Eco-epidemiological Factors Associated with Hyperendemic Dengue Haemorrhagic Fever in Maracay City, Venezuela

By

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Abstract

Present research describes the establishment of dengue haemorrhagic fever (DHF) in Venezuela (1989), and dengue dynamics in Maracay city from 1993 and 2001. We also studied the relationships between DHF and weather variables, and explored the relationships between the disease and indicators of public services and *Aedes aegypti* pre-adult (House, Breteau Index) and adult (resting) parameters in neighbourhoods with no (apparent) dengue, low, and high dengue incidence/persistence. Our analysis suggests that DHF emerged and got established in Venezuela as a result of a combination of the introduction of new, more pathogenic strains of dengue, high and widespread adult mosquito populations resulting from inadequate public services, lack of effective vector control, and dengue hyperendemicity. DF and DHF were well correlated with rainfall and humidity; however, transmission continued during the distinct dry seasons, when breeding places generated by water-storing devices produced high adult densities of *Aedes aegypti*. DF and DHF were associated with the frequency and length of water-supply interruptions, mosquito adults per room, human population density, neighbourhood area, and with the persistence or history of dengue transmission in the locality. Even low dengue/persistence neighbourhoods showed deficiencies in public services and elevated adult mosquito densities, showing that the number of mosquitoes is not a limiting factor for dengue transmission in most of Maracay city.

Keywords: Dengue haemorrhagic fever, *Aedes aegypti*, ecology, Venezuela

Introduction

The first epidemic of dengue haemorrhagic fever (DHF) in Venezuela occurred in Maracay city in 1989. Since then this disease has become endemic/epidemic in the country[1,2,3,4,5]. For yet unknown reasons, Venezuela had accounted for most number of DHF cases (52.5%) and deaths (36%) in the American region until 1998[6]. It seems

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that the emergence of DHF in Venezuela was concurrent with the emergence of a new strain of DEN-2 from south-east Asia, the one that circulated in Cuba (1981) and Jamaica (1982)[7,8]. This newly-arrived strain of DEN-2 has been replacing the previously established, more benign strain[7]. Although the introduction of new virus strains could partly explain the appearance of DHF, it would be important to explain its higher prevalence in Venezuela.

One explanation could be the increased local abundance and geographical spread of *Aedes aegypti*, the main dengue vector[9]. Venezuela could be particularly vulnerable since most of the human population is concentrated in cities at low altitude along the Caribbean coast, where environmental conditions are conducive for *Aedes aegypti*[10]. A study of 30 coastal towns in Venezuela showed that insufficient piped water supply and deficiencies in garbage collection were significantly associated with high infestation levels of *Aedes aegypti*. Water storing containers, mainly metal drums (200 lt.), were the most common breeding sites[11]. Some traditional customs, such as the use of flower vases in cemeteries, also contribute to high *Aedes aegypti* growth within cities[12,13] Studies on the population dynamics of *Aedes aegypti* in an urban centre under such conditions have demonstrated high densities of adult populations during each month of the year, despite the distinct and long dry season[14].

Longitudinal studies undertaken in Maracay city during 1993-98 indicated that DF and DHF were present in each of the 8 municipalities and showed positive relationship with human population density. In general, DF and DHF were highly correlated at the neighbourhood level (linear regression R2 = 0.91) with 3 (clinically diagnosed) DF cases for each case of DHF. At a finer scale, most neighbourhoods (84%) showed dengue cases during the period of the study, and 83.4% of those with DF also had DHF cases. An analysis of the consistency in temporal occurrence of dengue per neighbourhood was performed correlating cases of DF, and of DHF, between years, resulting in each correlation being significant[5]. These results implied that neighbourhoods producing large (or small) numbers of dengue cases in one year continued to do so in each of the years considered. This high temporal consistency was likely to be the result of hyper-endemicity, where different serotypes alternated in time. It was also demonstrated that neighbourhoods showing longer dengue persistence (maximum number of consecutive months with cases) also had the highest DF and DHF incidence and prevalence, allowing us to stratify the city in: 56 neighbourhoods with no (apparent) dengue, 238 with low incidence/persistence (dengue persistence 1-5 months 1993-98), and 54 with high incidence/persistence (6-50 months). The high incidence/persistence neighbourhoods accounted for 70% of all cases reported during the study, but occupied only 34% of the city's land area. Those neighbourhoods included the most populated localities[5].

