State of Chikungunya in Various Countries: A Review

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DECLARATION

I hereby solemnly declare that the reiew paper titled " **Status of Chikungunya in Various Countries: A Review**" submitted by the undersigned has been carried out under the supervision of Dr. M. Mahboob Hossain, Professor Microbiology Program, Department of Mathematics and Natural Sciences BRAC University, Department of Mathematics and Natural Sciences, BRAC University, Dhaka. It is further declared that the research work presented here is original work. Any reference to work done by any other person or institution or any material obtained from other sources have been duly cited and referenced.

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State of Chikungunya in Various Countries: A Review

Abstract

In the last few decades, chikungunya virus transmitted by *Aedes* spp mosquitoes has re-emerged in Africa, southern and southeastern Asia, and the Indian Ocean Islands as the cause of large outbreaks of human disease. The disease is characterized by the symptoms of fever, headache, myalgia, rash, and both acute and persistent arthralgia. The virus is endemic to tropical regions, but the spread of Aedes albopictus into Europe and the Americas coupled with high viremia in infected travelers returning from endemic regions increases the risk that this virus could establish itself in new endemic areas. This paper focuses on the re-emergence of this disease, epidemiology, world perspective, Bangladesh perspective and molecular diagnosis of Chikungunya.

Introduction

Chikungunya fever is a viral disease which is transmitted by Chikungunya Virus (CHIKV), which is an arthropod-borne *alphavirus*. This virus uses *Aedes* species mosquitoes as a vector for transmission of the disease from one person to another. It was first recognized as a human pathogen during the 1950s in Africa, and since then, cases have been identified in many countries in Africa and Asia.[1]

The disease typically characterized with acute illness with fever, skin rash, and incapacitating arthralgia.[2] Chikungunya virus (CHIKV) is the etiological agent and a member of the Alphavirus genus in the Togaviridae family.

This fever occurs in Africa, Asia, and the Indian subcontinent. Human infections in Africa have been at relatively low for a number of years.[3] In December 2013, France reported 2 laboratory-confirmed autochthonous cases of in the French part of the Caribbean island of St Martin. Since then, local transmission has been confirmed in over 43 countries and territories in the American region.[4]

World Perspective of chikungunya

First Chikungunya case acquired in the United States reported in Florida

Seven months after the mosquito-borne virus chikungunya was recognized in the Western Hemisphere, the first locally acquiredcase of the disease has detected in the continental United States.[5] The case was reported in Florida, a male who had not recently traveled outside the United States. The Centers for Disease Control and Prevention is working closely with the Florida Department of Health to investigate how the patient contracted the virus; CDC will also monitor for additional locally occurred U.S. cases in the coming weeks and months.

Since 2006, the United States has averaged 28 imported cases of chikungunya per year in travelers returning from epidemic countries.[6] In 2009, 243 travel-associated cases have been reported in 31 states and two territories.[7] However, the newly reported case represents the first time that mosquitoes in the continental United States are thought to have spread the virus to a non-traveler.[8] In 2010 Puerto Rico and the U.S. Virgin Islands reported 121 and two cases of locally acquired chikungunya respectively.[9]

"The arrival of chikungunya virus, first in the tropical Americas and now in the United States, underscores the risks posed by this and other exotic pathogens," said Roger Nasci, Ph.D., chief of Centers for Disease Control and Prevention (CDC)'s Arboviral Diseases Branch. "This emphasizes the importance of CDC's health security initiatives designed to maintain effective surveillance networks, diagnostic laboratories, and mosquito control programs both in the United States and around the world."[10]Chikungunya virus is transmitted to people by two species of mosquitoes, *Aedes aegypti*,and *Aedes albopictus*. Both species are found in the southeastern United States; *Aedes albopictus* is also found further north up the East Coast, through the Mid-Atlantic States and is also found in the lower Midwest.[11]

CDC and the Florida Department of Health are assessing whether there are additional locally acquired cases and are providing advice to the public on ways to prevent further spread of the virus by controlling mosquitoes and making aware people about personal and household protection measures to avoid mosquito bites.[12] CDC has asked state health departments to report the incident of chikungunya to help track the virus in the United States. Local transmission occurs when a mosquito bites someone who is already infected with the virus and then bites another person.[13]

Almost 200 imported chikungunya cases between 2006 and 2013 have triggered a local outbreak.[14] However, more chikungunya-infected travelers coming into the United States increases the chances of local chikungunya transmission.

Outbreaks of chikungunya have been previously reported from different countries in Africa, Asia, Europe, India, and the Middle East, and on the French side of the Caribbean island of St. Martin.[15] The virus spread rapidly in St. Martin through the Caribbean in December 2013 and into South and Central America. Local transmission has been reported in 23 countries in the hemisphere prior to the United State case.[16]

People infected with chikungunya virus normally develop fever and joint pain, muscle aches, headaches, joint swelling or rash.[17] Travelers returning from regions with chikungunya activity and those living in regions where the virus has been reported in the United States should seek medical care if they experience chikungunya symptoms. Health care providers in regions with reported cases should be on the alert for possible cases. People infected with chikungunya should protect themselves by wearing insect repellents, using air conditioning or window and door screens to keep mosquitoes out, wearing long pants and long-sleeved shirts when possible, and emptying standing water outside your home. Protecting yourself and others from mosquito bites during the first few days of illness can help prevent other mosquitoes from becoming infected and reduce the risk of further spread.

