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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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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.

64

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.

72

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.

81

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]
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/] [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.^{1,2}

147

148 It is a well-known fact that states of political and civil unrest create conditions for the emergence
149 and spread of infectious diseases³. 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 region⁴. 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^{5,6}. Official data are likely underestimates given the existence of
157 informal border crossings. Reports of disease spillover to neighbouring countries are increasing⁷

158

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 government⁸. 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.⁹

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 Organization¹⁰.
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 2015¹¹, 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 region¹². 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)¹². *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
192 246,859¹². 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 plains¹³. 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^{13,14}. 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* Root¹⁵, *An. albitarsis* Lynch s.l. and *An.*
204 *nuneztovari* Gabaldon s.l.^{16,17}, 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* breeding¹⁸. 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^{2,19}. 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.²⁰

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 worldwide⁷, threatening the
240 successful implementation of the Global Malaria Action plan.²¹

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 species²². Human infection with *T. cruzi* leads in approximately 40% of cases to severe and
246 irreversible cardiac and intestinal pathology²³. 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)^{24,25}. 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%²⁶.
251 Seroprevalence among young children (0-10) was reduced to 0.5% between 1990-98²⁶.
252 Regrettably, the 1990s saw the national CD control program reduced and decentralised²⁶.
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 dismantled²⁷. Seroprevalences observed
265 in Lara State in 2011 also suggest some active transmission (0.57%, <10 years old, Table S1,
266 **Figure 3a**)²⁷⁻²⁹. 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 lives³⁰. 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 possible²⁶. 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 1970s²⁶. 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 14³¹) as well as Ecuador (3.5%, Manabi, Loja, Guayas (2001-2003)³² 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**)^{33,34} 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 mortality³⁵. Urbanization and deforestation of wooded areas
294 where the triatomines are present may also be contributing to this situation². 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.³⁶

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 antiserum³⁷. 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)³⁸. 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 outbreaks³⁹. 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*³⁸.

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.⁴⁰

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.⁴⁰ 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 Esparta⁴⁰. 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 signs⁴¹. 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 foci⁴⁰.

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.^{42-44,34,35,36,37,38,39} 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 months⁴⁵.

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^{46,47}. In the last four years, the two
362 major epidemics that swept the American continent were caused by the chikungunya and Zika

363 arboviruses⁴⁸. 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 death⁴⁹. 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 years⁵⁰. 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 cases⁵¹.

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 Venezuela⁵²⁻⁵⁵. 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 threshold⁵⁶. 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%⁵⁷, the observed attack rate in populated urban areas reached 40-50%,
402 comparable or higher than that reported in other countries^{58,59}. 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 population⁶⁰. 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 Health⁵⁷. Moreover, an important, yet unknown, number of atypical and
409 severe/fatal cases of chikungunya⁶¹ occurred but were not reported by health personnel because
410 of fear of governmental reprisal.^{1,62}

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 population⁶³. 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 Americas⁶⁴. 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 started⁶³. 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^{65,66} 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 zone⁶⁷. 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)⁶⁸ when immunization programs
432 have been halted pose a further threat. No facilities exist for rapid laboratory diagnosis for either
433 virus in Venezuela.⁶⁹ 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.⁷⁰

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.⁷¹

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 1961⁷². 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 1960s⁷².

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)². 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 area⁷³, and parasite transmission now remains in just 25% of the
474 Venezuelan Yanomami southern Amazonian region⁷⁴. 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^{2,72}.