In an attempt to understand the differential spatial occurrence of dengue in Maracay city, we tried to understand the relationship between the *Aedes aegypti* indicies, water supply and interruptions and the dengue incidence in different neighbourhoods. The study attempted to explain the progression of the disease in Maracay city from 1993 and 2001, and the relationship between weather variables and dengue.

Materials and methods

Maracay city (10^0 07′ – 10^0 20′ N; 67^0 24′ – 67^0 38′ W; 436 m altitude) has 8 districts with an approximate total population of 1 million people (1998, National Census Bureau), distributed in 348 neighbourhoods occupying 109 km2 land area. The mean annual precipitation, temperature and relative humidity were 1,044 mm, 25,4^0 C, and 75.4% respectively (1993–1999; Venezuelan Air Force). There is a rainy season from May to October, and a dry season from November to April.

Dengue data at the national level came from an integration of clinically reported cases (Ministry of Health, Pan American Health Organization (PAHO)). Dengue data for Maracay came from raw paper forms of the clinically diagnosed cases (State Health Department) that were reviewed and incorporated into a Geographical Information System[(5)]. Criteria for DF and DHF followed PAHO's case-definition[(15)]. *Aedes* indices (House, Breteau) were investigated in each of 100 houses from 59 neighbourhoods during the dry season and 104 neighbourhoods during the rainy season in 1998 and 1999. Adult *Aedes aegypti* were searched for in approximately 100 houses from 11 neighbourhoods in the dry seasons (n=1096 houses) and 29 neighbourhoods in the rainy season (n = 2466). Adults were collected from the main room of each house with a CDC backpack aspirator[(16)]. Questionnaires asking the households about the quality of public services were applied in the same neighbourhoods as above. The questions required the households to rank the frequency of piped water supply interruptions (1=daily, 2=several times a week, 3=several times a month, 4=seldom), length of interruption in water supply (1=hours, 2=days, 3=weeks), and the frequency of house garbage collections (1=daily, 2=2 or 3 times a week, 3=once a week, 4= once every 2 weeks, 5=never).

Statistical methods

Associations between variables were analysed with Pearson's correlation coefficients (α=0.05). Statistical comparisons of mean neighbourhood areas and inhabitants among levels of dengue incidence/persistence were made with Analysis of Variance (ANOVA; α=0.05). Ordinal variables (public service variates) between types of neighbourhoods were compared using Mann-Whitney tests (α=0.05). Means for metric variables with homogeneous variances were compared using Student tests (α=0.05) for independent samples.