Infection with chikungunya virus is not normally fatal, but the joint pain can often be severe and debilitating. This virus is not transmitted from person to person. There is no vaccine and no specific treatment for infection but research is underway in both areas. Patients may recover in about a week, although long-term joint pain happens in some people.[18]

Arrival of chikungunya New World: Prospects for Spread and Impact on Public Health:

For the first time in known scientific history, the chikungunya virus has established its mosquito-human transmission cycle in the Americas.[19] The history of dengue control, recent findings on chikungunya strain variation and public health preparedness suggest the further spread of this outbreak.

This mosquito-borne virus causes a feverish illness typically accompanied by rash and severe, debilitating, arthralgia. Pain and swelling are usually found in the hands, wrists, ankles. And feet can persist for years to cause not only major public health effects but also economic damage due to lost human productivity.[20] Though most cases are not life-threatening but slightly increased mortality is associated with CHIKV infection. It is believed that the virus is originated in Africa, where it still circulates enzootically among nonhuman

primates and is transmitted by arboreal *Aedes* mosquitoes.[21],[22]

After its discovery in 1952, the first documented CHIKV emergence spread to generate urban outbreaks in India and Southeast Asia.[23] This introduction has been found to an Eastern/Central/Southern African (ECSA) enzootic CHIKV lineage that evolved sometime during or before the early 1950s.[24] The resultant "Asian" endemic/epidemic CHIKV lineage persisted in Southeast Asia, where it continues to circulate sporadically in the urban cycle, spread among humans by *A. aegypti* without conclusive evidence of an enzootic component (Table 1). The second documented CHIKV emergence starts in coastal Kenya in 2004[25] and spread independently into islands in the Indian Ocean and to India, presumably via infected air travelers, a documented source of introductions.[26]-[27]-[28] Later, autochthonous transmission occurred in Italy[29]and France[30], initiated by infected travelers from India (Table 1). Although many imported cases were also found in the Americas, including in dengue-endemic locations with both *A. aegypti* and *A. albopictus* vectors, no local transmission was detected. As with the Asian lineage, the etiologic CHIKV strain, called the Indian Ocean lineage (IOL) was again found as a descendent from an enzootic ECSA strain.[31] However, some Indian Ocean lingage adapted to a new vector, *A. albopictus*, through adaptive mutations in the El and E2 envelope glycoprotein genes. It allowed the new epidemic IOL strains to use both *A. aegypti* and *A. albopictus* as vectors, resulting in millions of human cases. Because *A. albopictus* can survive in low temperature and is generally less adapted to urban habitats than *A. aegypti*, IOL CHIKV strains adapted to this vector circulated both in temperate climates like Italy and in more rural habitats where the former species is more common than the latter.[32]

Table 1:**Representative chikungunya fever outbreaks documented in the literature.**

Year	Location	Estimated number of cases	Virus genotype*	Notes
1952-1953	Tanzania	Incidence estimatedat 23%	ECSA	Suspected vector A. *aegypti*
1961-1963	Cambodia	Six confirmed	Not determined	
1956, 1975—1977	South Africa	Not reported	ECSA	No *A. aegypti* involvement
1957, 1961—962, 1971	Zimbabwe	38 suspected (one confirmed), 1962	ECSA	No *A. aegypti* involvement
1958, early 1960s	Thailand (Bangkok and other locations)	Estimated 40,000 cases in early 1960s	Asian	Suspected vector *A. aegypti*
1962-1965	India (various locations including Calcutta, Madras)	273 confirmed	Asian	Up to 38% human seroprevalence after outbreak, incidence in some locations estimated ated at 40%; principal vector *A. aegypti*
1962-1964	Bangkok, Thailand	44,000—72,000 estimated	Asian	Principal vector *A. aegypti*
1966	Viet Nam	Ten confirmed	Not determined	U.S. soldiers
1969	Nigeria	**55** confirmed	Not determined	
1998	Selangor State, Malaysia	51 cases reported	Not determined	

Table 1(continued):Representative chikungunya fever outbreaks documented in the literature.

Year	Location	Estimated number of cases	Virus genotype*	Notes
1999-2000	Democratic Republic of Congo	40,000 estimated	ECSA	
2004-2005	Coastal Kenya, Lamu Island	Not reported	IOL	Principal vector *A. aegypti* on Lamu
				Island
2005-2011	Comoros, Maurituis, La	300,000	IOL	Principal vector *A.*
	Reunion	estimated in		*albopictus* on La
		La Reunion		Reunion
2005-2008	India, Sri Lanka	1.4-6.5	IOL (El-	Vectors *A.*
		million	226A or V in different outbreaks)	*albopictus* or *A. aegypti*, depending on location
2006	Bagan Panchor Malaysia	>200 reported	Asian	
2006	Douala and Yaound' Camer*oon*	54 confirmed	ECSA	Suspected vector *A. africanus*
2006-2007	Libreville Gabon	Seven *onfirmed*	ECSA	Suspected vector *A. albopictus*
		0000 estimated		
2007	Emilia Romagna Italy	205 confirmed	IOL (introduced by traveler from India)	Principal vector *A* albopictus
2007-2008 (nonepidemic period)	Moshi, Tanzania	55 confirmed	Not determined	
2008	Thailand	224 *confirmed*, 46,000 estimated	IOL	Suspected vector *A. albopictus*
2008	Rural Malaysia	34 confirmed	IOL	Suspected vector *A. albopictus*

Table 1(continued):Representative chikungunya fever outbreaks documented in the literature.