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 treatment⁷⁵. 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 community². 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

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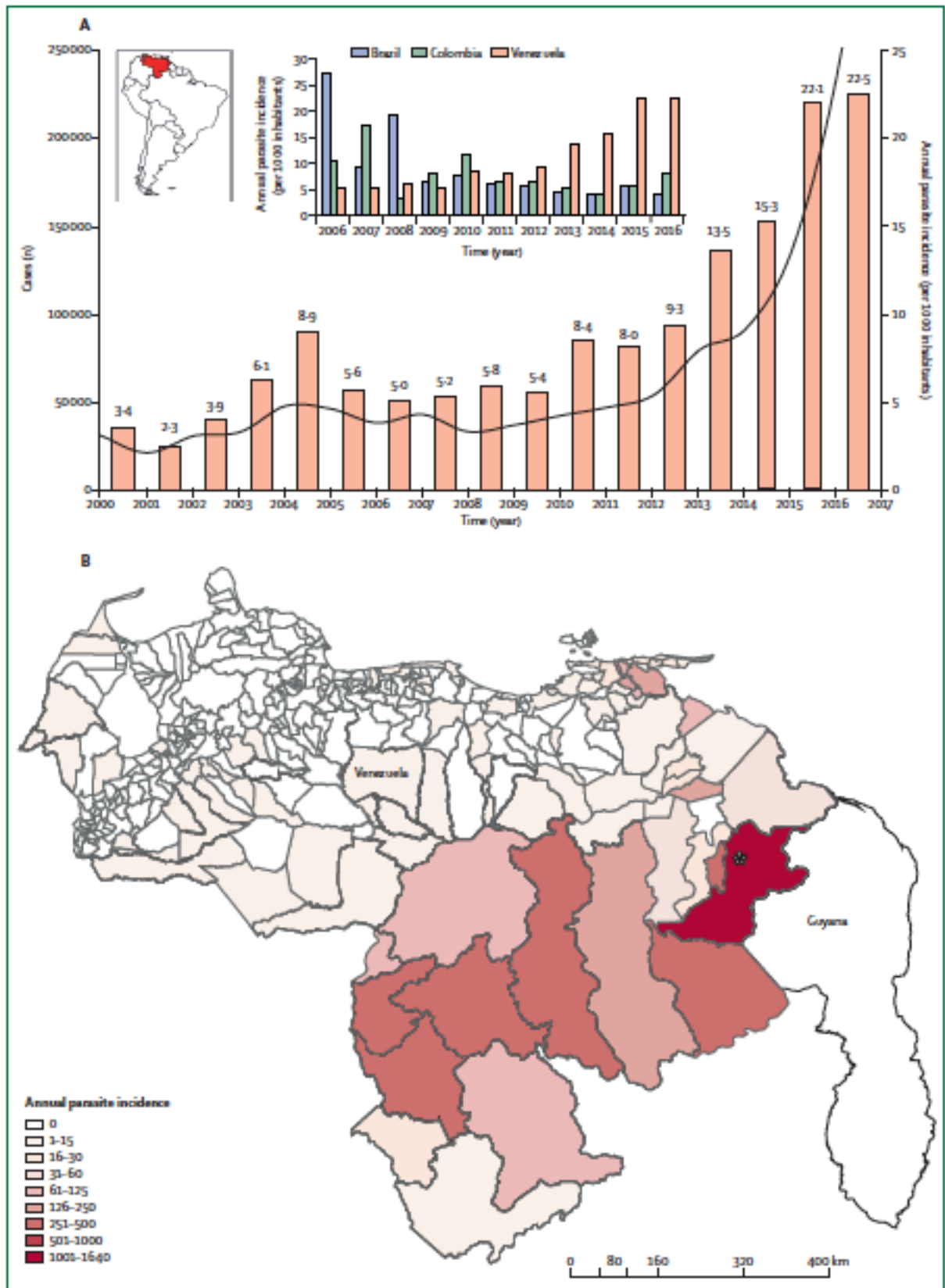
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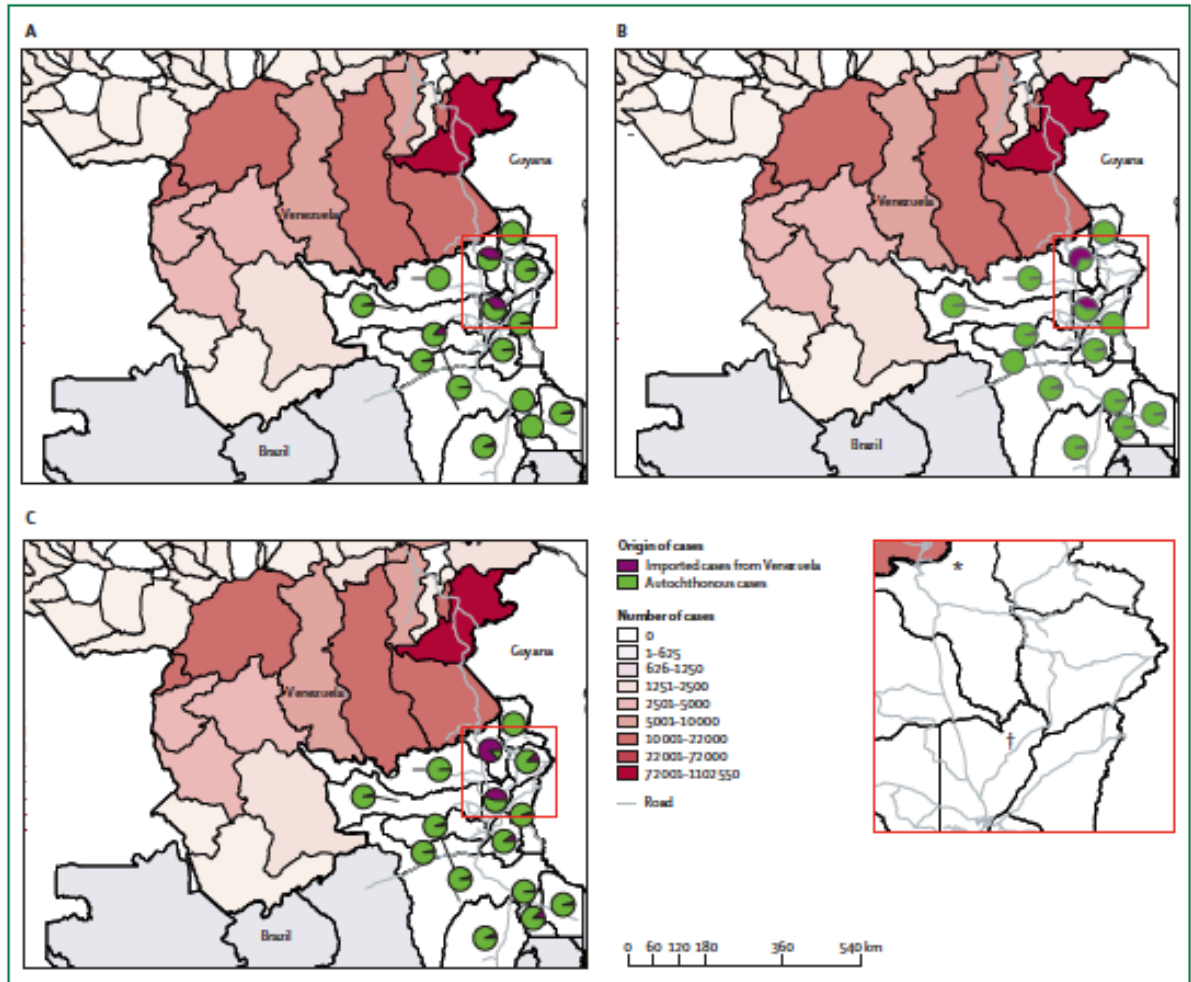


