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Grillet, Maria E; Hernandez-Villena, Juan V; Llewellyn, Martin S; Paniz-Mondolfi, Alberto E; Tami, Adriana; Vincenti-Gonzalez, Maria F; Marquez, Marilianna; Mogollon-Mendoza, Adriana C; Hernandez-Pereira, Carlos E; Plaza-Morr, Juan D; +38 more... Blohm, Gabriella; Grijalva, Mario J; Costales, Jaime A; Ferguson, Heather M; Schwabl, Philipp; Hernandez-Castro, Luis E; Lamberton, Poppy HL; Streicker, Daniel G; Haydon, Daniel T; Miles, Michael A; Acosta-Serrano, Alvaro; Acquattela, Harry; Basanez, Maria G; Benaim, Gustavo; Colmenares, Luis A; Conn, Jan E; Espinoza, Raul; Freilij, Hector; Graterol-Gil, Mary C; Hotez, Peter J; Kato, Hirotomo; Lednicky, John A; Martinez, Clara E; Mas-Coma, Santiago; Morris, J Glen; Navarro, Juan C; Ramirez, Jose L; Rodriguez, Marlenes; Urbina, Julio A; Villegas, Leopoldo; Segovia, Maikell J; Carrasco, Hernan J; Crainey, James L; Luz, Sergio LB; Moreno, Juan D; Gonzalez, Oscar O Noya; Ramirez, Juan D; Alarcon-de Noya, Belkisyole; (2019) Venezuela's humanitarian crisis, resurgence of vector-borne diseases, and implications for spillover in the region. LANCET INFECTIOUS DISEASES, 19 (5). E149-E161. ISSN 1473-3099 DOI: https://doi.org/10.1016/S1473-3099(18)30757-6

DOI: https://doi.org/10.1016/S1473-3099(18)30757-6

Venezuela's humanitarian crisis, resurgence of vector-borne diseases and implications for spillover in the region: a review and a call for action.

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Summary

In recent years Venezuela has faced a severe economic crisis precipitated by political instability and declining oil revenue. Public health provision has suffered particularly. Herein, we assess the impact of Venezuela's healthcare crisis on vector-borne diseases and the spillover to neighbouring countries. Between 2000-2015 Venezuela witnessed a 365% increase malaria cases followed by a 68% increase (319,765 cases) in late 2017. Neighbouring countries such as Brazil have reported an escalating trend of imported cases from Venezuela from 1,538 (2014) to 3,129 (2017). Active Chagas disease transmission is reported with seroprevalence in children (<10 years) as high as 12.5% in one community tested (N=64). There has been a nine-fold rise in the mean incidence of dengue between 1990 to 2016. Estimated rates of chikungunya and Zika are 6,975 and 2,057 cases per 100,000 population, respectively, during their epidemic peaks. The re-emergence of many vector-borne diseases represents a public health crisis in Venezuela and has the possibility of severely undermining regional disease elimination efforts. National, regional and global authorities must take action to address these worsening epidemics and prevent their expansion beyond Venezuelan borders.

Structured Summary

Background:

In recent years Venezuela has faced a severe economic crisis precipitated by political instability and a significant reduction in oil revenue. Public health provision has suffered particularly. Long-term shortages of medicines and medical supplies and an exodus of trained personnel have occurred against the backdrop of a surge in vector-borne parasitic and arboviral infections. Herein, we aim to assess comprehensively the impact of Venezuela's healthcare crisis on vector-borne diseases and the spillover to neighbouring countries.

Methods

Alongside the on-going challenges affecting the healthcare system, health-indicator statistics have become increasingly scarce. Official data from the Ministry of Health, for example, are no longer available. To provide and update on vector-borne disease in Venezuela, this study used individualized data from nongovernmental organizations, academic institutions and professional colleges, various local health authorities and epidemiological surveillance programs from neighbouring countries, as well as data available through international agencies.

Findings

Between 2000-2015 Venezuela witnessed a 365% increase malaria cases followed by a 68% increase (319,765 cases) in late 2017. Neighbouring countries such as Brazil have reported an escalating trend of imported cases from Venezuelan from 1,538 (2014) to 3,129 (2017). Active Chagas disease transmission is reported with seroprevalence in children (<10 years) as high as 12.5% in one community tested (N=64). There has been a nine-fold rise in the mean incidence of dengue between 1990 to 2016. Estimated rates of chikungunya and Zika are 6,975 and 2,057 cases per 100,000 population, respectively, during their epidemic peaks.

Interpretation

The re-emergence of many arthropod-borne endemic diseases has set in place an epidemic of unprecedented proportions, not only in Venezuela but in the region. Data presented here demonstrates the complex determinants of this situation. National, regional and global authorities must take action to address these worsening epidemics and prevent their expansion beyond Venezuelan borders.

Search strategy and selection criteria

Malaria. Venezuela and Latin America data were sourced from PAHO Malaria Surveillance Indicators [Available from: http://ais.paho.org/phip/viz/malaria_surv_indicators_popup.asp] [cited 2018 May 05] and Observatorio Venezolano de la Salud / Documentos Oficiales [Available from: https://www.ovsalud.org/publicaciones/documentos-oficiales/] [cited 2018 May 05]. Data from Brazilian border state data were accessed via the Brazilian Ministry if Health, Sistema de Vigilância. Epidemiológica – Malária [Available from: http://200.214.130.44/sivep_malaria/] [cited 2018 May 05]. Data for Colombian cases was accessed via the Instituto Nacional de Salud. Estadísticas SIVIGILA 2017 [Available from: http://www.ins.gov.co/lineas-de-accion/Subdireccion-Vigilancia/sivigila/Estadsticas%20SIVIGILA/Forms/public.aspx]. [cited 2018 May 05].

Chagas. Data for Chagas Disease Oral cases in Venezuela originates from English and Spanish language literature and patient records at the Institute de Medicine Tropical, Caracas. Historical serological data for Chagas disease in Venezuela and elsewhere was sourced from the literature. Recent serological data are derived from unpublished records at the Instituto de Medicina Tropical, Universidad Central de Venezuela. Caracas, Venezuela and the Centro de Medicina Tropical de Oriente, Universidad de Oriente (UDO) Núcleo Anzoátegui, Barcelona, Venezuela. Data for vector abundance and infection rates (2014-2016) are also derived from unpublished records at the at the Instituto de Medicina Tropical, Universidad Central de Venezuela. Caracas, Venezuela. Data for Colombian cases was accessed via the Instituto Nacional de Salud. Estadísticas SIVIGILA 2017 [Available from: http://www.ins.gov.co/lineas-de-accion/Subdireccion-Vigilancia/sivigila/Estadsticas%20SIVIGILA/Forms/public.aspx]. [cited 2018 May 05].

Leishmaniasis. Human Cutaneous Leishmaniasis Data from 1990-2016 were sourced from the National Sanitary Dermatology programme of the Ministery of Health, available from the Venezuelan Health Observatory (https://www.ovsalud.org/publicaciones/documentos-oficiales/). Data for Colombian cases was accessed via the Instituto Nacional de Salud. Estadísticas SIVIGILA 2017 [Available from: http://www.ins.gov.co/lineas-de-accion/Subdireccion-Vigilancia/sivigila/Estadsticas%20SIVIGILA/Forms/public.aspx]. [cited 2018 May 05].