Year	Location	Estimated number of cases	Virus genotype*	Notes
2008	Singapore	231 confirmed	101, (El - 226A)	Principal vector *A. aegypti*
2010	Frejus, France	Two confirmed	IOL (El- 226A; imported from India)	Suspected vector *A. albopictus*
2010	Ndangui, Gabon (forested region)	12 confirmed	Not determined	Principal vector *A. albopictus*
2010	Guangdong Province, China	173 suspected, ten confirmed	IOL	Suspected vector *A. alhopiclus*
2011	Cambodia	24 confirmed	IOL	
2012	Bhutan	78 suspected	IOL (El 226A)	
201 3—present	Caribbean Sea islands	>3,000 confirmed as of March 2014	Asian	Principal vector *A.* aegypti

Source.- IOL strains had EI-226V unless otherwise noted.

During the IOL CHIK epidemics, the nearly completely naive human populations in the Americas and the presence of both epidemic vectors, combined with the arrival of infected travellers, raised major concerns that an epidemic in the Caribbean and/or Latin America was certain.[33] However, with the subsidence of epidemic transmission in many parts of Asia, this risk was considered to have declined, because fewer infected travelers were documented in recent years.Thus, the detection of active CHIKV circulation in Saint Martin beginning in October 2013[34] was surprising in many parts of Asia.

There are much bad news and only very few good news in the 2013 CHIKV introduction into the Caribbean. The bad news is: (1) CHIKV appears to be spreading almost uncontrolled, in the Caribbean, with over 4,300 confirmed cases as of May 23rd. The autochthonous transmission has resulted in at least 176 CHIK cases in French Guiana on South America. If transmission cannot be controlled quickly there, the historic inability to control dengue suggests that CHIKV will spread all over Latin America. Most of the Latin American population is presumably naive, setting the stage for major epidemics and rapid transmission. Diagnostic capabilities for CHIKV in Latin America remain very limited, and it is possible that undetected circulation is already occurring in this area because of the difficulty in clinically distinguishing dengue from CHIK and finally, there could be the potential for

CHIKV to establish an enzooticmonkey human cycle in the Americas, as occurred for yellow fever virus hundreds of years ago after its importation from Africa.[35]

If there is any good news regarded to this CHIK outbreak, it is that the etiologic strain, a member of the old Asian lineage, does not infect *A. albopictus* as efficiently as the adapted IOL strains, and is epistatically constrained in its ability to adapt to this vector via the EI-226 protein substitution.[36] This suggests that most CHIKV transmission in the Americas will happen via *A. acgypti*, which may limit geographic spread, especially to temperate climates where this Mosquito does not normally occur. However, *A. aegypti* reinfestation of most tropical and subtropical areas of Latin America since the 1970s,[37] along with its persistence in the southern United States, leaves hundreds of millions of people at risk for CHIKV infection. The presence of the closely related Mayaro alphavirus in South America could provide limited cross-protection[38]but this virus circulates enzootically, mainly in forested regions, where *A. aegypti*-borne CHIKV is expected to be less common. Finally, the introduction of CHIKV during the beginning of the dry season in the Caribbean and northern hemisphere of Latin America may improve prospects for containing its transmission, at leasttemporarily.

Bangladesh perspective-Chikungunya Outbreak in Bangladesh:

Outbreak of CHIK virus infection occured earlier in Bangladesh: first outbreak inRajshahi and Chapainawabganj 2008 affecting 39 people, outbreak in 2011 in Dohar, Dhaka affecting 196 people.[39]-[40] Sporadic cases happened in 2013, 2014, and 2015 in Dhaka with big outbreaks in December 2016. Case reports were earlier made on four patients of CHIKV infection from Bangladesh.[41] In 2017 a large number of febrile illness with joint pain involvement were reported from different areas of Dhaka city which prompted the Directorate General of Health Services(DGHS), Ministry of Health and Family Welfare, Government of Bangladesh(GOB) to investigate the vector, cases and confirmed the Chikungunya outbreak in Dhaka. Subsequently, few numbers of cases was also reported from a number of districts outside Dhaka. A large number of media reports, editorial, TV talk showhappened. The government immediately responded by arranging creation of public and professional awareness, vector control measures and management of patients.[42] The Public health system in city areas in Bangladesh is relatively weak, care is provided by different healthcare providers and organizations in a fragmented manner. The low capacity of the surveillance system and facility for confirming the causes of viral illness. Institute of Epidemiology Disease Control and Research (IEDCR), Dhaka, Bangladesh investigated all

the previous and present outbreak of Chikungunya. In the present outbreak, 1248 cases of febrile illness with suspected CHIK virus infection since the outbreak were tested, out of which 939 were found to be PCR positive from 9th April to 9th August 2017.[43]