Figure 2: Malaria cases reported in eastern Venezuela and neighbouring Roraima State, Brazil (A) 2014, (B) 2015, and (C) 2016. Pie charts indicate origin of cases. Inset shows the locations of Pacaraima and Boa Vista. *Pacaraima. †Boa Vista.

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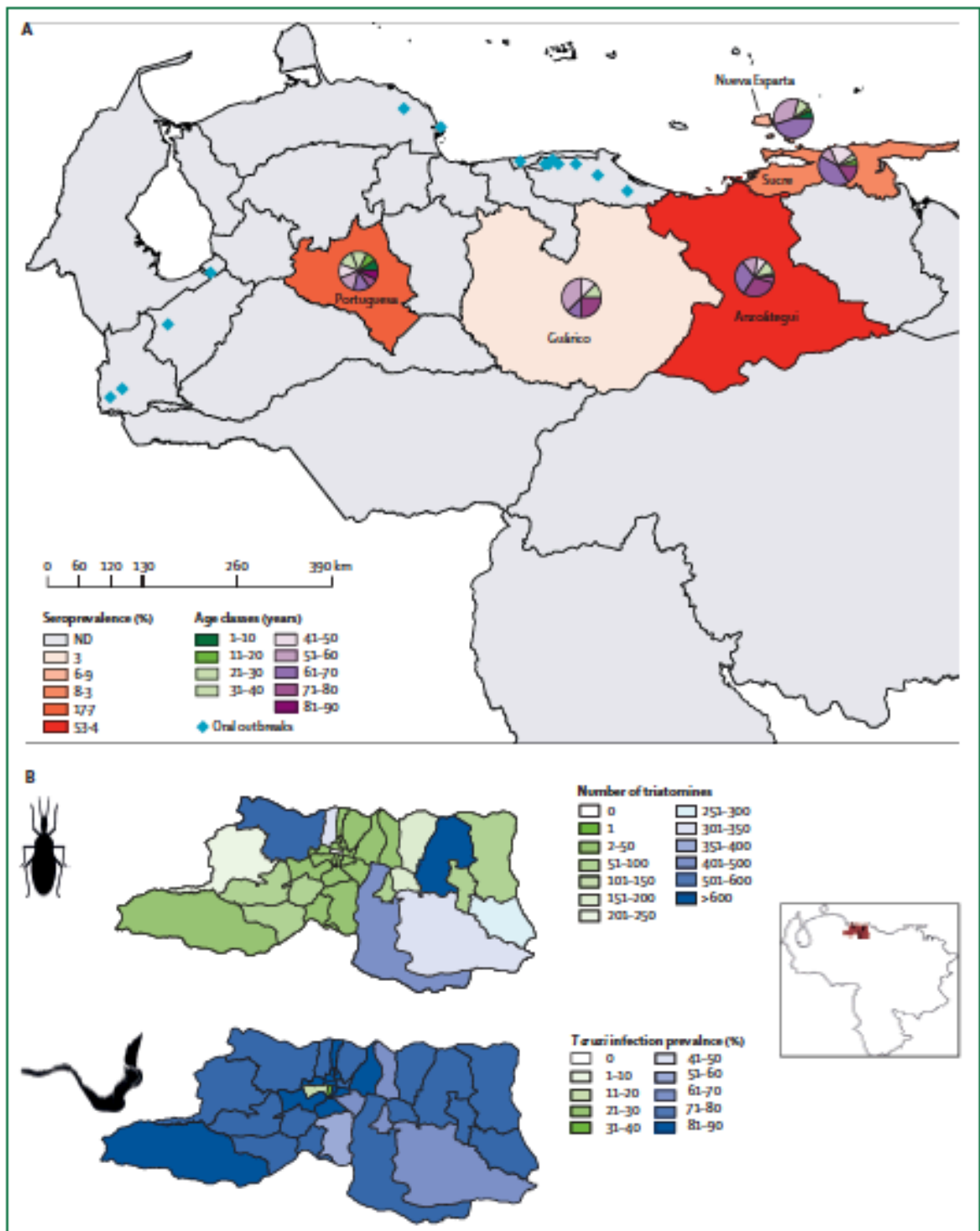


