

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

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4 Working group on vector-borne diseases in Venezuela

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7 **Corresponding author:**

8 Dr. Martin Llewellyn, PhD

9 Institute of Biodiversity, Animal Health and Comparative Medicine, University of  
10 Glasgow, Glasgow, Scotland, United Kingdom

11 Phone - 00441413305571

12 [martin.Llewellyn@glasgow.ac.uk](mailto:martin.Llewellyn@glasgow.ac.uk)

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17 **Summary**

18 In recent years Venezuela has faced a severe economic crisis precipitated by political instability  
19 and declining oil revenue. Public health provision has suffered particularly. Herein, we assess the  
20 impact of Venezuela’s healthcare crisis on vector-borne diseases and the spillover to  
21 neighbouring countries. Between 2000-2015 Venezuela witnessed a 365% increase malaria cases  
22 followed by a 68% increase (319,765 cases) in late 2017. Neighbouring countries such as Brazil  
23 have reported an escalating trend of imported cases from Venezuela from 1,538 (2014) to 3,129  
24 (2017). Active Chagas disease transmission is reported with seroprevalence in children (<10  
25 years) as high as 12.5% in one community tested (N=64). There has been a nine-fold rise in the  
26 mean incidence of dengue between 1990 to 2016. Estimated rates of chikungunya and Zika are  
27 6,975 and 2,057 cases per 100,000 population, respectively, during their epidemic peaks. The re-  
28 emergence of many vector-borne diseases represents a public health crisis in Venezuela and has  
29 the possibility of severely undermining regional disease elimination efforts. National, regional  
30 and global authorities must take action to address these worsening epidemics and prevent their  
31 expansion beyond Venezuelan borders.

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56 **Structured Summary**

57 **Background:**

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

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65 **Methods**

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

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73 **Findings**

74 Between 2000-2015 Venezuela witnessed a 365% increase malaria cases followed by a 68%  
75 increase (319,765 cases) in late 2017. Neighbouring countries such as Brazil have reported an  
76 escalating trend of imported cases from Venezuelan from 1,538 (2014) to 3,129 (2017). Active  
77 Chagas disease transmission is reported with seroprevalence in children (<10 years) as high as  
78 12.5% in one community tested (N=64). There has been a nine-fold rise in the mean incidence of  
79 dengue between 1990 to 2016. Estimated rates of chikungunya and Zika are 6,975 and 2,057  
80 cases per 100,000 population, respectively, during their epidemic peaks.

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82 **Interpretation**

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

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97 **Search strategy and selection criteria**

98 **Malaria.** Venezuela and Latin America data were sourced from PAHO Malaria Surveillance  
99 Indicators [Available from: [http://ais.paho.org/hip/viz/malaria\\_surv\\_indicators\\_popup.asp](http://ais.paho.org/hip/viz/malaria_surv_indicators_popup.asp)]  
100 [cited 2018 May 05] and Observatorio Venezolano de la Salud / Documentos Oficiales  
101 [Available from: <https://www.ovsalud.org/publicaciones/documentos-oficiales/>] [cited 2018 May  
102 05]. Data from Brazilian border state data were accessed via the Brazilian Ministry of Health,  
103 Sistema de Vigilância Epidemiológica – Malária [Available from:  
104 [http://200.214.130.44/sivep\\_malaria/](http://200.214.130.44/sivep_malaria/)] [cited 2018 May 05]. Data for Colombian cases was  
105 accessed via the Instituto Nacional de Salud. Estadísticas SIVIGILA 2017 [Available from:  
106 [http://www.ins.gov.co/lineas-de-accion/Subdireccion-](http://www.ins.gov.co/lineas-de-accion/Subdireccion-Vigilancia/sivigila/Estadsticas%20SIVIGILA/Forms/public.aspx)  
107 [Vigilancia/sivigila/Estadsticas%20SIVIGILA/Forms/public.aspx](http://www.ins.gov.co/lineas-de-accion/Subdireccion-Vigilancia/sivigila/Estadsticas%20SIVIGILA/Forms/public.aspx)]. [cited 2018 May 05].

108 **Chagas.** Data for Chagas Disease Oral cases in Venezuela originates from English and Spanish  
109 language literature and patient records at the Institute de Medicine Tropical, Caracas. Historical  
110 serological data for Chagas disease in Venezuela and elsewhere was sourced from the literature.  
111 Recent serological data are derived from unpublished records at the Instituto de Medicina  
112 Tropical, Universidad Central de Venezuela. Caracas, Venezuela and the Centro de Medicina  
113 Tropical de Oriente, Universidad de Oriente (UDO) Núcleo Anzoátegui, Barcelona, Venezuela.  
114 Data for vector abundance and infection rates (2014-2016) are also derived from unpublished  
115 records at the at the Instituto de Medicina Tropical, Universidad Central de Venezuela. Caracas,  
116 Venezuela. Data for Colombian cases was accessed via the Instituto Nacional de Salud.  
117 Estadísticas SIVIGILA 2017 [Available from: [http://www.ins.gov.co/lineas-de-](http://www.ins.gov.co/lineas-de-accion/Subdireccion-Vigilancia/sivigila/Estadsticas%20SIVIGILA/Forms/public.aspx)  
118 [accion/Subdireccion-Vigilancia/sivigila/Estadsticas%20SIVIGILA/Forms/public.aspx](http://www.ins.gov.co/lineas-de-accion/Subdireccion-Vigilancia/sivigila/Estadsticas%20SIVIGILA/Forms/public.aspx)]. [cited  
119 2018 May 05].

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

126 **Arboviruses.** For dengue, chikungunya and Zika, we used the number of cases reported and  
127 notified for the Surveillance System of the Venezuelan Ministry of Health at national level  
128 during the corresponding epidemics of 2014 and 2015, respectively. Source: Observatorio  
129 Venezolano de la Salud / Documentos Oficiales [Available from:  
130 <https://www.ovsalud.org/publicaciones/documentos-oficiales/>] [cited 2018 May 05]. Latin  
131 America data were sourced from PAHO Dengue Surveillance Indicators [Available from:  
132 [https://www.paho.org/hq/index.php?option=com\\_topics&view=rdmore&cid=3274&Itemid=407](https://www.paho.org/hq/index.php?option=com_topics&view=rdmore&cid=3274&Itemid=40734&lang=es)  
133 [34&lang=es](https://www.paho.org/hq/index.php?option=com_topics&view=rdmore&cid=3274&Itemid=40734&lang=es)] [cited 2018 May 05]

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141 **Introduction**

142

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

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148 It is a well-known fact that states of political and civil unrest create conditions for the emergence  
149 and spread of infectious diseases<sup>3</sup>. Venezuela is no exception. With a decaying healthcare  
150 infrastructure, an exodus of trained medical personnel (a full medical professor earns <\$10 US  
151 dollars a month), and the decline of all public health programs, the country is witnessing a surge  
152 and expansion of vector-borne diseases. The UN High Commission for Refugees (UNHCR)  
153 estimates that in the period of 2014-2018, 1.5 million Venezuelans have departed Venezuela for  
154 other countries throughout the Latin American and Caribbean region<sup>4</sup>. By March 2018, around  
155 40,000 Venezuelan had been estimated to be residing in Brazil, whereas at least 600,000 people  
156 have sought shelter in Colombia<sup>5,6</sup>. Official data are likely underestimates given the existence of  
157 informal border crossings. Reports of disease spillover to neighbouring countries are increasing<sup>7</sup>