Despite low case fatality, the disease is connected with substantial health burden and economic loss to the affected population having prolonged disability in some patients.
It is necessary to conduct the detailed investigation of the outbreak with documentation of cases. IEDCR and DGHS, GOB did an excellent job in the case and vector investigation detected *Aedes albopictus* in all outbreaks. *A. aegypti* are the predominant vector with few *A albopictus*.[44] For future prevention is needed to have an Integrated Vector Control Management Plan for strict vector control all along not during such an outbreak only, to have a good surveillance (patient and vector) which is considered to be one of the important pillars of public health for vector-borne diseases, and effective community education.[45] Chikungunya outbreak in Dhaka shows the necessity of improving public health capacity of Bangladesh for the control of vector borne diseases.

Molecular Diagnosis of Chikungunya virus (CHIKV) and Dengue virus (DENY) and its concomitant circulation in South Indian population:

Having known for its menace in tropical countries such as Africa and Asia, dengue fever is happened by a class of pathogens called as Flavivirus that belongs to the family of Flaviviridae and Chikungunya, being caused by the *Alphavirus* of family Togavirida.[46] Both diseases are transmitted to humans by day-biting *Aedes aegypti* and *Aedes albopictus* mosquitoes and almost cause similar clinical symptoms like fever, rashes, joint pain; a headache, fatigue, nausea, vomiting, and body pain are the symptoms for both the diseases that makes diagnosis difficult.[47] Concomitant circulation of both these viruses in humans was reported and apprehended by serological analysis but their results did not confirm about the on-going infection with both the viruses[48].Co-infection of these viruses show similar clinical signs, but different disease patterns. Unavailability of viral-specific diagnostic tools complicates medical management strategies and hence clinically viable and easily available molecular markers are the need of the hour. Here, a study was conducted to establish a easy diagnosis method for the screening of Chikungunya and dengue fever through in-house designed RT-PCR approach.

Blood sample of 1024 patient from Kerala and Andhra Pradesh were tested for the screening of dengue and chikungunya. In the current cross-sectional study, we found that nearly 46/105 samples (43.8%) were positive for DENV, 34/105 samples (32%) were positive for CHIKV and 24/105 samples (23%) were positive for the presence of both viruses in the Andhra Pradesh region.[49] In contrast to the above figures, patients from Kerala were found to be positive for dengue with 16.1% (148/919), positive for CHIKV at 2.3% (21/919) and surpris-ingly only 0.1% (1/919) of people were found to be carrying both the viruses.[50] Serology analysis using dengue IgM in Andhra Pradesh and Kerala showed 60.9% (64/105) and 18.8% (173/919), respectively (Table 3).[51] To further validate our above findings, they ran RT-PCR to detect the presence of DENV RNA in blood samples of both Andhra Pradesh and Kerala patients. They concluded that, in Andhra Pradesh alone, 45.6% (21/46) of the samples showed positive for dengue serotype-2-, 54.6% (25/46) showed positive for more than one dengue type such as dengue type 2 and 3; co-infection was detected in 39.1%; 0.6% (4/46) of the samples being positive for type 2 and 4; mere 6.5%of all patient samples showed the presence of D-1, D-1/2, D-1/4, D-1/3, D-3/4, D-1/3/4, D-2/3/4 serotypes (Table 4).[52]

148/919 samples from Kerala were tested for DENV RNA by RT-PCR. Five samples could not be genotyped due to low copy number and 143 samples were analyzed for dengue serotype-specific PCR. Among 143 samples, dengue serotype 2 occupied 35.6% (51/143) and the remaining 64.3% (92/143) of the samples were diagnosed with other subtypes of dengue such as D-4 of 16.7% (24/143), D-3 ofl3.2% (19/143), respectively. Co-infection of D-2 and D-4 was found to be 12.5% (18/143), D-2 and D-3 were 7.6% (11/143) and co-infection was 13.9% (20/143) of the samples tested (Table 4).[53]

Table 1:Case definitions.

Case	Symptoms
Suspected	An acute illness characterized by sudden onset of fever with several of the following symptoms:
	joint pain, headache, backache, photophobia, arthralgia, rashes, etc.
Probable	Above symptoms with positive serology either when single serum sample was taken during
	acute onset phase or during the convalescence
Confirmed	A confirmation was done based on the following criteria:
	1. 4-fold difference in HI antibody levels
	2. Detection of IgM antibodies against Chikungunya virus
	3. Virus isolation from plasma on cell cultures
	4. Detection of CHIKV genomic RNA by RT-PCR

4.