Figure 3: Chagas disease and *Trypanosoma cruzi* distribution in Venezuela

(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, Venezuela, in 2007-16 by municipality. 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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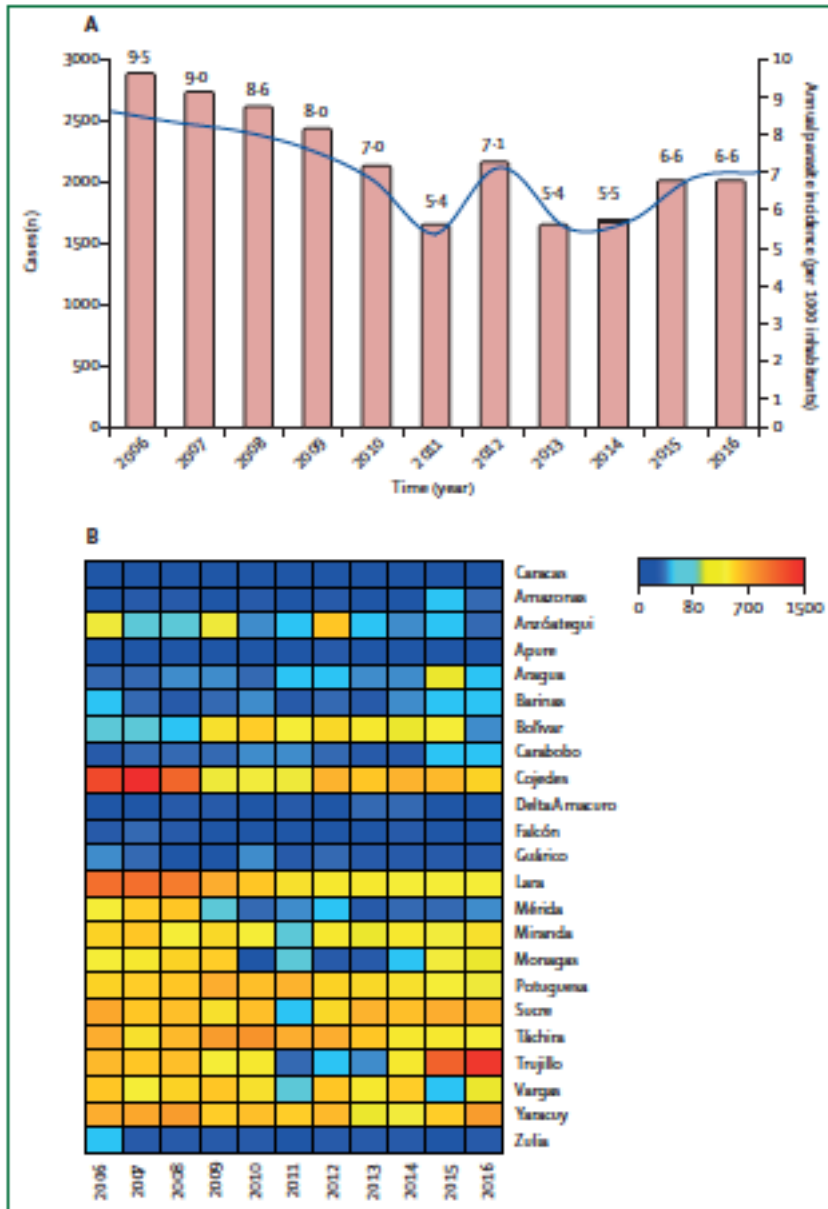


Figure 4: Annual parasite incidence and confirmed cases of cutaneous leishmaniasis in Venezuela (A) Number of confirmed cases (line) and annual incidence per 100 000 inhabitants (bars) in Venezuela, 2006-16. (B) Annual parasite incidence by state per 100 000 inhabitants for 2006-16 (increasing from blue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