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159 Disease surveillance and reporting has been equally impacted by Venezuela's healthcare crisis.  
160 Since 1938 the Venezuelan Ministry of Health uninterruptedly issued weekly and monthly  
161 epidemiological reports known as the "Boletín Epidemiológico". However, in 2007 it suffered a  
162 20 week interruption, regaining its periodicity in November 2014 when it was shut down by the  
163 government<sup>8</sup>. More recently in June 2018 the Venezuelan Center for Classification of Diseases -  
164 a part of the Division of Epidemiology and Vital Statistics of the Ministry of Health- in charge of  
165 providing PAHO/WHO with updated morbidity and mortality indicators was eliminated by the  
166 government after 63 years of uninterrupted activity.<sup>9</sup>

167

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

175

176 **Malaria: a regional menace.** Malaria, one of the most serious parasitic diseases of the  
177 tropics, is caused by species of the genus *Plasmodium* (Apicomplexa: Plasmodiidae) and  
178 transmitted among humans by the bites of infected female *Anopheles* mosquitoes  
179 (Diptera: Culicidae). The World Health Organization (WHO) has established an ambitious plan  
180 for control and elimination of the disease by 2030, and Latin America has made significant  
181 advances to reach that goal, particularly from 2000 to 2015<sup>11</sup>, when symptomatic disease  
182 declined by 62% (from 1,181,095 cases in 2000 to 451,242 in 2015) and malaria-related deaths  
183 by 61.2% (from 410 to 159). Nonetheless, in 2016 a considerable increase in case incidence  
184 (875,000) was reported in the region<sup>12</sup>. Venezuela accounted for 34.4% of the total reported

185 cases in 2016 and has shown dramatic increases since 2000, and particularly since 2012 (**Figure**  
186 **1a**).

187  
188 During 2016, *Plasmodium vivax* accounted for 71% of reported cases of malaria in Venezuela,  
189 followed by *P. falciparum* (20%) and other *Plasmodium* infections (~ 9% of mixed and *P.*  
190 *malariae* cases)<sup>12</sup>. *Plasmodium vivax* cases in Venezuela increased from 62,850 in 2014 to  
191 179,554 in 2016 (a 3-fold increase). By the end of 2017, this number had increased by 37% to  
192 246,859<sup>12</sup>. Since 2017, numbers of mixed malaria infections have increased, with double (*P.*  
193 *falciparum* and *P. vivax*) and triple (*P. vivax*, *P. falciparum* and *P. malariae*) infections  
194 exhibiting higher than expected rates from the usual occurrence for each species, reflecting a  
195 high level of malaria transmission. Before 2003, malaria in Venezuela followed an endemo-  
196 epidemic pattern. Major incidence peaks occurred every 3-6 years in the two main malaria  
197 ecological regions, namely, the southern lowland rainforest and savannahs of Guayana, and the  
198 wetlands of the north-eastern coastal plains<sup>13</sup>. From 2003 onwards, the Guayana region,  
199 particularly the Sifontes Municipality, south-eastern Bolívar State (Figure 1b), became the  
200 highest risk area for malaria in the country<sup>13,14</sup>. In Sifontes, malaria incidence is positively  
201 correlated with an increase in illegal mining activities and forest exploitation. A complex pattern  
202 of limited, albeit persistent hot-spots of *Plasmodium* transmission is maintained principally by  
203 *Anopheles* (soon to be *Nyssorhynchus*) *darlingi* Root<sup>15</sup>, *An. albitarsis* Lynch s.l. and *An.*  
204 *nuneztovari* Gabaldon s.l.<sup>16,17</sup>, which show high natural parasite infection rates (4.0%, 5.4% and  
205 0.5%, respectively).

206  
207 It has been observed that clearing forests for mining activities creates favourable conditions for  
208 *An. darlingi* and *An. albitarsis* breeding<sup>18</sup>. An increase in illegal mining activities is likely to be  
209 strongly linked to the economic crisis. Highly mobile, often immunologically naïve, human  
210 populations migrate from different regions of the country to mining areas in search of economic  
211 opportunities. Once they arrive, they live outdoors, constantly exposed to mosquito bites. Many  
212 internal migrants return to past-endemic malaria regions where viable *Anopheles* vector  
213 populations exist, reintroducing malaria to areas where this infection had been previously  
214 eliminated. In addition, financial constraints generated by the current crisis have severely limited  
215 the procurement of malaria commodities (e.g., insecticides, drugs, diagnostic supplies, mosquito  
216 nets, etc.), and hampered epidemiological surveillance, reporting activities, vector-control and  
217 disease-treatment efforts<sup>2,19</sup>. Internal economic migration of miners and their families combined  
218 with a lack of provision and implementation of curative and prevention services previously  
219 provided by the state has created ideal conditions for malaria epidemics and increases in  
220 morbidity and mortality. Since 2014, local malaria transmission has reemerged in new areas of  
221 the country producing a significant change in the epidemiological landscape of this disease.  
222 Endemic malaria transmission is now beginning to propagate across the whole country, including  
223 urban and peri-urban foci, combined with an increase in hot-spots which persist in the Guayana  
224 region (**Figure 1b**). However, the numbers presented in Figure 1 are likely to represent an  
225 underestimate of the current situation as *P. vivax* case relapses are often not reported. Such cases  
226 are on the rise due to primaquine and chloroquine non-adherence as a result of antimalarial drugs  
227 stock-outs. Furthermore, recent findings have revealed that there are four asymptomatic carriers  
228 per symptomatic case with similar findings in Colombia and Brazil.<sup>20</sup>

229

230 The rapidly increasing malaria burden in Venezuela and the exodus of its citizens continues to  
231 impact neighbouring countries, particularly Brazil and Colombia. According to the Brazilian  
232 Ministry of Health, a total of 47,968 malaria cases were reported in the neighbouring Roraima  
233 State from 2014 to 2017 (**Figure 2**), of which around 20% (9,399) were imported from  
234 Venezuela. Numbers of such cases increased from 1538 (2014) to 3129 (2017). Figures from  
235 2016 represent up to 45% and 86% of the reported malaria cases in the border municipalities of  
236 Pacaraima and Boa Vista, respectively (**Figure 2**). The continued upsurge of malaria in  
237 Venezuela could soon become uncontrollable; jeopardizing the hard-won gains of the malaria  
238 control programme in Brazil and other countries in the region. With 406,000 cases in 2017,  
239 Venezuela may now exhibit the largest malaria increase reported worldwide<sup>7</sup>, threatening the  
240 successful implementation of the Global Malaria Action plan.<sup>21</sup>