Arboviruses. For dengue, chikungunya and Zika, we used the number of cases reported and notified for the Surveillance System of the Venezuelan Ministry of Health at national level during the corresponding epidemics of 2014 and 2015, respectively. Source: Observatorio Venezolano de la Salud / Documentos Oficiales [Available from: https://www.ovsalud.org/publicaciones/documentos-oficiales/] [cited 2018 May 05]. Latin America data were sourced from PAHO Dengue Surveillance Indicators [Available from: https://www.paho.org/hq/index.php?option=com_topics&view=rdmore&cid=3274&Itemid=40734&lang=es] [cited 2018 May 05]

Introduction

Over the last two decades, Venezuela has transitioned into a deep socioeconomic and political crisis. Once recognized as a regional leader for public health and vector control policies and programming, Venezuela's healthcare has fallen into a state of collapse, creating a severe and ongoing humanitarian crisis with no end in sight.[1,2]

It is a well-known fact that states of political and civil unrest create conditions for the emergence and spread of infectious diseases[3]. Venezuela is no exception. With a decaying healthcare infrastructure, an exodus of trained medical personnel (a full medical professor earns <$10 US dollars a month), and the decline of all public health programs, the country is witnessing a surge and expansion of vector-borne diseases. The UN High Commission for Refugees (UNHCR) estimates that in the period of 2014-2018, 1.5 million Venezuelans have departed Venezuela for other countries throughout the Latin American and Caribbean region[4]. By March 2018, around 40,000 Venezuelan had been estimated to be residing in Brazil, whereas at least 600,000 people have sought shelter in Colombia[5,6]. Official data are likely underestimates given the existence of informal border crossings. Reports of disease spillover to neighbouring countries are increasing [7]

Disease surveillance and reporting has been equally impacted by Venezuela's healthcare crisis. Since 1938 the Venezuelan Ministry of Health uninterruptedly issued weekly and monthly epidemiological reports known as the "Boletín Epidemiológico". However, in 2007 it suffered a 20 week interruption, regaining its periodicity in November 2014 when it was shut down by the government [8]. More recently in June 2018 the Venezuelan Center for Classification of Diseases - a part of the Division of Epidemiology and Vital Statistics of the Ministry of Health- in charge of providing PAHO/WHO with updated morbidity and mortality indicators was eliminated by the government after 63 years of uninterrupted activity.[9]

Recently, the return of measles and other vaccine-preventable childhood infections in Venezuela has been highlighted by the Pan American Health Organization-World Health Organization[10]. Herein, we provide a comprehensive overview of the growing epidemics of the major vector-borne diseases - malaria, Chagas disease (CD), leishmaniasis and arboviral infections - in Venezuela and their ongoing spillover to neighbouring countries based on the limited data available. We examine the potential impact of such spillover and urge regional healthcare authorities to declare a public health emergency of hemispheric concern.

Malaria: a regional menace. Malaria, one of the most serious parasitic diseases of the tropics, is caused by species of the genus *Plasmodium* (Apicomplexa: Plasmodidae) and transmitted among humans by the bites of infected female *Anopheles* mosquitoes (Diptera: Culicidae). The World Health Organization (WHO) has established an ambitious plan for control and elimination of the disease by 2030, and Latin America has made significant advances to reach that goal, particularly from 2000 to 2015[11], when symptomatic disease declined by 62% (from 1,181,095 cases in 2000 to 451,242 in 2015) and malaria-related deaths by 61.2% (from 410 to 159). Nonetheless, in 2016 a considerable increase in case incidence (875,000) was reported in the region[12]. Venezuela accounted for 34.4% of the total reported cases in 2016 and has shown dramatic increases since 2000, and particularly since 2012 (**Figure 1a**).

During 2016, *Plasmodium vivax* accounted for 71% of reported cases of malaria in Venezuela, followed by *P. falciparum* (20%) and other *Plasmodium* infections (~ 9% of mixed and *P. malariae* cases)[12]. *Plasmodium vivax* cases in Venezuela increased from 62,850 in 2014 to 179,554 in 2016 (a 3-fold increase). By the end of 2017, this number had increased by 37% to 246,859[12]. Since 2017, numbers of mixed malaria infections have increased, with double (*P. falciparum* and *P. vivax*) and triple (*P. vivax, P. falciparum and P. malariae*) infections exhibiting higher than expected rates from the usual occurrence for each species, reflecting a high level of malaria transmission. Before 2003, malaria in Venezuela followed an endemo-epidemic pattern. Major incidence peaks occurred every 3-6 years in the two main malaria ecological regions, namely, the southern lowland rainforest and savannahs of Guayana, and the wetlands of the north-eastern coastal plains[13]. From 2003 onwards, the Guayana region, particularly the Sifontes Municipality, south-eastern Bolívar State (Figure 1b), became the highest risk area for malaria in the country[13,14]. In Sifontes, malaria incidence is positively correlated with an increase in illegal mining activities and forest exploitation. A complex pattern of limited, albeit persistent hot-spots of *Plasmodium* transmission is maintained principally by *Anopheles* (soon to be *Nyssorhynchus) darlingi* Root[15], *An. albitarsis* Lynch s.l. and *An. nuneztovari* Gabaldon s.l.[16,17], which show high natural parasite infection rates (4.0%, 5.4% and 0.5%, respectively).

It has been observed that clearing forests for mining activities creates favourable conditions for *An. darlingi* and *An. albitarsis* breeding[18]. An increase in illegal mining activities is likely to be strongly linked to the economic crisis. Highly mobile, often immunologically naïve, human populations migrate from different regions of the country to mining areas in search of economic opportunities. Once they arrive, they live outdoors, constantly exposed to mosquito bites. Many internal migrants return to past-endemic malaria regions where viable *Anopheles* vector populations exist, reintroducing malaria to areas where this infection had been previously eliminated. In addition, financial constraints generated by the current crisis have severely limited the procurement of malaria commodities (e.g., insecticides, drugs, diagnostic supplies, mosquito nets, etc.), and hampered epidemiological surveillance, reporting activities, vector-control and disease-treatment efforts[2,19]. Internal economic migration of miners and their families combined with a lack of provision and implementation of curative and prevention services previously provided by the state has created ideal conditions for malaria epidemics and increases in morbidity and mortality. Since 2014, local malaria transmission has reemerged in new areas of the country producing a significant change in the epidemiological landscape of this disease. Endemic malaria transmission is now beginning to propagate across the whole country, including urban and peri-urban foci, combined with an increase in hot-spots which persist in the Guayana region (**Figure 1b**). However, the numbers presented in Figure 1 are likely to represent an underestimate of the current situation as *P. vivax* case relapses are often not reported. Such cases are on the rise due to primaquine and chloroquine non-adherence as a result of antimalarial drugs stock-outs. Furthermore, recent findings have revealed that there are four asymptomatic carriers per symptomatic case with similar findings in Colombia and Brazil.[20]

The rapidly increasing malaria burden in Venezuela and the exodus of its citizens continues to impact neighbouring countries, particularly Brazil and Colombia. According to the Brazilian Ministry of Health, a total of 47,968 malaria cases were reported in the neighbouring Roraima State from 2014 to 2017 (**Figure 2**), of which around 20% (9,399) were imported from Venezuela. Numbers of such cases increased from 1538 (2014) to 3129 (2017). Figures from 2016 represent up to 45% and 86% of the reported malaria cases in the border municipalities of Pacaraima and Boa Vista, respectively (**Figure 2**). The continued upsurge of malaria in Venezuela could soon become uncontrollable; jeopardizing the hard-won gains of the malaria control programme in Brazil and other countries in the region. With 406,000 cases in 2017, Venezuela may now exhibit the largest malaria increase reported worldwide[7], threatening the successful implementation of the Global Malaria Action plan.[21]