Results

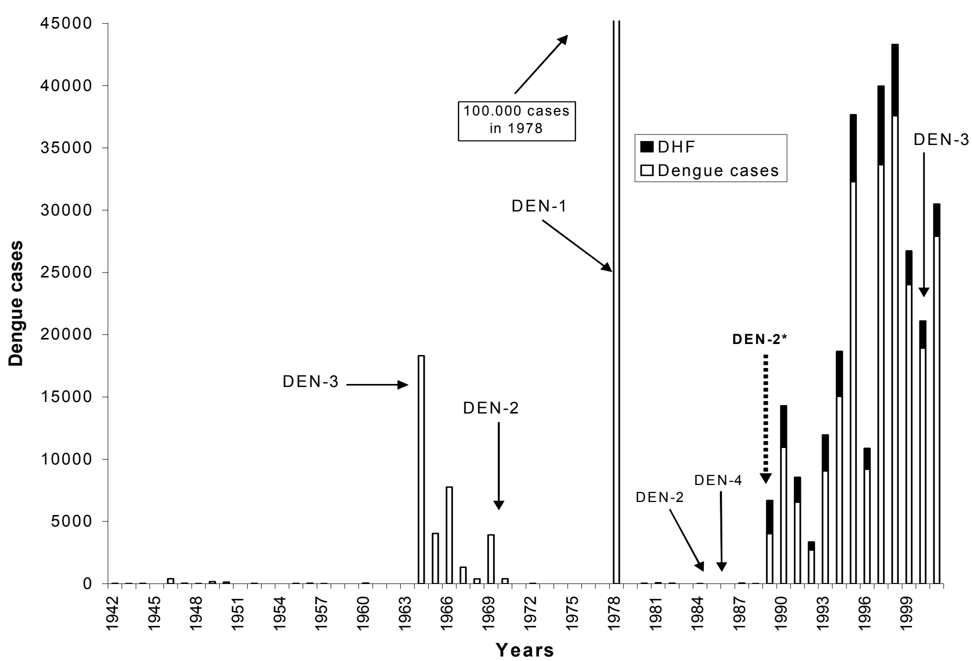
Dengue in Venezuela and Maracay City

The reported dengue epidemics in Venezuela were relatively isolated in time and caused by single serotypes until the 1970s (hypoendemicity; Figure 1). The pattern suggests that the different dengue serotypes causing epidemics could not get established in the country, and that epidemics corresponded with dengue virus introductions. During 1989-2001, a total of

273,556 dengue cases were reported in Venezuela, of which 41,646 were DHF cases (15.2%). During the first DHF epidemic (1989-1990) in Maracay, the predominant dengue serotype was DEN-2, with the simultaneous circulation of DEN-1 and DEN-4[4]. Therefore, apart from the introduction of a more pathogenic DEN-2 strain at that time, there also was dengue hyper-endemicity[7,8]. Therefore, it is apparent that since 1989 there have been DHF epidemics every year, and it has become endemic in large cities, such as Maracay (Figure 1).

DEN-3 appeared in Venezuela in September 2000 (D Tovar, National Institute of Hygiene, pers. com. 2001), and it was the prevalent serotype circulating in Maracay during the epidemic of 2001 (G Comach, Regional Dengue Laboratory, pers. com. 2001). From 1993-2001 there have been 17,726 clinically diagnosed dengue cases in Maracay, of which 3,703 (21%) were DHF cases, with 13 deaths (0.35% case fatality rate). The yearly reported dengue cases fluctuated in time (713-4,597), and the highest values corresponded to the DEN-3 epidemic in 2001. The morbidity rates varied between 51 and 311 cases per 100,000 inhabitants, whereas the mortality rates changed from 0 to 0.37 per 100,000 inhabitants, without an apparent relationship between these two variables (Table 1). The case fatality rate varied between 0 and 0.38%.

Figure 1: ***History of dengue epidemics in Venezuela 1942-2001. A South-East Asian DEN-2* strain was associated with the emergence of dengue haemorrhagic fever in Venezuela***



Source : Ministry of Health, PAHO

Dengue trends in Maracay

DF and DHF were reported during each month of the year, with peaks of varying intensity during the wet seasons since 1993 (Figure 2). It would seem as 3-year cycles of DF and DHF epidemics had been established in Maracay (e.g. lowest in 1996 and 1999). The introduction of DEN-3 by the end of 2000, and the epidemic caused by this serotype in 2001, seemed to have changed that temporal pattern. The years of lowest dengue (1996 and 1999) were preceded by years of peak dengue, and on each occasion, there was a delay in the appearance of dengue epidemics in the following year. For example, maximum dengue incidence was registered between July and August for most years, with the exception of 1997 and 2000, when peak dengue showed up between October and November/December.