Table 2: Oligonucleotide primers used and the expected size of the products

Primer	Sequence (5'-3')	Genome position	Expected size (bp)
DEN-F	5'-TCAATATGCTGAAACGCGCGAGAAACCG-3'	134-161[a]	
DEN-CR	5'-TTGCACCAACAGTCAATGTCTTCAGGTTC-3'	616-644a	511
DEN I -R	5'-CGTCTCAGTGATCCGGGGG-3'	568-586b	482
DEN2-R	5'-CGCCACAAGGGCCATGAACAG 3'	232-252'	119
DEN3-R	[5']-TAACATCATCATGAGACAGAGC 3'	400-421'	290
DEN4-R	5'-CTCTGTTGTCTTAAACAAGAGA 3'	506-527'	392

a. The genome positions of Dl and D2 are given according to the *Dengue virus* type 2 published sequence.[54]
b. The map positions of the *Dengue virus* type-specific primers (TS1, TS2, TS3, and TS4) are given according to their respective published sequences.[55]

Table 3. Results of reverse transcriptase polymerase chain reaction and ELISA tested for dengue and chikungunya* .

place	Positive for dengue RT-PCR	Dengue IgM by ELISA	Positive for chikungunya RT-PCR	Co-infection CHIKV/DENV	DENV vs. Co-infection CHIKV and DENV p value (n = 1024)	CHIKV vs. Co-infection CHIKV and DENV p value (n = 1024)
Andhra Pradesh	43.8% (46/105)	60.9% (64/105)	32% (34/105)	23% (24/105)	0 (59.9% vs. 23.1%)	< 0.001 (34.3% vs. 23.1%)
Kerala	16.1% (148/919)	18.8% (173/919)	2.3% (21/919)	0.1% (1/919)		

Desired significance level 0.01.

Table 4. Detection of dengue serotype specific by reverse transcriptase polymerase chain reaction in patient samples.

Place	Dengue Serotype specific RT-PCR			
	D-2	Other than D-2 [b]	D-2 vs. CHIKV p value (n = 189) [*]	Other than D2 vs. CHIKV p value (n = 189) [*]
Kerala	35.6% (51/143)	64.3% (92/143)	< 0.001	0
Andhra Pradesh	45.6% (21/46)	54.3% (25/46)	(38% vs. 17.4)	(62% vs. 174%)

a Five samples that could not be genotyped, due to low copy number of DENV RNA.

b D-1, D-1/2, D-1/4, D-1/3, D-3/4, D-1/3/4, D-2/3/4.

* Desired significance level 0.01.

There have been very few reports on the co-existence of CHIKV and DENV, particularly in those living in regions endemic to CHIKV and DENV. Infections with CHIKV and DENV present similar clinical symptoms in pa-bents. Accordingly, there have been reports of co-infection with CHIKV and DENV in Asian countries. Some of the data on co-infection is based on the serological diagnosis of the patient samples but it shows little details on live infection. In this context, we have proven that the in-house designed primers for RT-PCR-based tool enabled a diverse yet commendable diagnosis of CHIKV and DENV as well as co-infections of both the viruses. In our study, we found that 23% (24/105) and 0.1% (1/919) of the samples were positive for both CHIKV as well as DENV in AP and Kerala respectively, suggesting the co-existence of these two viruses in these patients. Although the virulence and viral loads of CHIKV strains isolated during this study are yet to be established, the clinical spectrum of the two infections is very much similar and can co-exist in the same host.[56]This study also reflects a comparative study of clinical features between monotypic and dual infection cases with chikungunya virus and Dengue virus in west Bengal, India.[57]

The sequence found from the RT-PCR assay can be used for phylogenetic neighborhood joining tree analysis and genotyping of the isolates. Thus, the assay can also use as a tool for rapid clustering of isolates for the genotyping of viruses from different outbreaks. RT-PCR can be used as a potential rapid test to detect dengue and chikungunya viral infections simultaneously in clinical samples along with the determination of DENV serotypes.
False negatives are always plausible if diagnostic tests for both the viruses are not performed. It has shown that it is possible for clinicians to use simple clinical and laboratory variables to predict these infections.

Estimating economic attributable to Chikungunia: Chikungunya virus disease emerged in Latin America in 2013, originally as an epidemic that rapidly progressed to an endemic disease in those countries with suitable ecoepidemiological conditions, including Colombia.[58] CHIKV has many health implications which include considerable disability with a consequent economic burden on health care systems in Latin America. Disease expansion is associated with lack of transmission control and the frequency with which patients develop chronic sequelae, including post-chikungunya chronic inflammatory rheumatism. Although disease costs in this area have not yet been estimated and published, reports of previous epidemics in India showed that direct and indirect costs may be as high as US$ 3.7 million at the first administrative level.[59] The disease burden in newly endemic areas in Latin America

may be expected to be higher than that reported in India with consequent greater disease costs for the area.[60]-[61] An important context for this is that the costs associated with dengue are already high, with an abundant vector and dengue attack rates for CHIK compared to dengue. The numbers of territories and populations which may be affected are also considered in our region.[62] There are no specific therapeutic measures for treatment and preventing CHIK, no risk factors for severe or chronic forms of the disease have yet exhaustively been identified and good quality studies have not yet been published which will improve the management of disease sequelae. Recently, non-biological disease modifying anti-rheumatic drugs (DMARDS) and doses have been proposed, based on national[63]and international[64]recommendations. Furthermore, even though previous studies report disability rates which cause concern, these may be under-estimates because disability associated with the acute phase of the disease was not considered. Mortality is now being reported in Colombia and surrounding regions in 2015.[65] Reliable estimates of disability-adjusted life years (DALYs) lost and the costs of the disease in Latin American countries are unknown, and there is insufficient information regarding accurate estimates of disease evolution, management, and the proportion of atypical, complicated and/or congenital cases. New cost estimates need to be prepared for the effect that the CHIK epidemic may have on the new endemic areas in Latin America, bearing in mind that 2015 may be worse than 2014 in terms of morbidity and mortality, and probably in DALYs and healthcare costs.[66] The aim of our study wasto estimate DALYs lost for the year 2014 in Colombia attributable to CHIK considering both the acute phase of the disease and chronic disability caused by pCHIK-CIR. Cost estimations were based on national guidelines for CHIK clinical management and pCHIK-CIR chronic sequelae, and used data from three hospitals in Colombia that have cared for patients with complicated CHIK who required hospitalization.