Chagas Disease: persistent endemism and resurgence. Chagas disease (CD) is caused by the kinetoplastid parasite *Trypanosoma cruzi t*hat currently infects approximately six million people world-wide. CD is a complex zoonosis involving multiple mammal and blood sucking triatomine bug species [22]. Human infection with *T. cruzi* leads in approximately 40% of cases to severe and irreversible cardiac and intestinal pathology[23].CD has remained endemic in Venezuela since its first description in 1919. In the 1960s and 1970s seroprevalence was 43.9% overall, and 20.4% in young children (aged <10 years, a key indicator of active transmission)[24,25]. Efforts to interrupt CD transmission, alongside widespread insecticide use against malaria vectors, succeeded in reducing sero-prevalance to 9.2% and the geographical extent of transmission risk by 52% [26]. Seroprevalence among young children (0-10) was reduced to 0.5% between 1990-98[26]. Regrettably, the 1990s saw the national CD control program reduced and decentralised[26]. Moreover, CD control in Venezuela is hindered by the ecology of the principal vector, *Rhodnius prolixus*, which frequently invades and colonises rural houses from wild foci after insecticide spraying. Thus, even prior to the current economic crisis, Venezuela was at risk of resurgent CD. Since 2012, the surveillance and control of CD transmission in Venezuela have been abandoned. By piecing together unpublished data from several sources we can report herein multiple hotspots of new and active disease transmission.

In the Andes and Western Venezuela, CD is present throughout different states regardless of the geographical or climatic landscape. Seroprevalences obtained from three endemic communities (2014-2016) in Portuguesa States show considerable active transmission (12.5%, <10 years old, **Table S1**, **Figure 3a**). Also, house infestation indices were estimated to be as high as 24.8% in some hotspots at the time the CD control-program was dismantled[27]. Seroprevalences observed in Lara State in 2011 also suggest some active transmission (0.57%, <10 years old, Table S1, **Figure 3a**)[27-29]. Recent estimates for this and other western States are not available, however, CD may well be resurgent as no surveillance or preventative measures are in place. At the time of writing an outbreak of acute Chagas in Táchira State reported in the Colombian media had infected 40 people and claimed eight lives[30]. Eleven cases of ‘spillover’ acute disease in total were confirmed in Venezuelan nationals by the Colombian authorities in the last six months. In contrast to western Venezuela, in the 2000s, studies suggested that elimination of vectorial transmission of CD in eastern Venezuela was possible[26]. However, recent data reveals that active transmission is now present in Nueva Esparta State (2.5%, <10 years old, 2016, **Table S2, Figure 3a**), Anzoátegui State (8%, 11-20 years old, 2014, **Table S2, Figure 3a**) and Sucre State

(2%, 11-20 years old, 2012, Table S2). In Nueva Esparta, most seropositive subjects were among the young and the elderly – possibly reflecting the success of the former control program and current resurgence of the disease (**Table S2, Figure 3a**). Overall sero-prevalence among children from the data we report (4.3%, <10 years old, **Table S3**) indicates resurgent infection and resembles rate estimates from the 1970s[26]. However, our sample sizes are at least one order of magnitude lower than historical studies, although the serological approaches were similar (ELISA, IHA and FC). Nationally, seroprevalences over all age groups (15.7%, **Table S3**) exceed those in endemic provinces in Colombia (Boyaca, 2·2% 2007-09; Santander 0.2%, 2013-14[31]) as well as Ecuador (3.5%, Manabi, Loja, Guayas (2001-2003)[32] by a substantial margin. It is not clear whether blood banks are still being screened for CD in Venezuela, however in the current crisis it seems unlikely.

Oral CD transmission has also become an issue of great concern. Between 2007 and 2018 sixteen outbreaks of oral CD have been recorded nation-wide and ten have been managed through the outpatient clinic of the Institute of Tropical Medicine, Caracas ((**Table S4**, **Figure 3**)[33,34] The updated data are shown in Table S4 with 321 cases and 23 deaths in ten years. Such outbreaks have frequently been associated to consumption of artisan fruit juices contaminated with infected triatomines (especially the vector species *Panstrongylus geniculatus*) or their feces, exhibiting a severe clinical course and high mortality[35]. Urbanization and deforestation of wooded areas where the triatomines are present may also be contributing to this situation[2]. Half of these outbreaks have occurred in and around Caracas, though reports from other geographic regions are arising with many undiagnosed cases remaining unreported due to the non-specific signs and symptoms as well as physicians' unfamiliarity with the acute phase of the disease. Current severe drug shortages have forced patients to cross the borders in search of treatment and/or medical care in neighbouring countries. Moreover, the monitoring of these patients is essential because treatment with the only existing drugs (Benznidazole and Nifurtimox) is not totally effective, a situation exacerbated by the current low availability of these agents in Venezuela, as well as the medical personnel to administer them.[36]

Linked to several oral CD outbreaks in and around Caracas are increasing reports of peri-urban transmission of *T. cruzi* in Venezuela. This phenomenon was first reported in 2005 where 76.1% of the disease vector *Panstrongylus geniculatus* recovered from the Capital District and Miranda and Vargas states were naturally infected with *T. cruzi* and that 60.2% of their gut contents gave a positive reaction to human antiserum[37]. Ongoing collections between 2007-2016 has continued to reveal a preponderance of *P. geniculatus* (98.96%), as well as *Triatoma nigromaculata* (0.58%), *Triatoma maculata* (0.37%), *Rhodnius prolixus* (0.07%) and *Panstrongylus rufutuberculatus* (0.02%) (Figure 3b)[38]. Vector infection rates with *T. cruzi* over this period have been consistently high (75.7%). Intradomiciliary triatomine nymphs also present in 16 of the 32 parishes (3.42% of vectors captured) suggest active colonisation of houses by these insects. Preliminary molecular analysis of blood meals identify humans as by far the most common blood feeding source among insects collected 2007-2016. Furthermore, molecular epidemiological analyses clearly identify parasites from these peri-urban transmission cycles as the source of local oral outbreaks[39]. It is not known to what extent vectors are also transmitting parasites directly to human populations in the metropolitan district (i.e. not orally via contaminated food).

However, given high rates of feeding on humans, as well high infection levels, vectoral transmission remains a possibility despite the supposed low vectoral capacity of *P. geniculatus*[38].

Leishmaniasis: an early wake-up call. Leishmaniasis refers to a spectrum of diseases caused by a several trypanosomatid species belonging to the genus *Leishmania* (old and new world) and subgenus *Viania* (new world). *Leishmania* is transmitted via the bite of infected phlebotomine sandflies. In Venezuela, leishmaniasis is widely distributed, with most endemic zones located throughout the valleys of the coastal mountain range, the Yaracuy River basin (West), some areas of the central plains (Llanos) and the Andean mountain forests. Isolated endemic foci south of the Orinoco River in the Amazon basin have also been reported, but still remain to be fully characterized.[40]

As per data of the National Sanitary Dermatology programme of the Minister of Health, 61,576 cases of cutaneous leishmaniasis (CL) occurred between the period 1990-2016, with approximately 75% of the cases occurring in the States of Táchira, Mérida, Trujillo, Lara, Miranda and Sucre (**Figure 4a&b**). In recent years, leishmaniasis-endemic regions in Venezuela have expanded significantly, linked to ever-increasing trends towards urbanization, deforestation, environmental changes and the emergence of focal peri-urban transmission cycles as reported in several cities in the States of Lara and Trujillo.[40] There is nothing in the available data to suggest that the frequency of different clinical manifestations of CL (muco-cutaneous, disseminated and diffuse) – has been impacted by the crisis.