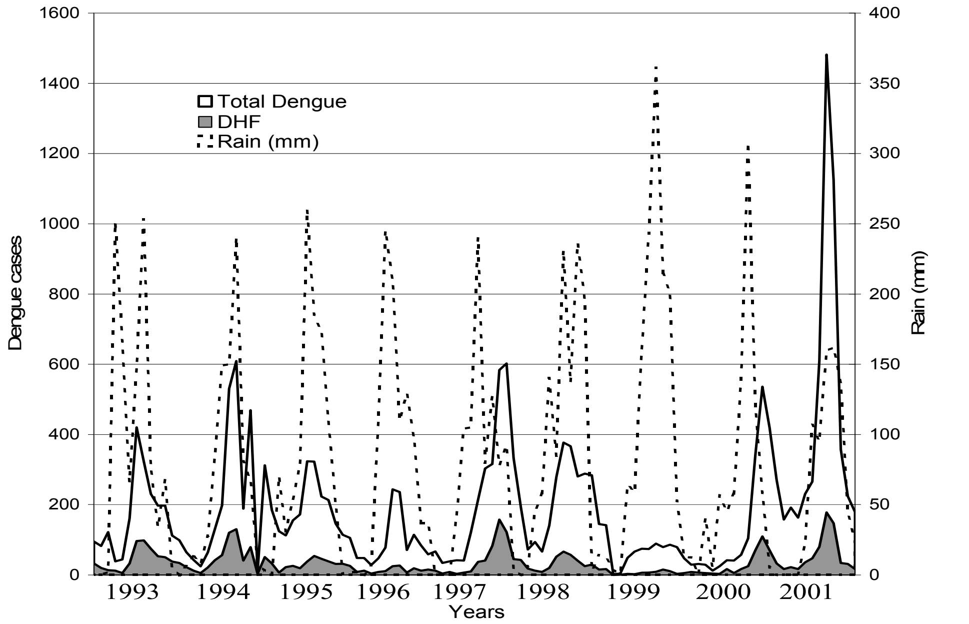
Peaks of DF and DHF cases were near concurrent with rain peaks, showing a significant correlation with the amount of rain ($r=0.43$, $P<0.05$; $r=0.26$, $P<0.05$, respectively). In spite of the markedly seasonal pattern of dengue incidence in Maracay, dengue transmission continued during the dry seasons. Figures for dry season prevalence of total dengue (21.9%) and DHF cases (22.1%) were high during the study[5]. An example of the continuous dengue circulation during the dry season was the presence of dengue cases from December 2000 to April 2001 (Figure 2), when low rainfall was recorded in 5 months (5.6 mm).

Table 1: *Clinically diagnosed DF and DHF in Maracay City, Venezuela, 1993–2001*

Year	Total dengue	DHF	% DHF	Deaths	Morbidity rate per 100,000	Mortality rate per 100,000	Case fatality rate (%)
1993	1,495	528	35.3	0	125	0	0
1994	1,864	565	30.3	1	138	0.1	0.18
1995	2,006	398	19.8	5	149	0.37	1.25
1996	989	174	17.6	2	73	0.15	1.15
1997	2,165	530	24.5	2	155	0.15	0.38
1998	2,200	389	17.7	2	157	0.15	0.51
1999	713	79	11.1	0	51	0	0
2000	1,697	381	22.5	1	115	0.1	0.26
2001	4,597	659	14.3	0	311	0	0

Source: State Health Department

Figure 2: ***Clinically diagnosed cases of dengue fever and dengue haemorrhagic fever, and rainfall (mm) by month in Maracay City, Venezuela, 1993–2001***



The temperature tends to increase and the relative humidity to decrease towards the end of the dry season, whereas relative humidity remains high during the rainy season and several weeks thereafter. DF showed a positive correlation with the relative humidity (r=0.40, P<0.05) and a negative correlation with the evaporation rate (r=-0.42, P<0.05). Despite good correlations with the weather, it seems other variables also influenced the annual patterns of dengue. For example, the low dengue incidence in 1996 and 1999 could not be explained by the lack of rain, but perhaps by the population herd immunity due to the prevailing serotypes causing large numbers of infections in the previous years. Also, the major epidemic in 2001 caused by DEN-3 can be explained by the lack of population immunity, since this serotype had not been present in Venezuela since the 1960s.

Variables related to dengue transmission

The DF and DHF incidence and persistence, population density and other variables were compared among neighbourhoods with (i) no apparent dengue (56 neighbourhoods), (ii) low (238) and (iii) high (54) incidence/persistence (Table 2). Statistical tests were performed mainly between the variables of low and high dengue neighbourhoods, because few neighbourhoods with no (apparent) cases of dengue were sampled. Neighbourhoods with higher DF and DHF incidence and persistence were more populated, occupying larger areas, and exhibited more water storage due to frequent and longer interruptions in piped water supply (Table 2). Despite the significant differences observed in the quality of water supply, the low incidence/ persistence neighbourhoods also showed lesser water storage due to smaller interruptions in piped water supply.