241

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

259

260 In the Andes and Western Venezuela, CD is present throughout different states regardless of the  
261 geographical or climatic landscape. Seroprevalences obtained from three endemic communities  
262 (2014-2016) in Portuguesa States show considerable active transmission (12.5%, <10 years old,  
263 **Table S1, Figure 3a**). Also, house infestation indices were estimated to be as high as 24.8% in  
264 some hotspots at the time the CD control-program was dismantled<sup>27</sup>. Seroprevalences observed  
265 in Lara State in 2011 also suggest some active transmission (0.57%, <10 years old, Table S1,  
266 **Figure 3a**)<sup>27-29</sup>. Recent estimates for this and other western States are not available, however,  
267 CD may well be resurgent as no surveillance or preventative measures are in place. At the time  
268 of writing an outbreak of acute Chagas in Táchira State reported in the Colombian media had  
269 infected 40 people and claimed eight lives<sup>30</sup>. Eleven cases of ‘spillover’ acute disease in total  
270 were confirmed in Venezuelan nationals by the Colombian authorities in the last six months. In  
271 contrast to western Venezuela, in the 2000s, studies suggested that elimination of vectorial  
272 transmission of CD in eastern Venezuela was possible<sup>26</sup>. However, recent data reveals that active  
273 transmission is now present in Nueva Esparta State (2.5%, <10 years old, 2016, **Table S2,**  
274 **Figure 3a**), Anzoátegui State (8%, 11-20 years old, 2014, **Table S2, Figure 3a**) and Sucre State

275 (2%, 11-20 years old, 2012, Table S2). In Nueva Esparta, most seropositive subjects were among  
276 the young and the elderly – possibly reflecting the success of the former control program and  
277 current resurgence of the disease (**Table S2, Figure 3a**). Overall sero-prevalence among children  
278 from the data we report (4.3%, <10 years old, **Table S3**) indicates resurgent infection and  
279 resembles rate estimates from the 1970s<sup>26</sup>. However, our sample sizes are at least one order of  
280 magnitude lower than historical studies, although the serological approaches were similar  
281 (ELISA, IHA and FC). Nationally, seroprevalences over all age groups (15.7%, **Table S3**)  
282 exceed those in endemic provinces in Colombia (Boyaca, 2.2% 2007-09; Santander 0.2%, 2013-  
283 14<sup>31</sup>) as well as Ecuador (3.5%, Manabi, Loja, Guayas (2001-2003)<sup>32</sup> by a substantial margin. It  
284 is not clear whether blood banks are still being screened for CD in Venezuela, however in the  
285 current crisis it seems unlikely.

286

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

303

304 Linked to several oral CD outbreaks in and around Caracas are increasing reports of peri-urban  
305 transmission of *T. cruzi* in Venezuela. This phenomenon was first reported in 2005 where 76.1%  
306 of the disease vector *Panstrongylus geniculatus* recovered from the Capital District and Miranda  
307 and Vargas states were naturally infected with *T. cruzi* and that 60.2% of their gut contents gave  
308 a positive reaction to human antiserum<sup>37</sup>. Ongoing collections between 2007-2016 has continued  
309 to reveal a preponderance of *P. geniculatus* (98.96%), as well as *Triatoma nigromaculata*  
310 (0.58%), *Triatoma maculata* (0.37%), *Rhodnius prolixus* (0.07%) and *Panstrongylus*  
311 *rufutuberculatus* (0.02%) (Figure 3b)<sup>38</sup>. Vector infection rates with *T. cruzi* over this period have  
312 been consistently high (75.7%). Intradomiciliary triatomine nymphs also present in 16 of the 32  
313 parishes (3.42% of vectors captured) suggest active colonisation of houses by these insects.  
314 Preliminary molecular analysis of blood meals identify humans as by far the most common blood  
315 feeding source among insects collected 2007-2016. Furthermore, molecular epidemiological  
316 analyses clearly identify parasites from these peri-urban transmission cycles as the source of  
317 local oral outbreaks<sup>39</sup>. It is not known to what extent vectors are also transmitting parasites  
318 directly to human populations in the metropolitan district (i.e. not orally via contaminated food).



319 However, given high rates of feeding on humans, as well high infection levels, vectoral  
320 transmission remains a possibility despite the supposed low vectoral capacity of *P. geniculatus*<sup>38</sup>.

321

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

330

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

340

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

352

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

358

359 **Arboviruses: an expanding threat.** Viruses that are transmitted by arthropod vectors  
360 (arboviruses) have been expanding either steadily or in explosive (re)-emergent epidemics in  
361 recent years, posing a growing threat to global public health<sup>46,47</sup>. In the last four years, the two  
362 major epidemics that swept the American continent were caused by the chikungunya and Zika

363 arboviruses<sup>48</sup>. Concomitantly, dengue, another arboviral disease endemic in the Latin American  
364 region, is increasing its spread to previously unaffected areas. All three arboviruses are  
365 transmitted by the same mosquito, *Aedes (Stegomyia) aegypti* (L.), with a potential role for the  
366 invasive species *Ae. (Stegomyia) albopictus* (Skuse) as well.

367

368 A member of the Flaviviridae family, dengue virus has become a major public health problem in  
369 Venezuela. Four dengue virus serotypes (DENV-1 to DENV-4) co-circulate in the country, each  
370 of them capable of causing the entire range of dengue-related disease symptoms. Infected  
371 individuals can be asymptomatic or present with clinical manifestations varying from mild  
372 febrile illness, to severe disease and death<sup>49</sup>. Venezuela is witnessing an upswing in incidence,  
373 frequency and magnitude of dengue epidemics against a background of perennial endemic  
374 transmission. Dengue incidence has leaped from an average of 39.5 cases per 100,000 population  
375 in the early 1990's to a 9-fold higher mean incidence of 368 cases per 100,000 population  
376 between 2010 and 2016 (**Figure 5a**). Within the country, the temporal increase in dengue cases  
377 mirrors the national dengue incidence with regions of higher population density (central regions)  
378 and those bordering Colombia and Brazil (border regions) exhibiting a higher incidence (**Figure**  
379 **5b**). Worryingly, a total of six increasingly large epidemics were recorded nationally between  
380 2007-2016 compared with four epidemics in the previous 16 years<sup>50</sup>. The largest occurred in  
381 2010, when approximately 125,000 cases including 10,300 (8.6%) with severe manifestations  
382 were registered. During that year, Venezuela ranked third in the number of reported dengue cases  
383 in the American continent and second in the number of severe cases<sup>51</sup>.