Visceral Leishmaniasis is prevalent in three endemic foci across Venezuela. The central foci that embraces the states of Guarico-Carabobo-Cojedes and Aragua, the western foci embracing Portuguesa, Lara and Trujillo; and the eastern foci which includes Sucre, Anzoategui and the insular state of Nueva Esparta [40]. Between 1961 and 1991 reports revealed the occurrence of 675 cases nationwide, however this may be an underestimate of the real situation. More recent sero-epidemiological surveys indicate that during 2004-2012, there was a prevalence of 14.8% amongst 15,822 dogs evaluated, with Lara and Guarico demonstrating the highest seroprevalence with most dogs (81%) showing no clinical signs[41] . It is possible that migratory trends may be contributing to the spread of the disease from its traditional endemic rural niches into peri-urban ecotopes where the presence of vectors (*Lutzomyia longipalpis* and *Lutzomyia evansi*) may aid the installment of new authoctonous foci[40].

The risk of *Leishmania* transmission has historically been influenced by migrations, refugee crises, wars and states of civil unrest, including cross-border movement of cases and notably in recent conflicts in Syria and Yemen.[42-44,34,35,36,37,38].[39]. Cross-border dispersal of *Leishmania* species from Venezuela is already occurring and several cases of VL and CL have been detected in Venezuelan migrants to Colombia in the last six months[45].

Arboviruses: an expanding threat. Viruses that are transmitted by arthropod vectors (arboviruses) have been expanding either steadily or in explosive (re)-emergent epidemics in recent years, posing a growing threat to global public health[46,47]. In the last four years, the two major epidemics that swept the American continent were caused by the chikungunya and Zika arboviruses[48]. Concomitantly, dengue, another arboviral disease endemic in the Latin American region, is increasing its spread to previously unaffected areas. All three arboviruses are transmitted by the same mosquito, *Aedes (Stegomya) aegypti* (L.), with a potential role for the invasive species *Ae. (Stegomya) albopictus* (Skuse) as well.

A member of the Flaviviridae family, dengue virus has become a major public health problem in Venezuela. Four dengue virus serotypes (DENV-1 to DENV-4) co-circulate in the country, each of them capable of causing the entire range of dengue-related disease symptoms. Infected individuals can be asymptomatic or present with clinical manifestations varying from mild febrile illness, to severe disease and death[49]. Venezuela is witnessing an upswing in incidence, frequency and magnitude of dengue epidemics against a background of perennial endemic transmission. Dengue incidence has leaped from an average of 39.5 cases per 100,000 population in the early 1990's to a 9-fold higher mean incidence of 368 cases per 100,000 population between 2010 and 2016 (**Figure 5a**). Within the country, the temporal increase in dengue cases mirrors the national dengue incidence with regions of higher population density (central regions) and those bordering Colombia and Brazil (border regions) exhibiting a higher incidence (**Figure 5b**). Worryingly, a total of six increasingly large epidemics were recorded nationally between 2007-2016 compared with four epidemics in the previous 16 years[50]. The largest occurred in 2010, when approximately 125,000 cases including 10,300 (8.6%) with severe manifestations were registered. During that year, Venezuela ranked third in the number of reported dengue cases in the American continent and second in the number of severe cases[51].

The combination of poverty-related socioeconomic factors, such as increasingly crowded living conditions, growing population density, precarious homes and long-lasting deficits in public services including frequent and prolonged interruptions in water supply and electricity have been linked with a greater risk of acquiring dengue infection in Venezuela[52–55]. These inadequacies have obliged residents to store water within households maintaining suitable breeding conditions for *Ae. aegypti* vectors during the dry season and throughout the year, driving perennial dengue transmission. Additionally, the failure of vector control programs has resulted in the proportion of houses infested with *Ae. aegypti* to surpass the WHO transmission threshold[56]. Such conditions set the stage for subsequent arboviral epidemics.

Venezuela was not spared from the havoc that the epidemics of chikungunya (in 2014) and Zika (a year later).. The impact of these epidemics was amplified by the lack of timely official information, lack of preparedness, and the worsening economic and health crisis resulting in acute shortages of diagnostics medicines and medical supplies, and an overburdened health system. Both epidemics rapidly spread through densely inhabited regions where dengue transmission is high. Although nationally, the attack rate of chikungunya was estimated to be between 6.9% and 13.8%[57], the observed attack rate in populated urban areas reached 40-50%, comparable or higher than that reported in other countries[58,59]. The total number of chikungunya cases in Venezuela reported to PAHO in 2014 (by epidemiological week 51) was 34,945, with an incidence of 121.5 per 100,000 population[60]. Given the paucity of official information since October 2014, estimates created based on excess fever cases not explained by another cause suggest that there were more than 2 million cases of chikungunya, resulting in an incidence of 6,975 cases per 100,000 population, more than 12 times the rate reported officially by the

Venezuelan Ministry of Health[57]. Moreover, an important, yet unknown, number of atypical and severe/fatal cases of chikungunya[61] occurred but were not reported by health personnel because of fear of governmental reprisal.[1,62]

In January 2016, the Zika epidemic struck Venezuela concomitantly with a rise in dengue transmission. The Zika outbreak evolved in a similar manner as chikungunya, rapidly affecting a high proportion of the population. Lack of preparedness and of official communication once again sparked alarm. The incidence of symptomatic cases during the peak of the epidemic was estimated at 2,057 cases per 100,000 population[63]. Current estimates of serologically (IgG) Zika positivity in pregnant women have reached roughly 80%. As in other countries, an increase in the number of cases of Guillain-Barré syndrome (GBS) was observed during the epidemic. However, Venezuela experienced a rise of 877% (9.8 times higher) in GBS incidence compared to the pre-Zika baseline incidence, one of the highest (if not the highest) reported in the Americas[64]. The number of GBS cases surged from a mean of 214 annual cases reported before Zika to more than 700 confirmed cases since the epidemic started[63]. Cases of microcephaly and other congenital disorders related to Zika infections in pregnancy in Venezuela have been reported, but the incidence remains to be determined by ongoing studies.