Aedes aegypti's indices (House Index, Breteau Index) in both dry and wet seasons were relatively high and similar in neighbourhoods with low and high dengue incidence/persistence. The most abundant breeding place of *Aedes aegypti* in Maracay was the metal drum used for water storage, followed by miscellaneous containers, discarded tyres and ornamental plants (Table 2). Despite the lack of significant differences between indices in both types of neighbourhoods, some breeding habitats were significantly more abundant in areas with higher dengue incidence, such as animal watering pans, water-storing tanks, and potted plants/flower vases (Table 2). Although metal drums used for water storing seemed to be more abundant in neighbourhoods with higher dengue incidence, the difference was not statistically significant. This can be explained by the low productivity of metal drums due to lack of food. The number of female adult *Aedes aegypti* captured in the main room of houses was significantly larger in neighbourhoods with higher dengue incidence/persistence (2.2 adults), although the vector was relatively abundant in neighbourhoods with low dengue incidence/persistence (1.5 adults).

Table 2: *Annual DF and DHF incidence, and disease persistence (maximum number of consecutive months with cases) per neighbourhood in Maracay City, Venezuela (1993–2000)#*

Dengue and related variables per neighbourhood (Mean/sample size)	Neighbourhoods stratified according to dengue incidence and persistence		
	No apparent dengue	Low	High
Total dengue incidence (cases)	0 (56)	15 (238)	155 (54)
DHF incidence (cases)	0 (56)	4 (238)	35 (54)
Total dengue per 100,000 inhabitants	0 (42)	977 (230)	1,895 (49)
DHF per 100,000 inhabitants	0 (42)	238 (230)	445 (49)
Dengue persistence (months)	0 (56)	<u>2</u> (238)	<u>12</u> (54)
Neighbourhood area (hectares)	25.4 (56)	<u>24.0</u> (238)	<u>69.3</u> (54)

Dengue and related variables per neighbourhood (Mean/sample size)	Neighbourhoods stratified according to dengue incidence and persistence		
	No apparent dengue	Low	High
Inhabitants	1,269 (42)	3,658 (230)	19,355 (49)
Frequency of water supply interruptions	2.4 (6)	2.6 (82)	2.0 (35)
Length of water supply interruptions	1.6 (6)	1.8 (82)	2.3 (35)
Frequency of garbage collection	2.3 (6)	2.1 (82)	2.1 (35)
House Index in dry season	24 (2)	21 (36)	20 (21)
House Index in rainy season	17 (5)	20 (67)	23 (32)
Breteau Index in dry season	32 (2)	32 (36)	31 (21)
Breteau Index in rainy season	27 (5)	30 (67)	38 (32)
Animal pans per 100 houses	1.6 (5)	1.5 (67)	2.6 (32)
Water tanks per 100 houses	1.4 (5)	1.3 (67)	2.8 (32)
Metal drums per 100 houses	10.8 (5)	12.4 (67)	14.9 (32)
Potted plants and flower vases per 100 houses	4.6 (5)	3.0 (67)	4.3 (32)
Old appliances per 100 houses	0 (5)	0.3 (67)	0.1 (32)
Containers in plants per 100 houses	0.2 (5)	0.1 (67)	0.2 (32)
Tires per 100 houses	1.2 (5)	4.6 (67)	5.7 (32)
Miscellaneous containers per 100 houses	7.4 (5)	7.0 (67)	4.5 (32)
Aedes aegypti females per room	N/A	1.5 (20)	2.2 (14)

Statistical comparisons were made only between neighbourhood with low and high dengue incidence/persistence, since only a few neighbourhoods without apparent data were sampled. Underlined values were statistically significant (PC 0.05)

Discussion

Emergence of DHF in Venezuela

The establishment of DHF in Venezuela as an endemic/epidemic disease was associated with the introduction of more pathogenic dengue virus strains, hyperendemicity and uncontrolled *Aedes aegypti* populations, generated by rainfall and water-storing practices. Our results showed significant associations of DF and DHF incidence with deficiencies in water supply at the neighbourhood level in Maracay. This was in tune with previous studies in several Venezuelan urban centres[10,11]. Public service deficiencies are the likely structural and long-lasting problems of neighbourhoods. It is perhaps for this reason that we have found that neighbourhoods are consistent in their temporal dengue patterns. The same neighbourhoods producing large numbers of cases in one year continued to do so throughout the study period. Also, neighbourhoods producing large numbers of cases exhibited high degrees of dengue endemicity, as estimated by dengue persistence (maximum number of consecutive months a neighbourhood produced dengue cases)[5]. If these conditions get compounded with multivirus circulation then it is not surprising to find endemic DHF.