384

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

394

395 Venezuela was not spared from the havoc that the epidemics of chikungunya (in 2014) and Zika  
396 (a year later). The impact of these epidemics was amplified by the lack of timely official  
397 information, lack of preparedness, and the worsening economic and health crisis resulting in  
398 acute shortages of diagnostics medicines and medical supplies, and an overburdened health  
399 system. Both epidemics rapidly spread through densely inhabited regions where dengue  
400 transmission is high. Although nationally, the attack rate of chikungunya was estimated to be  
401 between 6.9% and 13.8%<sup>57</sup>, the observed attack rate in populated urban areas reached 40-50%,  
402 comparable or higher than that reported in other countries<sup>58,59</sup>. The total number of chikungunya  
403 cases in Venezuela reported to PAHO in 2014 (by epidemiological week 51) was 34,945, with an  
404 incidence of 121.5 per 100,000 population<sup>60</sup>. Given the paucity of official information since  
405 October 2014, estimates created based on excess fever cases not explained by another cause  
406 suggest that there were more than 2 million cases of chikungunya, resulting in an incidence of  
407 6,975 cases per 100,000 population, more than 12 times the rate reported officially by the

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

411  
412 In January 2016, the Zika epidemic struck Venezuela concomitantly with a rise in dengue  
413 transmission. The Zika outbreak evolved in a similar manner as chikungunya, rapidly affecting a  
414 high proportion of the population. Lack of preparedness and of official communication once  
415 again sparked alarm. The incidence of symptomatic cases during the peak of the epidemic was  
416 estimated at 2,057 cases per 100,000 population<sup>63</sup>. Current estimates of serologically (IgG) Zika  
417 positivity in pregnant women have reached roughly 80%. As in other countries, an increase in  
418 the number of cases of Guillain-Barré syndrome (GBS) was observed during the epidemic.  
419 However, Venezuela experienced a rise of 877% (9.8 times higher) in GBS incidence compared  
420 to the pre-Zika baseline incidence, one of the highest (if not the highest) reported in the  
421 Americas<sup>64</sup>. The number of GBS cases surged from a mean of 214 annual cases reported before  
422 Zika to more than 700 confirmed cases since the epidemic started<sup>63</sup>. Cases of microcephaly and  
423 other congenital disorders related to Zika infections in pregnancy in Venezuela have been  
424 reported, but the incidence remains to be determined by ongoing studies.

425  
426 Beyond chikungunya, Zika and dengue viruses, other circulating arboviruses with epidemic  
427 potential exist in Venezuela. Mayaro has caused recent outbreak<sup>65,66</sup> and is often confused with  
428 chikungunya. Oropouche (Madre de Dios virus, outbreak in Perú, 2016) was recently detected in  
429 the Llanos of Venezuela, outside its typical distribution zone<sup>67</sup>. The occurrence of cryptic  
430 transmission cycles and cases due to epizootic strains of Venezuelan Equine Encephalitis and  
431 Madariaga virus (South American Eastern Equine Encephalitis)<sup>68</sup> when immunization programs  
432 have been halted pose a further threat. No facilities exist for rapid laboratory diagnosis for either  
433 virus in Venezuela.<sup>69</sup> The most common and effective VEE vaccine, TC-83, can longer be  
434 bought or produced in the Venezuela. The Agricultural Research Institute (INIA), with limited  
435 production capacity, has no financial support and production is paralyzed. Although there are no  
436 reliable official records of equine inventories, wild donkeys without owners and without sanitary  
437 control, and persistent circulation of epizootic VEE strains in inter-epizootic periods in different  
438 sites of the plains and the Catatumbo region, increases the threat of latent outbreaks and their  
439 potential international dispersal.<sup>70</sup>

440  
441 The whole of Latin America is experiencing increased risks and outbreaks associated with  
442 arboviruses. Although there is currently no evidence to suggest that the prevalence of certain  
443 arboviruses like dengue is higher in Venezuela than in other countries (Figure 5a), the lack of  
444 public health infrastructure available for diagnosis and treatment is now a disproportionate  
445 problem in Venezuela compared with other countries in the region. Furthermore, given the  
446 current situation, widespread underreporting of cases by comparison to other countries in the  
447 region is also possible. The lower incidence and lack of parallel increase after 2013 of dengue in  
448 Venezuela compared to Colombia and Brazil, for example (Figure 5a), strongly suggest chronic  
449 underreporting. In light of the precarious possibilities for cure in Venezuela combined with the  
450 high level of population displacement, emigrating infected individuals could be unwittingly  
451 causing a spillover of arboviral diseases to neighbouring countries, a process that has not yet  
452 been quantified. The first major outbreak of dengue on the island of Madeira in 2012-2013 is an

453 example of the disease export potential of Venezuela, as this outbreak was directly linked with a  
454 DENV-1 serotype from Venezuela.<sup>71</sup>

455

456 **A call for action.**

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

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

478

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

486

487 Fortunately, many solutions are within reach, even with limited resources. A good example is the  
488 recent successful bi-national strategy for the elimination of malaria on the Peru-Ecuador border.  
489 Collaboration at the operational level that included strengthening surveillance, community  
490 personnel trained to collect blood smears from febrile persons within their border communities,  
491 prompt effective diagnosis, case definition (indigenous, imported, introduced, induced, cryptic),  
492 and treatment<sup>75</sup>. Where state infrastructure fails, however, surveillance can be achieved via the  
493 mobilisation of citizen scientists and informal networks of healthcare professionals.  
494 Technological advances in low-cost sample preservation, passive sampling and *in situ*  
495 diagnostics can also contribute. Education to raise awareness among communities at risk from  
496 disease can be achieved via social media, initiatives at schools and information campaigns at

497 public centers. Surveillance data are power and must be used as an advocacy tool to raise  
498 awareness among Venezuelan and regional authorities, and ultimately better allow them to  
499 recognise the growing crisis, cooperate, and accept international medical interventions. Relevant  
500 international health authorities such as the WHO Global Outbreak Alert and Response Network  
501 (GOARN) must also move towards maintaining accurate disease surveillance and response  
502 systems in the region along with collaboration with other strategic partners in order to provide  
503 timely humanitarian assistance throughout this ongoing crisis. The wider scientific community  
504 must support this process by engaging with their Venezuelan and regional colleagues,  
505 contributing to a robust, non-partisan evidence base for such interventions. Ultimately national  
506 and international political commitments are essential to stop a health crisis that threatens the  
507 whole region.

508

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

521 **Figure Legends:**

522

523 **Figure 1. (a) Number of confirmed malaria cases (line) and Annual parasite incidence (API:**  
524 **No. of confirmed malaria cases/1,000 inhabitants, bars) in Venezuela from 2000 to 2016 (inset**  
525 **left: map of Venezuela (red) in South America, inset right: case comparison of annual incidence**  
526 **(Y-axis) for Colombia, Brazil & Venezuela). Temporal pattern of incidence indicates an**  
527 **exponential increasing trend ( $R^2= 0.78$ ,  $P = 1.07 \times 10^{-5}$ ,  $N=18$ ) in Venezuela. (b) API for each**  
528 **municipality in Venezuela during 2016**