Beyond chikungunya, Zika and dengue viruses, other circulating arboviruses with epidemic potential exist in Venezuela. Mayaro has caused recent outbreak[65,66] and is often confused with chikungunya. Oropouche (Madre de Dios virus, outbreak in Perú, 2016) was recently detected in the Llanos of Venezuela, outside its typical distribution zone[67]. The occurrence of cryptic transmission cycles and cases due to epizootic strains of Venezuelan Equine Encephalitis and Madariaga virus (South American Eastern Equine Encephalitis)[68] when immunization programs have been halted pose a further threat. No facilities exist for rapid laboratory diagnosis for either virus in Venezuela.[69] The most common and effective VEE vaccine, TC-83, can longer be bought or produced in the Venezuela. The Agricultural Research Institute (INIA), with limited production capacity, has no financial support and production is paralyzed. Although there are no reliable official records of equine inventories, wild donkeys without owners and without sanitary control, and persistent circulation of epizootic VEE strains in inter-epizootic periods in different sites of the plains and the Catatumbo region, increases the threat of latent outbreaks and their potential international dispersal.[70]

The whole of Latin America is experiencing increased risks and outbreaks associated with arboviruses. Although there is currently no evidence to suggest that the prevalence of certain arboviruses like dengue is higher in Venezuela than in other countries (Figure 5a), the lack of public health infrastructure available for diagnosis and treatment is now a disproportionate problem in Venezuela compared with other countries in the region. Furthermore, given the current situation, widespread underreporting of cases by comparison to other countries in the region is also possible. The lower incidence and lack of parallel increase after 2013 of dengue in Venezuela compared to Colombia and Brazil, for example (Figure 5a), strongly suggest chronic underreporting. In light of the precarious possibilities for cure in Venezuela combined with the high level of population displacement, emigrating infected individuals could be unwittingly causing a spillover of arboviral diseases to neighbouring countries, a process that has not yet been quantified. The first major outbreak of dengue on the island of Madeira in 2012-2013 is an example of the disease export potential of Venezuela, as this outbreak was directly linked with a DENV-1 serotype from Venezuela.[71]

A call for action.

For many decades, Venezuela was a leader in vector control and public health policies in Latin America, even more so after becoming the first WHO-certified country to eliminate malaria in most of its territory in 1961[72]. The interruption of malaria transmission was achieved through systematic and integrative infection and vector control, case management, preventive diagnosis, patient treatment, mass drug administration, community participation through volunteer community health workers and sanitary engineering such as housing improvement and water management. This integrative approach differs little from current 'best-practice' prevention, control and elimination of malaria. Indeed, the success Venezuelan public health intervention helped to stimulate interest in global malaria elimination during the 1960s[72].

Paradoxically, the onchocerciasis (a vector-borne helminth infection) elimination program in Venezuela has continued to work reasonably well. The program's success is underpinned by the commitment and resolve of its Venezuelan local health workers and indigenous health agents and under the regional support of the Onchocerciasis Elimination Program for the Americas (OEPA)[2]. As a result of long-term Mass Drug Administration (MDA) with ivermectin (labeled as Mectizan®; Merck & Co., Inc., Kenilworth, NJ, USA) on a biannual (and four times per year) basis starting in 2000, interruption of onchocerciasis has been achieved among the northern foci located in the coastal mountain area[73], and parasite transmission now remains in just 25% of the Venezuelan Yanomami southern Amazonian region[74]. This regional initiative has proven that the consensus of ministries of health, the endemic communities, non-governmental organizations, and public-private stakeholders, including the WHO, is required to develop and implement effective public health programs[2,72].

Venezuelans have endured a decade of political, social, and economic upheaval that has left a country in crisis. In addition to a return of measles and other vaccine-preventable infectious diseases, conditions are favouring the unprecedented emergence and transmission of vector borne diseases. Underpinning the current epidemic(s) is a lack of surveillance, a lack of education and awareness, and a lack of capacity for effective intervention. Successful control of the emerging crisis requires regional coordination and, as we demonstrate in this report, cross-border spillover is already ongoing, and expected to increase.

Fortunately, many solutions are within reach, even with limited resources. A good example is the recent successful bi-national strategy for the elimination of malaria on the Peru-Ecuador border. Collaboration at the operational level that included strengthening surveillance, community personnel trained to collect blood smears from febrile persons within their border communities, prompt effective diagnosis, case definition (indigenous, imported, introduced, induced, cryptic), and treatment[75]. Where state infrastructure fails, however, surveillance can be achieved via the mobilisation of citizen scientists and informal networks of healthcare professionals. Technological advances in low-cost sample preservation, passive sampling and *in situ* diagnostics can also contribute. Education to raise awareness among communities at risk from disease can be achieved via social media, initiatives at schools and information campaigns at public centers. Surveillance data are power and must be used as an advocacy tool to raise awareness among Venezuelan and regional authorities, and ultimately better allow them to recognise the growing crisis, cooperate, and accept international medical interventions. Relevant international health authorities such as the WHO Global Outbreak Alert and Response Network (GOARN) must also move towards maintaining accurate disease surveillance and response systems in the region along with collaboration with other strategic partners in order to provide timely humanitarian assistance throughout this ongoing crisis. The wider scientific community must support this process by engaging with their Venezuelan and regional colleagues, contributing to a robust, non-partisan evidence base for such interventions. Ultimately national and international political commitments are essential to stop a health crisis that threatens the whole region.

It must be recognized that the emergence or re-emergence of vector-borne neglected diseases is now extending beyond the borders of Venezuela. We have already seen how these diseases have extended into neighbouring Brazil and Colombia, but with increasing air travel and human migrations, the entire Latin American and Caribbean region is at heightened risk for disease re-emergence, as well as some US cities hosting the Venezuelan diaspora, including Miami and Houston. Accordingly, we call on the members of the Organization of American States (OAS) and other international political bodies to become better and more effectively engaged in strengthening Venezuela's now depleted health system by applying more pressure to the government to accept humanitarian assistance offered by the international communuty[2]. Without such international interventions there is a real possibility that public health gains achieved over the last 18 years through Millennium Development Goal 6 ("to combat AIDS, malaria, and other diseases") and the new Sustainable Development Goals could be soon reversed.

Figure Legends:

Figure 1. (a) Number of confirmed malaria cases (line) and Annual parasite incidence (API: No. of confirmed malaria cases/1,000 inhabitants, bars) in Venezuela from 2000 to 2016 (inset left: map of Venezuela (red) in South America, inset right: case comparison of annual incidence (Y-axis) for Colombia, Brazil & Venezuela). Temporal pattern of incidence indicates an exponential increasing trend (R^2= 0.78, P = 1.07x10^{-5}, N=18) in Venezuela. **(b) API for each municipality in Venezuela during 2016**

Figure 2. Map of malaria cases reported in Eastern Venezuela and neighbouring Brazilian Roraima state in Brazil (a) 2014, **(b)** 2015, **(c)** 2016. For Roraima state, maps indicate autochthonous (A) and imported (I) confirmed malaria cases coming from Venezuela.

Figure 3 (a) Update on the distribution of Chagas disease human seroprevalance data and sites of oral outbreaks in Venezuela. States for which data are available are coloured by percent overall seroprevalence (left to right: Nueva Esparta, Sucre, Anzoátegui, Guárico and Portuguesa). Pie charts indicate infection among different age classes. Blue diamonds indicate sites of reported oral outbreaks. (b) **Distribution of peri-urban vectors and *Trypanosoma cruzi* infection status around Caracas.** Upper map and legend detail details count data for triatomines brought to clinic at the Insitito de Medicine Tropical 2007-2016, by municipality. Lower map and legend show *T. cruzi* infection prevalence (%) in the same vectors.

Figure 4. (a) **Number of confirmed cases (line) and Annual cutaneous leishmaniasis incidence per 100,00 inhabitants (bars) in Venezuela from 2006 to 2016**. (b) **Incidence heatmap of cutaneous leishmaniasis by State per 100,000 inhabitants for the 2006-2016 period** (increasing from blue to red).