Estimation of DALYs related to CHIK

The estimated DALYs for CHIK using the method adopted by Murray for estimating the global burden of diseases (DAI.Ysl/4years of life lost [YLL]+years lost due to disability [YLD]; YLL$^1/_4$0 assuming no deaths reported in 2014; YLD$^1/_4$*DW*L [where I is an incidence of cases progressing to chronic disease; DW is disability weight; L is the duration of chronic disease]).[67]-[68] Although no DW is yet available for CHIK and pCHIK-CIR, for the acute phase of the disease the DW was used to utilize for dengue (0.172) and for the chronic rheumatic sequelae the DW for rheumatoid arthritis (0.233), was utilized. In these

calculations, it was not able to use age weighting or discounting giving the fact we have no access to the case by case information of age for each individual. This has been used in previous estimates for CHIK DALYs. The expected incidence of cases progressing to chronic disease (I) and duration of chronic disease (L) was assumed as previously reported in 2015.[69] It was expected that 47.6% (95% CI 45.08-50.13) of infected patients that would develop pCHIK-CIR, in a median time of 20.12 months as estimated in a recent report. These estimates were based on pooled data ($n^1/_4$1544), and subsequent weighting took account of the final follow-up time related to the population size in selected studies. Non-linear regression models were run to estimate the cumulative proportion of pCI IIKCIR over time and median time during which 50% of patients could present pCHIK-CIR).

DALYs lost were reported by department, municipality, and country adjusted by 100 000 population rates. Sensitivity analysis was performed calculating the respective 95% CI using the software Epi Dat 3.1 (Xunta de Galicia, Spain), according to the technique provided by Armitage and Berry.[70]

Comparative study on chikungunya

Chikungunya virus the aetiological agent of chikungunya fever (CHIKF), which presents as an acute onset high fever with a headache, back pain, muscle, and joint pain. The joint pain can vary in intensity but is often very intense, predominates at the ankles, wrists, and phalanges and is coupled with swelling. CHIKF is usually a self-limiting disease, and serious outcomes (e.g. neurological complications) and fatalities appear to be rare.[71]-[72] However, up to 60% of infections are followed by chronic arthritic conditions, with recurrent debilitating joint pain several years post-infection.[73]-[74]

CHIKV exists as a single serotype thought to confer life-long immunity in recovered individuals. There is, however, sufficient variation to discern three genotypes, namely the enzootic West African (WAf), and East /Central/South African (ECSA), and the epidemic Asian genotypes. The ECSA recently gave rise to the Indian Ocean Lineage (IOL) responsible for epidemics in the Indian Ocean islands, mainland India and Europe beginning in 2004.[75] The expansion of thislineage has -been attributed to adaptive mutations in the El and E2 envelope glycoproteins that provide a fitness advantage in *Aedes albopictus* without reducing fitness in *A. aegypti*[76]and permit rapid lineage diversification.[77]-[78]

In light of the dramatic re-emergence of CHIKV in Asia, the intensity of global travel and the widespread prevalence of *A. aegypti* and *A. albopictus*, the emergence of CHIKV in the

Americas was long anticipated.[79] As expected, numerous imported (travel-related) cases were subsequently documented in the Americas, none of which resulted in local transmission until December 2013 when autochthonous transmission was documented in the Caribbean island of St. Martin.[80] The etiologic virus, which belongs to the Asian genotype rather than the IOL, spread rapidly first amongst the islands of the Caribbean archipelago then on to the mainland Americas. As of 7 August, 2015 CHIKF cases were confirmed in 50 countries/territories in the Caribbean and mainland Americas with approximately 1.7 million suspected/confirmed cases since October 2013.[81]-[82] CHIKV belonging to the ECSA genotype was also recently documented in Brazil but has not been confirmed elsewhere in the Americas.[83]

Although CHIKF is rarely life-threatening, the symptoms can be severely incapacitating, rendering patients unable to perform normal tasks or go to work. As a result, particularly in immunologically naive populations where attack rates can be as high as 30-50% and the vast majority of infections are symptomatic, the disease burden, potential to overwhelm public health systems and indirect costs can be very significant.[84] Clinical overlap and confusion with other acute undifferentiated fevers e.g. dengue disease (which can be fatal) are additional concerns in affected regions.