529

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

533

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

542

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

547

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

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562

563 **Conflict of Interest**

564

565 We declare that we have no conflicts of interest.

566

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568

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572

573 **Contributions**

574

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

577

578 **Authors and affiliations:**

579

580 Grillet ME, PhD Prof<sup>1\*</sup>, Hernández JV, BSc<sup>1\*</sup>, Llewellyn MS, PhD<sup>2\*+</sup>, Paniz-Mondolfi A, MD-  
581 PhD<sup>3,4\*</sup>, Tami A, MD-PhD<sup>5\*</sup>, Vincenti-Gonzalez MF, PhD<sup>5</sup>, Marquez M, BSc<sup>3,6</sup>, Mogollon-  
582 Mendoza A, MD<sup>3,6</sup>, Hernandez-Pereira CE, BSc<sup>3,6</sup>, Plaza-Morr J, BSc<sup>3,7</sup>, Blohm G, PhD<sup>3,8</sup>,  
583 Grijalva MJ, PhD Prof<sup>9,10</sup>, Costales JA, PhD<sup>9</sup>, Ferguson H, PhD Prof<sup>2</sup>, Schwabl P, MSc<sup>2</sup>,  
584 Hernandez-Castro LE, MSc<sup>11</sup>, Lambertson P, PhD<sup>2</sup>, Streicker D, PhD<sup>2,12</sup>, Haydon D, PhD Prof<sup>2</sup>,  
585 Miles MA, PhD Prof<sup>13</sup>, Acosta-Serrano A, PhD<sup>15</sup>, Acquattella H, MD-PhD Prof<sup>16</sup>, Basañez MG,  
586 PhD FRES<sup>15</sup>, Benaim G, PhD Prof<sup>4,17</sup>, Colmenares LA, MD<sup>18</sup>, Conn JE, PhD<sup>19,20</sup>, Espinoza R,  
587 PhD Prof<sup>21</sup>, Freilij H, MD-PhD<sup>22</sup>, Graterol-Gil MC, MD<sup>14</sup>, Hotez P, MD-PhD Prof<sup>23</sup>, Kato H,  
588 PhD Prof<sup>24</sup>, Lednicky J, PhD Prof<sup>8</sup>, Marchan E, PhD<sup>25</sup>, Martinez CE, PhD<sup>14</sup>, Mas-Coma S, PhD  
589 Prof<sup>26</sup>, Morocoima A, MD-MSc<sup>27</sup>, Morris JG, MD-PhD Prof<sup>8</sup>, Navarro JC, PhD Prof<sup>1,28</sup>,  
590 Ramirez JL, PhD Prof<sup>29</sup>, Rodriguez M, MLT<sup>14</sup>, Urbina JA, PhD Prof<sup>30</sup>, Villegas L, MD-PH<sup>31</sup>,  
591 Segovia MJ, MSc<sup>14\*</sup>, Carrasco HJ, PhD Prof<sup>14\*</sup>, Crainey JL, PhD<sup>32\*</sup>, Luz SLB, PhD<sup>32\*</sup>, Moreno  
592 J, PhD<sup>33\*</sup>, Noya O, MD-PhD Prof<sup>33,34\*</sup>, Ramirez JD, PhD<sup>35\*</sup>, Alarcón-de Noya B, MD-PhD  
593 Prof<sup>36\*</sup>.

594

595 \* **Contributed equally to this study.**

596 + **Corresponding author.**

597

598 <sup>1</sup>Laboratorio de Biología de Vectores y Parásitos, Instituto de Zoología y Ecología Tropical,  
599 Facultad de Ciencias, Universidad Central de Venezuela. Caracas, Venezuela. <sup>2</sup>Institute of  
600 Biodiversity, Animal Health and Comparative Medicine, University of Glasgow, Glasgow,

601 Scotland, United Kingdom.<sup>3</sup>Infectious Diseases Research Incubator and the Zoonosis and  
602 Emerging Pathogens Regional Collaborative Network. Department of Tropical Medicine and  
603 Infectious Diseases. Instituto de Investigaciones Biomédicas IDB. Clinica IDB Cabudare. Lara,  
604 Venezuela. <sup>4</sup>Instituto de Estudios Avanzados (IDEA), Caracas, Venezuela. <sup>5</sup>University of  
605 Groningen, University Medical Center Groningen, Department of Medical Microbiology,  
606 Groningen, The Netherlands <sup>6</sup>Health Sciences Department, College of Medicine, Universidad  
607 Centrooccidental Lisandro Alvarado. Barquisimeto, Lara, Venezuela. <sup>7</sup>Health Sciences  
608 Department, College of Medicine, Universidad Nacional Experimental Francisco de Miranda,  
609 Punto Fijo, Falcon, Venezuela. <sup>8</sup>Emerging Pathogens Institute, University of Florida,  
610 Gainesville. Department of Environmental and Global Health, College of Public Health and  
611 Health Professions, University of Florida, Gainesville, Florida, United States of America. Center  
612 for Research on Health in Latin America (CISeAL), Escuela de Ciencias Biológicas, Pontificia  
613 Universidad Católica del Ecuador.<sup>10</sup>Infectious and Tropical Disease Institute, Department of  
614 Biomedical Sciences, Heritage College of Osteopathic Medicine, Ohio University, Ohio, United  
615 States of America. <sup>11</sup>Medical, Veterinary & Life Sciences, Graham Kerr Building, University of  
616 Glasgow, Glasgow, Scotland. United Kingdom.<sup>12</sup>MRC-University of Glasgow Centre for Virus  
617 Research. University of Glasgow, Glasgow, Scotland, United Kingdom. <sup>13</sup>Department of  
618 Pathogen Molecular Biology, Faculty of Infectious and Tropical Diseases, London School of  
619 Hygiene and Tropical Medicine, London, United Kingdom. <sup>14</sup>Laboratorio de Biología Molecular  
620 de Protozoarios, Instituto de Medicina Tropical, Universidad Central de Venezuela. Caracas,  
621 Venezuela. <sup>15</sup>Department of Vector Biology and Department of Parasitology, Liverpool School  
622 of Tropical Medicine, United Kingdom. <sup>16</sup>Venezuelan National Academy of Medicine, Caracas,  
623 Venezuela. <sup>17</sup>Instituto de Biología Experimental, Facultad de Ciencias, Universidad Central de  
624 Venezuela, Caracas, Venezuela. <sup>18</sup>Instituto de Medicina Tropical, Universidad Central de  
625 Venezuela. Caracas, Venezuela. <sup>19</sup>Griffin Laboratory, Wadsworth Center, New York State,  
626 United States of America. Department of Health, Slingerlands, NY, USA. <sup>20</sup>School of Public  
627 Health, University at Albany - State University of New York, United States of America.  
628 <sup>21</sup>Hospital Miguel Pérez Carreño, Instituto Venezolano de los Seguros Sociales, Caracas,  
629 Venezuela. <sup>22</sup>Hospital de Niños Ricardo Gutiérrez, Ciudad Autónoma de Buenos Aires,  
630 Argentina. <sup>23</sup>Baylor College of Medicine National School of Tropical Medicine, Houston, Texas,  
631 United States of America. <sup>24</sup>Division of Medical Zoology, Department of Infection and  
632 Immunity, Jichi Medical University, Japan.<sup>25</sup>Instituto de Investigaciones en Biomedicina y  
633 Ciencias Aplicadas, Universidad de Oriente, Cumana, Venezuela.<sup>26</sup>Departamento de  
634 Parasitología, Universidad de Valencia. Valencia, España. <sup>27</sup>Centro de Medicina Tropical de  
635 Oriente, Universidad de Oriente (UDO) Núcleo Anzoátegui, Barcelona, Venezuela.  
636 <sup>28</sup>Universidad Internacional SEK, Facultad de Ciencias Naturales y Ambientales, Centro de  
637 Biodiversidad, Enfermedades Emergentes y Salud Ambiental, Quito, Ecuador. <sup>29</sup>Biotechnology  
638 Center, Instituto de Estudios Avanzados, Caracas, Venezuela. <sup>30</sup>Venezuelan Institute for  
639 Scientific Research (IVIC). <sup>31</sup>Asociación Civil Impacto Social (ASOCIS), Tumeremo, Bolívar  
640 State, Venezuela. <sup>32</sup>Instituto Leônidas e Maria Deane/ILMD/FIOCRUZ, Laboratório de Ecologia  
641 de Doenças Transmissíveis na Amazônia, Manaus, Amazonas, Brazil.<sup>33</sup>Centro de  
642 Investigaciones de Campo “Dr. Francesco Vitanza”, Servicio Autónomo Instituto de Altos  
643 Estudios “Dr. Arnoldo Gabaldon”, MPPS. Tumeremo, Bolívar, Venezuela.<sup>34</sup>Sección de  
644 Biohelmintiasis, Instituto de Medicina Tropical, Facultad de Medicina, Universidad, Central de  
645 Venezuela. <sup>35</sup>Grupo de Investigaciones Microbiológicas-UR (GIMUR), Programa de Biología,  
646 Facultad de Ciencias Naturales y Matemáticas, Universidad del Rosario, Bogotá,