Figure 5. (a) Annual dengue incidence (per 100,000 inhabitants) for the 1991-2016 period. Black vertical arrows indicate dengue epidemic years (inset: comparison of incidence data (Y-axis) for Colombia, Brazil & Venezuela). Dotted black line indicates an increasing linear trend (R^2= 0.27, t=2.99, P = 0.006, N=26). **(b) Heatmap showing the annual dengue incidence (increasing from blue to red) per State in Venezuela from 1991 to 2016.**

Acknowledgements

This work was supported in part by the Scottish Funding Council GCRF Small Grants Fund, SFC/AN/12/2017. The authors would like to dedicate this work to the memory of Xoan Noya Alarcon.

Conflict of Interest

We declare that we have no conflicts of interest.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication

Contributions

All authors were involved with writing the manuscript and/or data analysis and figure preparation.

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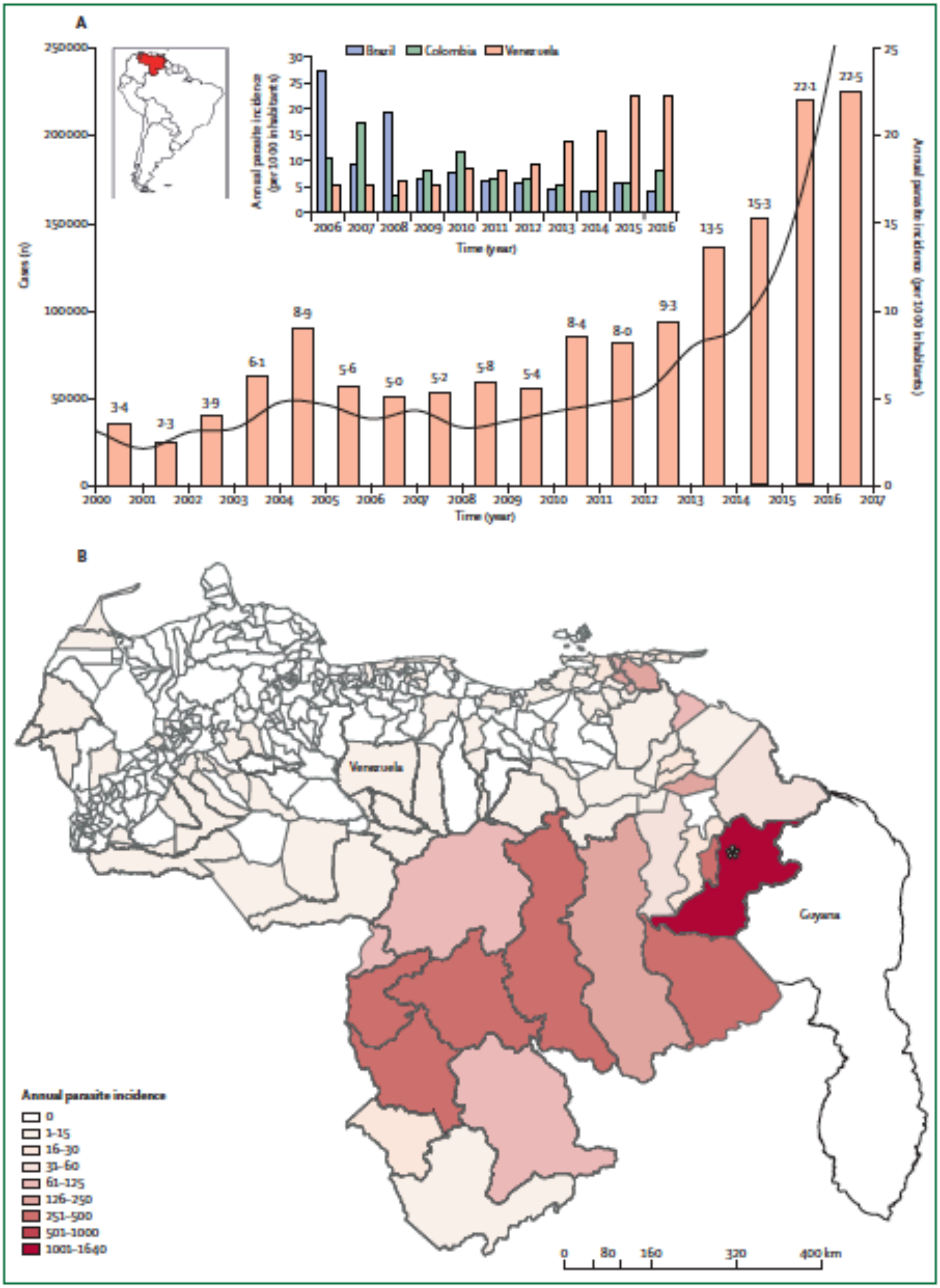
A
B
250000
200000
150000
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Cases (n)
Annual parasite incidence (per 1000 inhabitants)
25
20
15
10
5
0
3·4
2·3
3·9
6·1
8·9
5·6
5·0
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5·8
5·4
8·4
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2000
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Time (year)
Brazil
Colombia
Venezuela
30
25
20
15
10
5
0
Annual parasite incidence (per 1000 inhabitants)
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Time (year)
Venezuela
Guyana
Annual parasite incidence
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0
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160
320
400 km