The Caribbean twin-island Republic of Trinidad and Tobago reported its first cases of CHIKV infection in July 2014.[85] In this study, we report the genetic characterization of CHIKV and compare clinical, laboratory and epidemiological characteristics of patients with and without confirmed CHIKV or dengue virus infections who presented at a major hospital in Trinidad, during an acute undifferentiated febrile illness surveillance study.[86]

Epidemiology of chikungunya

Chikungunya is a mosquito-borne *alphavirus* that was first detected after a 1952 outbreak in Tanzania.[87] The virus has found in forested regions of sub-Saharan African in cycles involving nonhuman primate hosts and arboreal mosquito vectors. Phylogenetic studies show that the urban transmission cycle the transmission of a pathogen between humans and mosquitoes that exist in urban environments was established on multiple occasions from strains occurring on the eastern half of Africa in non-human primate hosts. This emergence and spread beyond Africa may have started as early as the 18th century. Currently, available data does notindicate whether the introduction of chikungunya into Asia occurred in the 19th century or after the 19th century, but this epidemic Asian strain causes outbreaks in India and

continues to circulate in Southeast Asia.[88]

A number of chikungunya outbreaks have occurred since 2005. An analysis of the chikungunya virus's genetic code shows that the increased severity of 2005--present outbreak may be due to a change in the genetic sequence, altering the virus' viral coat protein, which potentially permits it to multiply more easily in mosquito cells. The change allows the virus to use the Asian tiger mosquito (an invasive species) as a vector in addition to the more strictly tropical main vector, *Aedes aegypti*. In July 2006, a team analyzed the virus' RNA and determined the genetic changes that have occurred in various strains of the virus and identified those genetic sequences which led to the increased virulence of recent strains.

2005-06: Reunion

The largest outbreak of chikungunya ever recorded at the time occurred on the island of Réunion in the western rim of the Indian Ocean from late March 2005 to February 2006. At its height, the incidence peaked at about 25,000 cases per week or 3500 daily in early 2006. After an initial peak in May 2005, the incidence decreased and remained stable through the summer hemisphere winter, rising again at the beginning of October 2005. By mid-December, when Southern hemisphere summer temperatures are favorable for the mosquito vector, the incidence began to rise rapidly into the first two months of 2006. The number of reported cases was thought to be underestimated. The French government sent several hundred troops to help eradicate mosquitoes. Although confirmed cases were much lower, some estimates based on extrapolations from the number detected by sentinel physicians suggested that as many as 110,000 of Reunion's population of 800,000 people may have been infected. Twelve cases of meningoencephalitis cases were confirmed to be associated with chikungunya infection.

2006- India

In 2006, there was a large outbreak in India. States affected by the outbreak were Andhra Pradesh, Andaman & Nicobar Islands, Tamil Nadu, Karnataka, Maharashtra, Gujarat, Madhya Pradesh, Kerala, and Delhi. The initial cases were reported from Hyderabad and Secunderabad as well as from Anantpur district as early as November and December 2005 and are continued unabated. In Hyderabad alone, an average practitioner saw anywhere between 10 and 20 cases every day. Some deaths have been reported but it was thought to be due mainly to the inappropriate use of antibiotics and anti-inflammatory tablets. The major cause of mortality is due to severe dehydration, electrolyte imbalance and loss of glycemic control. Recovery is the rule except for about 3 to 5% incidence of prolonged arthritis. As this virus can cause thrombocytopenia, injudicious use of these drugs can cause erosions in the

gastric epithelium leading to exsanguinating upper GI bleed (due to thrombocytopenia). Also, the use of steroids for the control of joint pains and inflammation is dangerous and completely unwarranted. On average there are around 5,300 cases being treated every day. This figure is only from the public sector. The numbers from the private sector combined would be much higher.

There have been reports of a large scale outbreak of this virus in Southern India. At least 80,000 people in Gulbarga, Tumkur, Bidar, Raichur, Bellary, Chitradurga, Davanagere, Kolar and Bijapur districts in Karnataka state are known to have been affected since December 2005. A separate outbreak of chikungunya fever was reported from Malegaon town in Nasik district, Maharashtra state, in the first two weeks of March 2006, resulting in over 2000 cases. In Orissa state. at most 5000 cases of fever with muscle aches and headache were reported between February 27 and March 5, 2006.

2007: Italy

In September 2007, 130 cases were confirmed in the province of Ravenna, Northern Italy, in the contiguous towns of Castiglione di Cervia and Castiglione di Ravenna. One person died. The source of the outbreak was an Indian from Kerala, India.

2009: Thailand

By the end of September 2009, the Thai Ministry of Health reported more than 42,000 cases during the previous year in 50 provinces in the south of Thailand, including the popular tourist destination of Phuket. About 14 years had elapsed since the last appearance of the disease. In May 2009 the provincial hospital in Trang Province prematurely delivered a 6-year-old mate baby from his chikungunya-infected mother in the hopes of preventing mother-fetus virus transmission. After a cesarean delivery, the physicians discovered that he had also been infected with the chikungunya virus, and put him under intensive care. The child died from respiratorycomplications, possibly the only death from the outbreak, but the cause of death may not have been chikungunya since the child was delivered prematurely.

2011-15 Pacific Islands

Outbreaks in the Pacific Islands began in New Caledonia in 2011 and have since occurred in a number of Pacific countries. Fully 1/2 of the entire population of French Polynesia has come down with chikungunya Asian genotype (130,000 cases with 14 dead), exploding from a month earlier with 35,000 cases in December 2014; the first ever case was in 2013.