Temporal dengue patterns in Maracay City

The data showed good correlations between dengue and the meteorological variables associated with the ecological dynamics of *Aedes aegypti*. Positive correlations with rain should reflect a larger abundance of aquatic habitats for immature mosquitoes; however, in this study larval indices did not differ between seasons. Entomological data for Maracay city shows that mosquito productivity is associated with ornamental containers, miscellaneous containers, metal drums, tyres, and animal pans. However, the frequency with which miscellaneous containers are found with pupae is higher than in any other container, which in turn may be responsible for a larger adult population during the rainy season. It is also likely that a higher humidity during the rainy season could influence vectorial capacity due to increased longevity. The large number of breeding places of *Aedes aegypti* existing during the dry season in Maracay may account for sustained dengue transmission, resulting in DF and DHF endemicity in the city.

Apart from the seasonal influence of weather on dengue incidence, yearly variations indicated the need to understand the dynamics of population immunity to each dengue serotype in Maracay. The lowest yearly dengue incidence rates were observed in the years immediately after a dengue peak, but the 2-3 month delay in outbreaks in the following year could be due to the exhaustion of susceptibles to the prevailing serotype(s). On the other hand, the large epidemic (2001) observed after the entrance of DEN-3 may also reflect the lack of immunity to this serotype that had been absent in Venezuela since the 1960s.

Environmental variables and dengue

Neighbourhoods with higher dengue incidence/persistence were characterized as having a larger human population, larger area, more accentuated deficiencies in the frequency and length of water supply interruptions, and more *Aedes aegypti* female adults resting inside the main room of houses (Table 2). However, neighbourhoods with lower dengue incidence/ persistence exhibited some degree of deficiency of public services and relatively high *Aedes aegypti* densities (1.5 *Aedes* females per main room of houses). Such vector density is higher than that observed during some dengue epidemics (one *Aedes* female per house)[17,18]. If we consider that neighbourhoods in Maracay are not all isolated from each other, and that viruses could be frequently moved between neighbourhoods, the low incidence/ persistence of dengue in those neighbourhoods seems to point out that other variables may be determining the level and constancy of dengue transmission. In other words, *Aedes aegypti* infestation is generally high and does not seem to be a limiting factor for dengue transmission in Maracay. Within the limitations of this study, the other significant variables separating low from high-dengue neighbourhoods were the number of inhabitants and the area, which should be correlated (Table 2). It is not surprising to find this result since there probably is a population density threshold for dengue transmission[17]. More populated neighbourhoods could also imply a more frequent virus exchange with other infected neighbourhoods or cities, particularly in those including the main administrative and commercial centres of the city, and satellite towns of the Metropolitan Area of Maracay.

Implications for dengue control

Dengue control in Maracay city has been limited to emergency measures, such as outdoor spatial spraying of malathion (ultra low volume) from trucks around the block of notified dengue cases, campaigns for source reduction, and media efforts to obtain community involvement during epidemics. As the results of the temporal analysis showed, dengue persists as an endemic disease, and large epidemics resulting from the introduction of DEN-3 in 2000 could not be prevented with those control measures. Therefore, unless a change in the prevention/control approach takes place it is easy to predict the continued occurrence of endemic/epidemic DF and DHF in Maracay city.

Water storing due to deficiencies in piped-water supply is perhaps the greatest threat, followed by the widespread occurrence of miscellaneous, disposable containers, and the habit of keeping plants and flowers in water. Dengue control measures should be oriented towards drastic and permanent reductions in the number of containers holding water inside and outside buildings. A great deal of the solution to this problem could come from improving the water supply and garbage collection infrastructure, although it still would be necessary to modify behaviours such as those related to the use of plants and flowers in water (gardens, inside the house, cemeteries, etc.), animal watering pans, maintenance of roof gutters, etc. Those tasks could only be accomplished with an adequate infrastructure and personnel for mosquito control directed towards the sustained reduction of breeding places.

Acknowledgements

We express our gratitude to the Venezuelan Air Force, Department of Health, Aragua State, and the National Census Bureau for providing essential data, and to the following for their invaluable assistance in the field and the laboratory: Victor Aguilar, María González, Mónica Prado, Yelitza Moccó, Iris Obregón and Oscar Ruiz. This research was partially financed by the World Bank/ Department of Health (VEN/92/006; LP 021-009), and Fundacite Aragua.

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