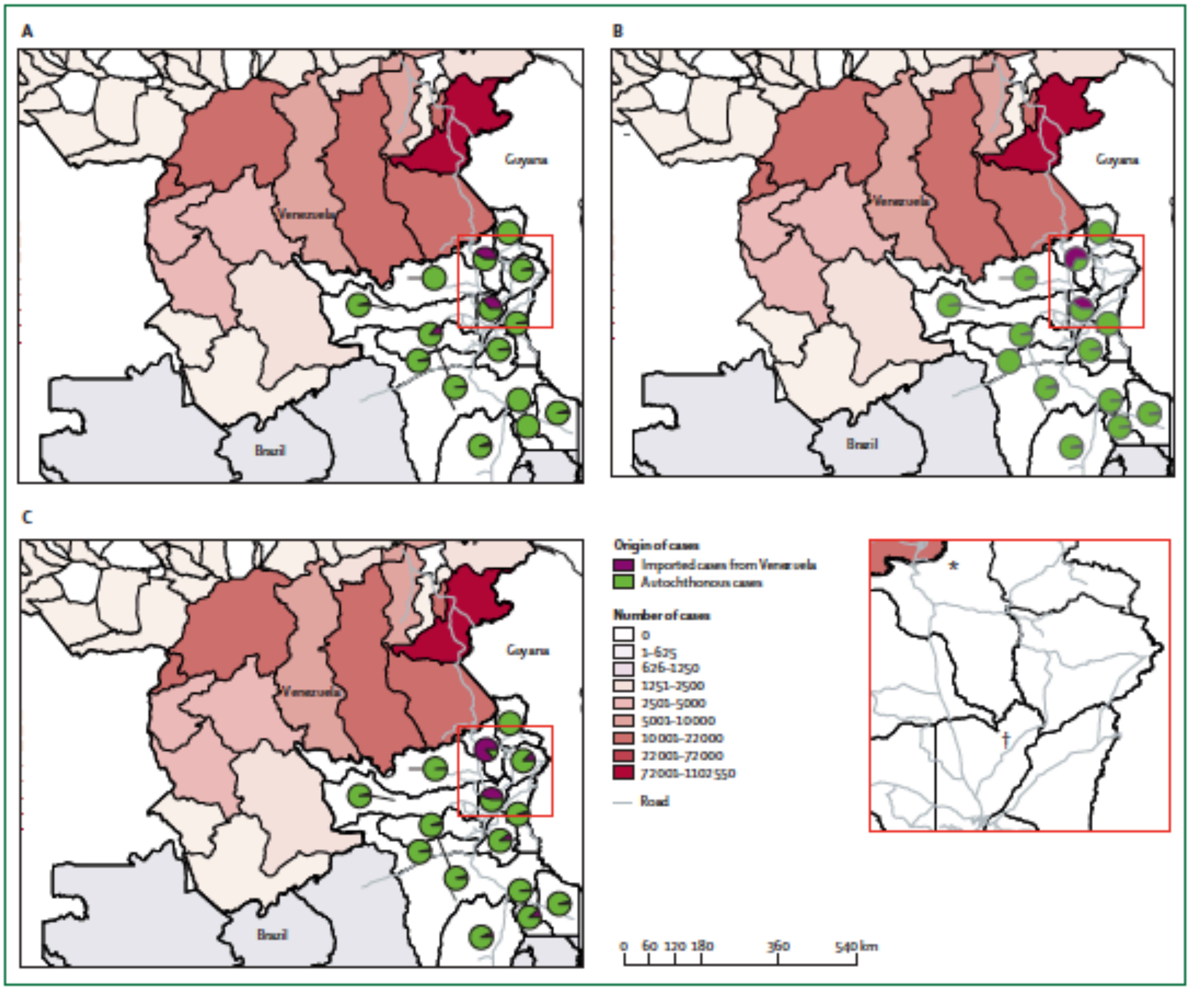

Figure 2: Malaria cases reported in eastern Venezuela and neighbouring Roraima State, Brazil
(A) 2014, (B) 2015, and (C) 2016. Pie charts indicate origin of cases. Inset shows the locations of Pacaraima and Boa Vista. *Pacaraima. †Boa Vista.

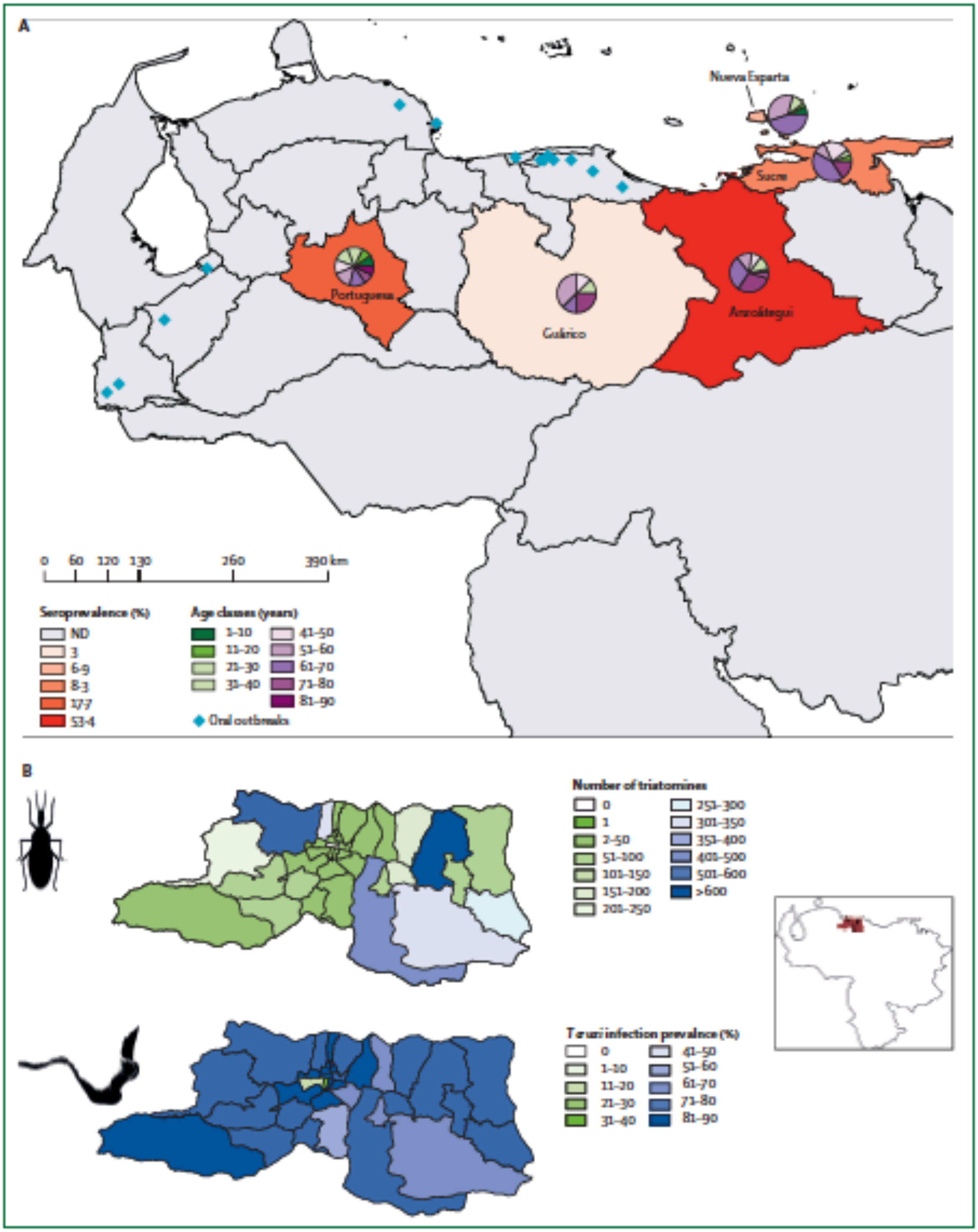

Figure 3: Chagas disease and *Trypanosoma cruzi* distribution in Venezuela

(A) Update on the distribution of Chagas disease human seroprevalance data and sites of oral outbreaks in Venezuela. States for which data are available are coloured by percentage overall seroprevalence. Pie charts indicate infection among different age classes. Blue diamonds indicate sites of reported oral outbreaks. (B) Distribution of peri-urban vectors and *T cruzi* infection status around Caracas. Upper map shows data for triatomines brought to the clinic at the Insituto de Medicine Tropical, Caracas, Venezuela, in 2007–16 by municipality. Lower map shows *T cruzi* infection prevalence (%) in the same vectors. Inset shows locations of sampled neighbourhoods in Venezuela. ND=no data available.