647 Colombia.<sup>36</sup>Sección de Inmunología, Instituto de Medicina Tropical, Facultad de Medicina  
648 Universidad Central de Venezuela (IMT-FM-UCV), Caracas, Venezuela.

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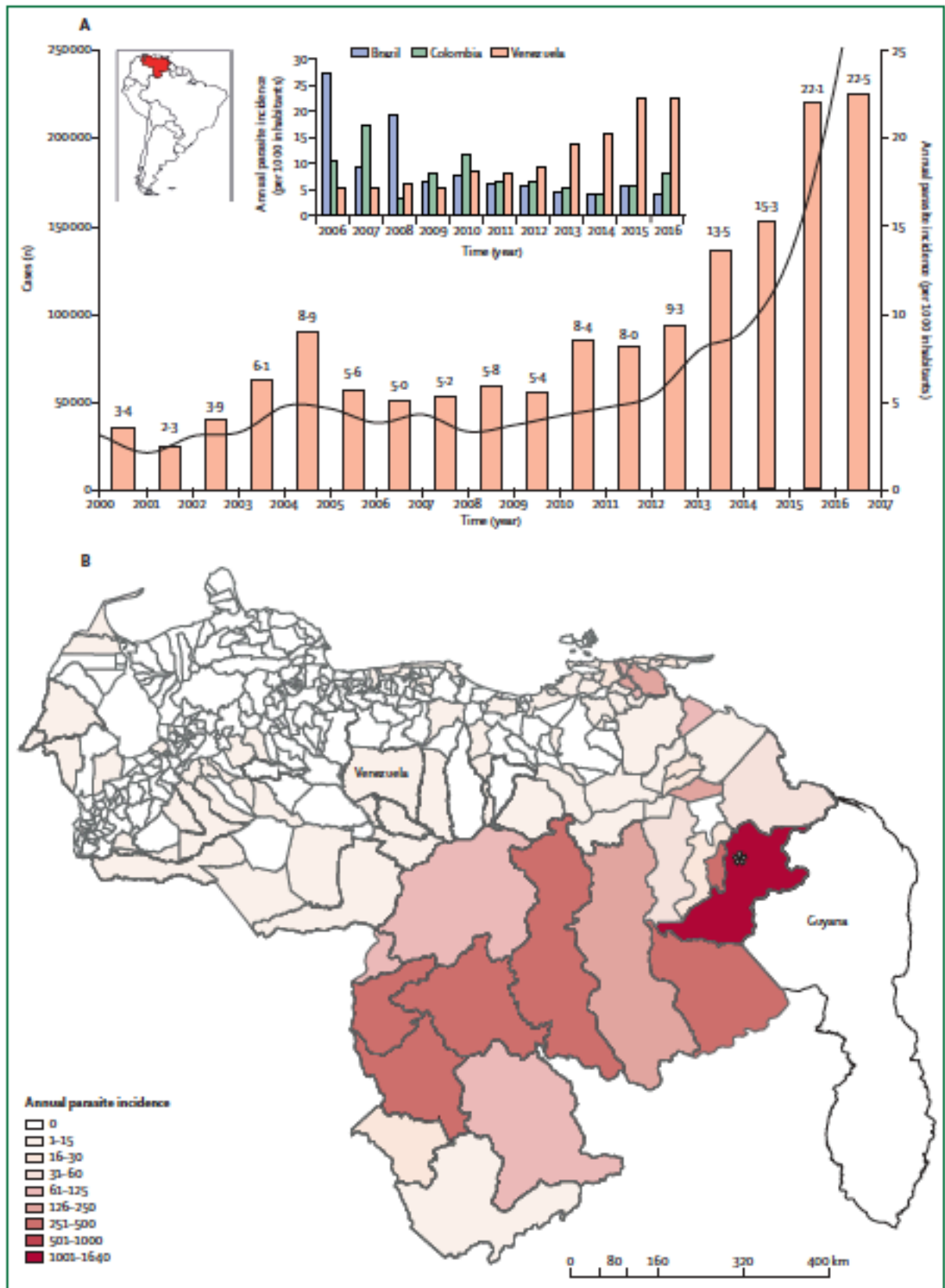
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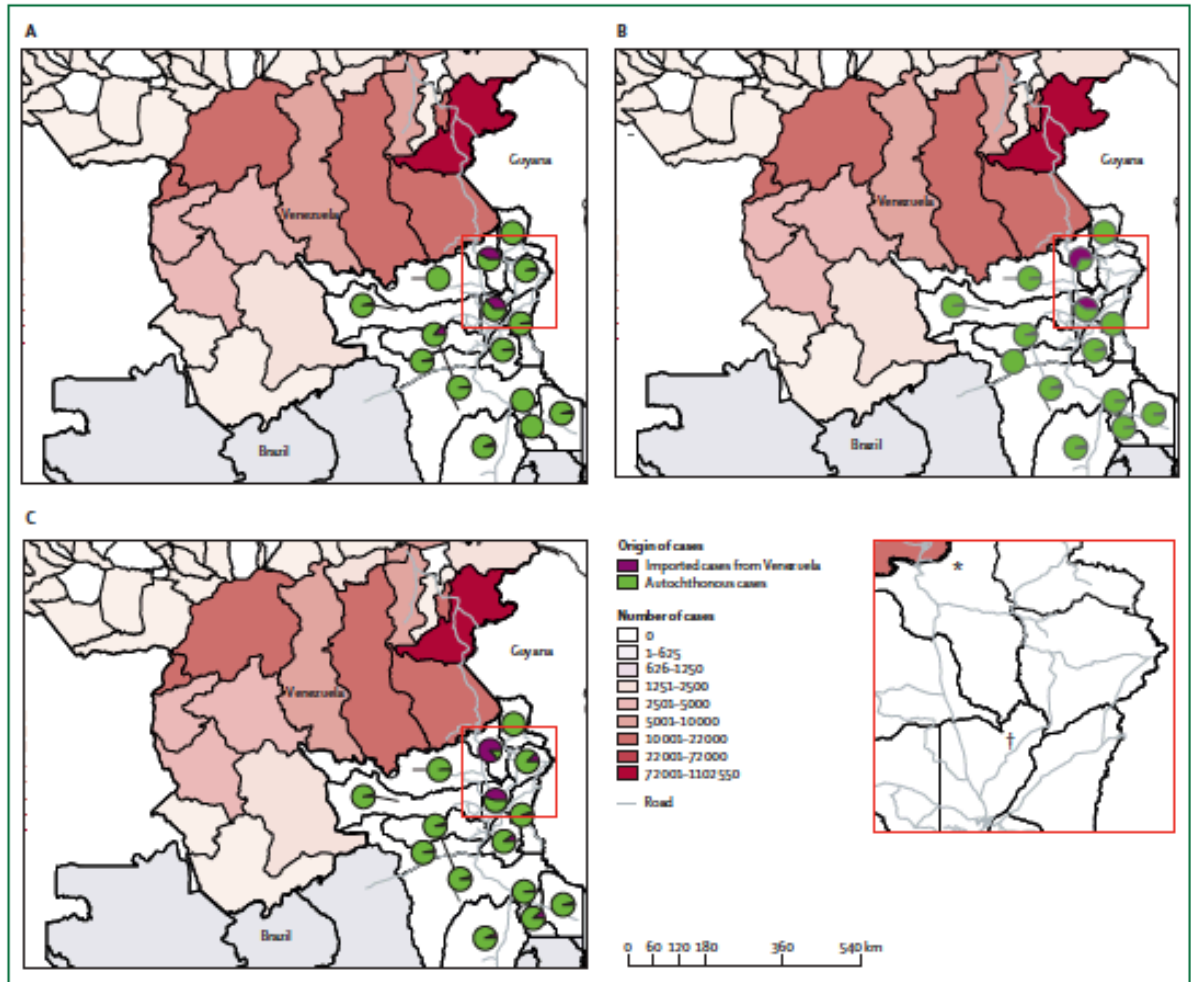