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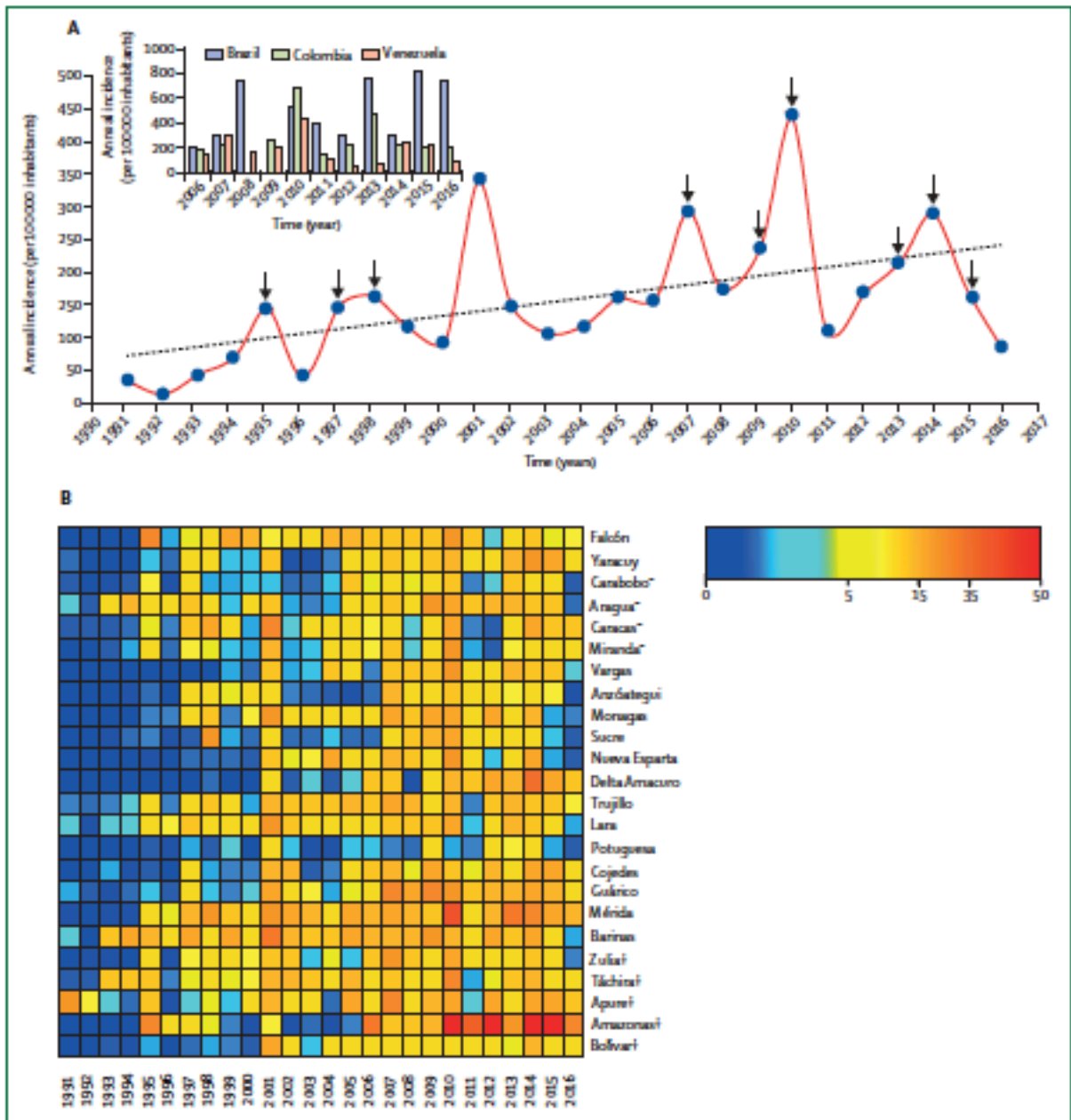


Figure 5: Annual incidence of dengue in Venezuela
 (A) Annual dengue incidence (per 100 000 inhabitants) for the 1991–2016 period. Black vertical arrows indicate dengue epidemic years. Dotted black line indicates an increasing linear trend ($R^2=0.27$, $t=2.99$, $p=0.006$, $n=26$). Inset shows comparison 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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