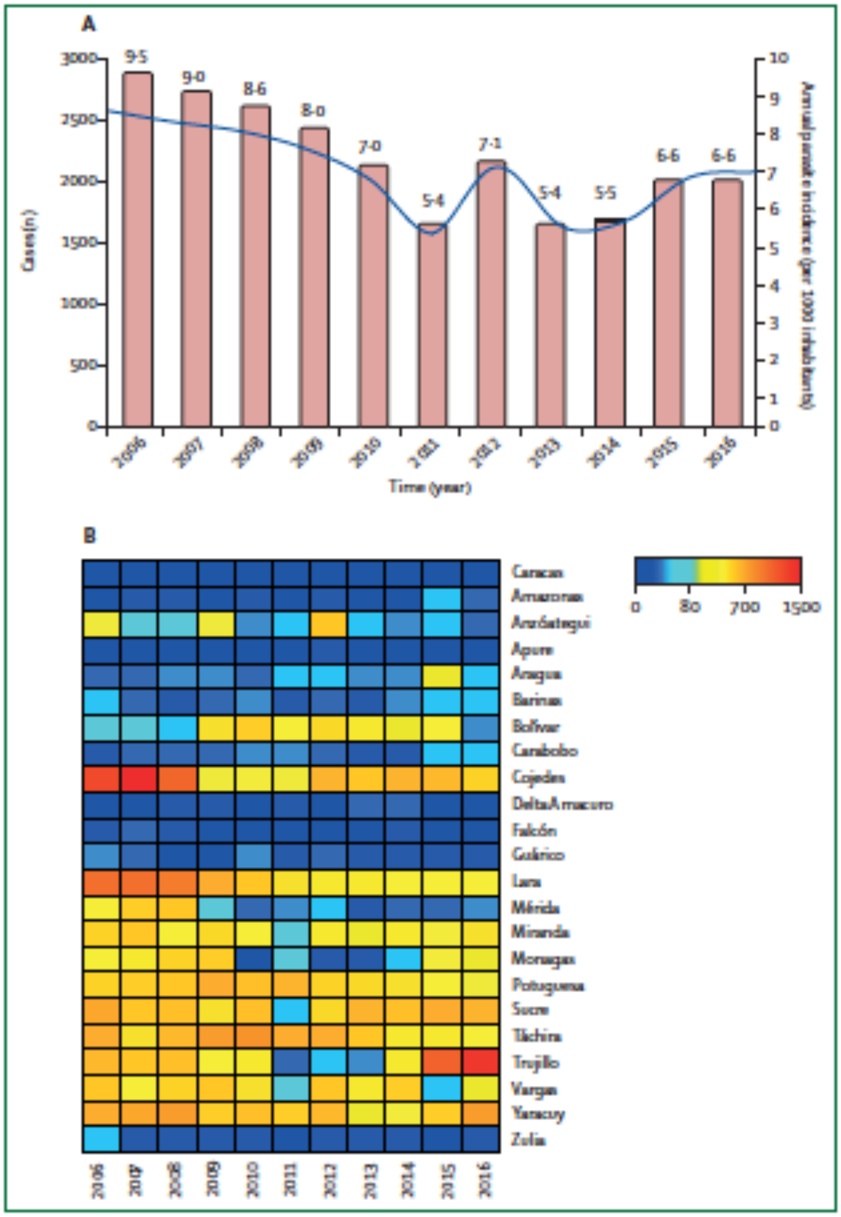

Figure 4: Annual parasite incidence and confirmed cases of cutaneous leishmaniasis in Venezuela
(A) Number of confirmed cases (line) and annual incidence per 100 000 inhabitants (bars) in Venezuela, 2006–16. (B) Annual parasite incidence by state per 100 000 inhabitants for 2006–16 (increasing from blue to red).

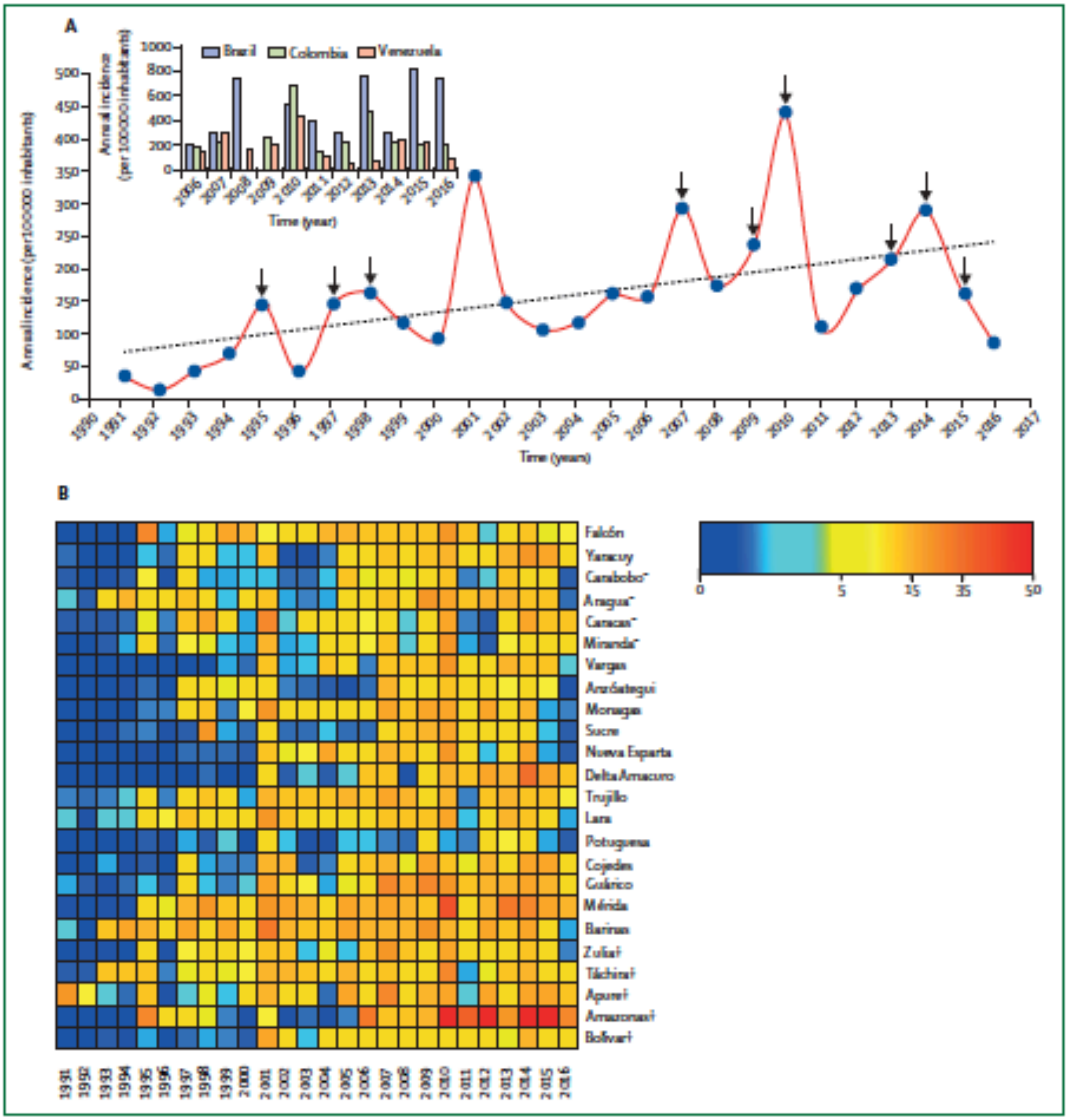

Figure 5: Annual incidence of dengue in Venezuela

(A) Annual dengue incidence (per 100 000 inhabitants) for the 1991–2016 period. Black vertical arrows indicate dengue epidemic years. Dotted black line indicates an increasing linear trend (R^2=0·27, t=2·99, p=0·006, n=26). Inset shows comparison of incidence data for Colombia, Brazil, and Venezuela. (B) Annual incidence by state per 100 000 inhabitants from 1991 to 2016 (increasing from blue to red). * Central region. †Border region.