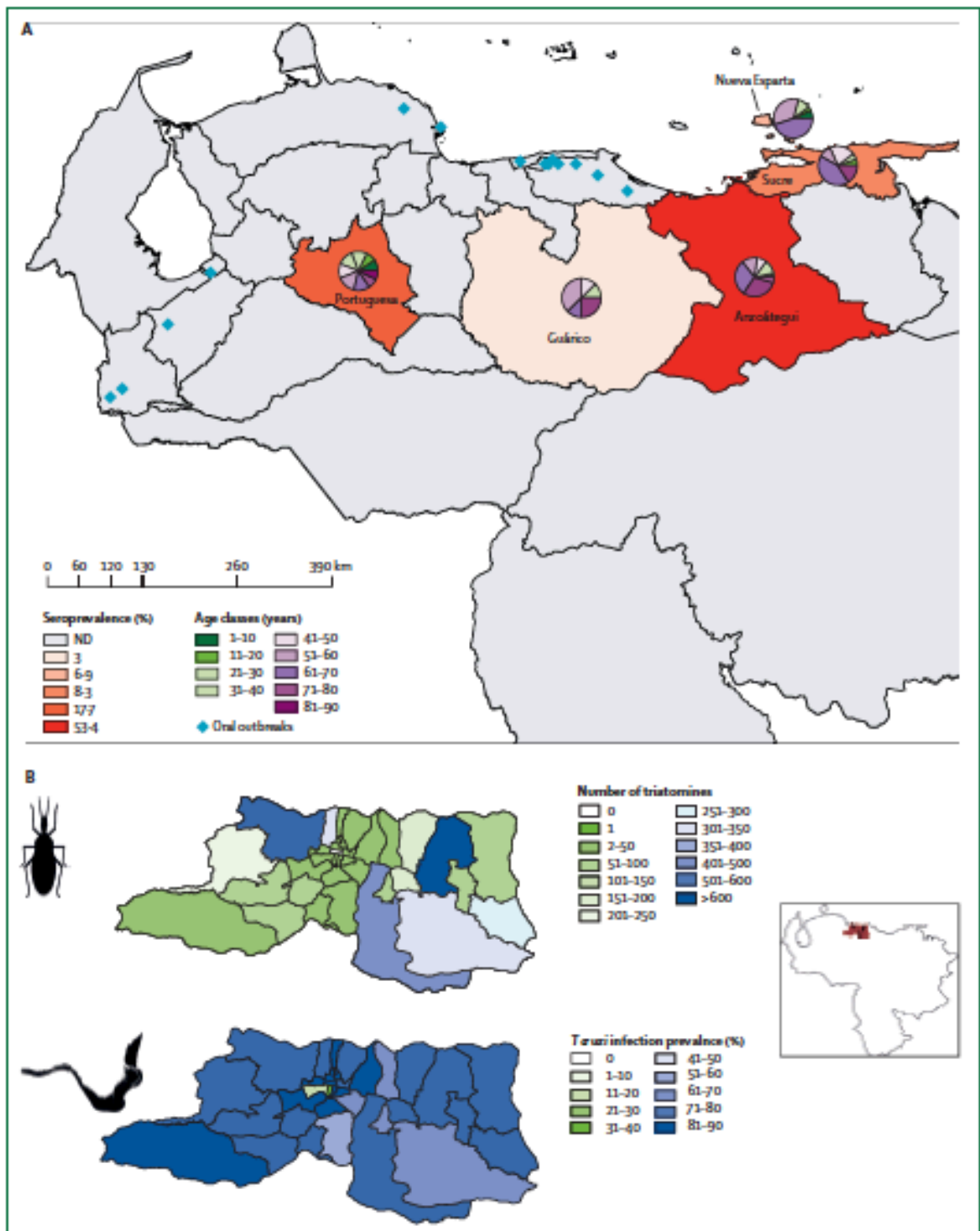
Figure 2: Malaria cases reported in eastern Venezuela and neighbouring Roraima State, Brazil (A) 2014, (B) 2015, and (C) 2016. Pie charts indicate origin of cases. Inset shows the locations of Pacaraima and Boa Vista. \*Pacaraima. †Boa Vista.

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

(A) Update on the distribution of Chagas disease human seroprevalence 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 Instituto de Medicina 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.

