environmental factors) that

have led to a re-emergence 12 years after the first massive epidemic on the Islands, should be investigated.

Author contributions

Philippe Gautret, Philippe Parola, Davidson H. Hamer, Emilie Javelle: Conceptualization, Methodology, Software, Supervision, Writing- Reviewing and Editing.

Pierre Dudouet, Carsten Schade Larsen, Frank von Sonnenburg, Marta Díaz-Menéndez, Elena Trigo, Federico Gobbi: Data curation, Investigation, Writing- Original draft preparation.

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