2012: Cambodia

An outbreak occurred in Cambodia with at least 1500 confirmed cases. Provinces for which

affection was confirmed were: Preah Vihear, Battambang, Kampong Thom. Kampong Chhnang, Kandal, Kampong Speu and Takeo.

2013-14: The Caribbean

In December 2013, it was confirmed that chikungunya was being locally transmitted in the Americas for the first time in the French Caribbean dependency of St. Martin, with 66 confirmed cases and suspected cases of around 181. It is the first time in the Americas that the disease has spread to humans from a population of infected mosquitoes.

By mid-January 2014. a number of cases had been confirmed in five countries: St. Martin, St. Barthelemy, Martinique, Guadeloupe, and the British Virgin Islands. At the start of April, at least ten nations had reported cases. By the start of May, there were more than 4,100 probable cases, and 31,000 suspected cases spanning 14 countries, including French Guiana, the only non-island nation with at least one reported case. On May 1, the Caribbean Public Health Agency (CARPHA) declared a Caribbean-wide epidemic of the virus.

2014: United States

On July 17, 2014, the first chikungunya case acquired in the United States was reported in Florida by the Centres for Disease Control and Prevention in a man who had not recently traveled outside the United States.Shortly after another case was reported of a person in Florida being infected by the virus, not having traveled outside the U.S.These were the first two cases where the virus was passed directly by mosquitoes to persons on the U.S. mainland. Aside from the locally acquired infections, there were 484 other cases reported in the United States as of 5 August 2014.

2014: Venezuela

In September 2014, the Central University of Venezuela stated that there could be between 65,000 and 1171,000 Venezuelans infected with chikungunya. Health Minister Nancy Perez stated that only 400 Venezuelans were infected with chikungunya.

2014: France

On October 20, 2014, 11 locally acquired cases of chikungunya were reported in Montpellier, Languedoc- Roussillon, in the South of France. Four hundred and forty nine imported cases of chikungunya were also reported throughout France during the period May—November 2014.

2014: Costa Rica

As of December 2014, Costa Rica had 47 reported cases of chikungunya, 40 of which originated abroad, while 7 were locally acquired.

2014: Brazil

On June 2014 six cases of the virus were confirmed in Brazil, two in the city of Campinas in the state of Sao Paulo. The six cases are Brazilian army soldiers who had recently returned from Haiti, where they were participating, in the reconstruction efforts as members of the United Nations Stabilisation Mission in Haiti. The information was officially released by Campinas municipality, which considers that it has taken the appropriate actions.

Nov 2014: Brazil has reported a local transmission of a different strain of chikungunya, that has never been documented in the Americas. This is an African genotype that was most likely introduced in Feira de Santana, Bahia state, from a returning traveler from Angola. The new genotype is more severe than the Asian genotype which is currently spreading through the Americas, and immunity to one genotype does not confer immunity to others. French Polynesia is among other regions experiencing ongoing outbreaks.

2014:El Salvador

On 25 September 2014, official authorities in El Salvador report over 30,000 confirmed cases of this new epidemic.

2014: Mexico

On 7 November 2014 Mexico reported an outbreak of chikungunya, acquired by local transmission, in the southern state of Chiapas. The outbreak extends across the coastline from the Guatemala border to the neighboring state of Oaxaca. Health authorities have reported a Cumulative load of 39 laboratory-confirmed cases (by the end of week 48). No suspected cases have been reported.

2014-2015: Colombia

The first cases were officially confirmed in July 2014. Between that month and the end of 20 as reported by the Colombian Health Institute Nacional de Salud - INS , there were 82,977 clinically confirmed cases and 611 cases confirmed through laboratory tests, bringing the total of through cases during 2014 in Colombia to 83.588. Seven of which led to deaths. These cases were reported in the following regions: Amazonas, AWntico, Arauca, Antioquia, Barranquilla, Bolivar, Boyaca, Caldas, Cartagena, Casanare, Cauca, Cesar, C6rdoba, Cundinamarca, Huila, La Guajira, Magdalena, Meta, Putumayo, NariFio, Norte de Santander, Sucre, Santander. Santa Marta, Risaralda, Tolima, San Andr6s and Valle del Cauca. According to news outlets, as of January 2015 at least one major city has issued sanitary alerts due to the expanding epidemic. By January 2015 the epidemic is considered to be in the initial expansion phase and it is expected by the Colombian National Health Institute Institute Nacional de Salud - INS) that the total number of cases will reach around 700,000 by the end of 2015 due to the in-country massive travel of tourists to and from regions where cases of

the disease have been confirmed and the vector *A. aegypti* is indigenous. It is expected that the disease will become endemic and sustain itself, with a pattern of outbreaks similar to dengue fever, due to the fact that both vector and natural reservoirs are indigenous in large areas of the country.

Conclusion

The arrival of CHIKV to the world will be a challenge to the public health system and a significant economic burden. The probability of autochthonous transmission in the rest of world is high due to the vector ubiquity. Economic development does not protect Countries from vector-borne diseases; modern lifestyles may amplify an epidemic through travel, Population aging, and production of solid waste that can shelter Aedes mosquitoes.

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