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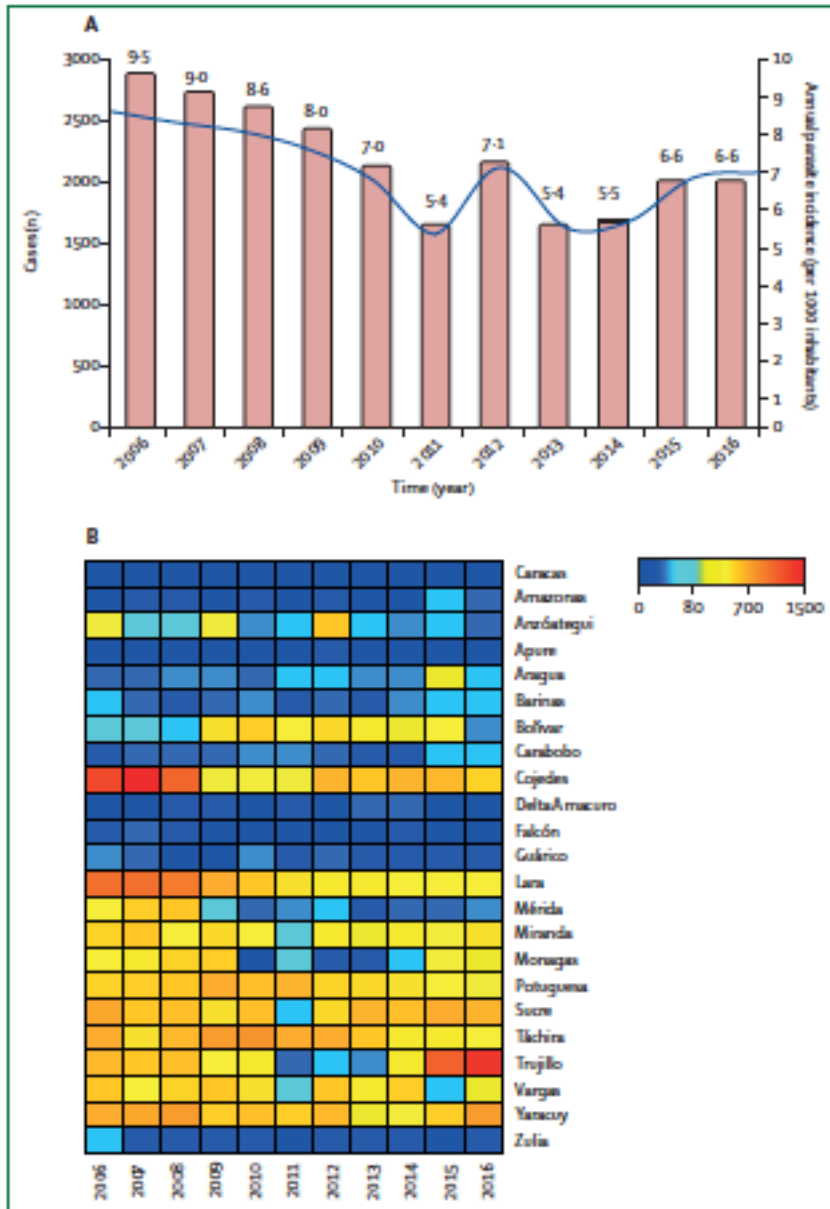
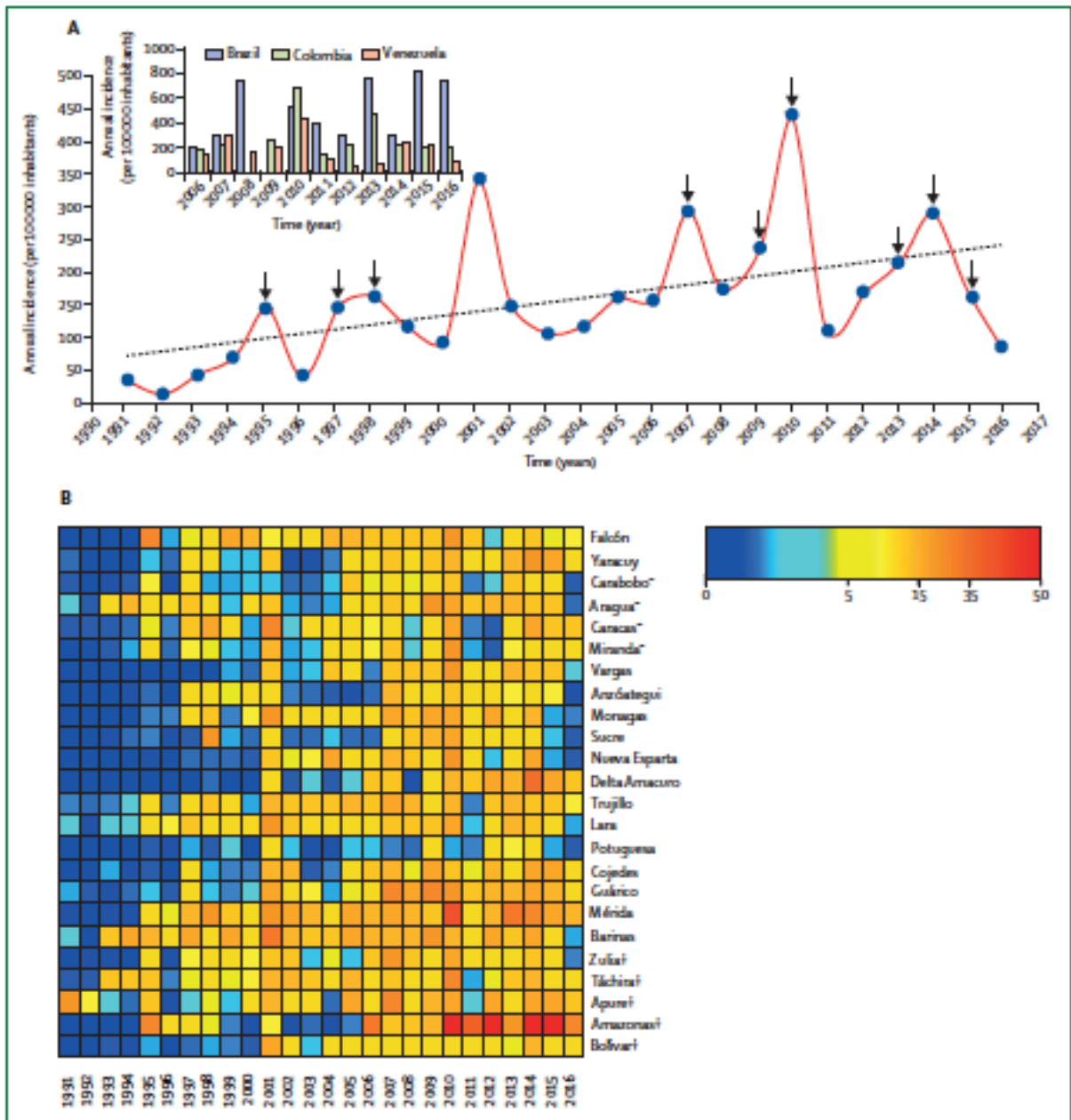


Figure 4: Annual parasite incidence and confirmed cases of cutaneous leishmaniasis in Venezuela (A) Number of confirmed cases (line) and annual incidence per 100 000 inhabitants (bars) in Venezuela, 2006-16. (B) Annual parasite incidence by state per 100 000 inhabitants for 2006-16 (increasing from blue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

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**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.

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