Chapter

Situation of Dengue after the Phenomenon of the Coastal El Niño

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Abstract

Coastal El Niño is a weather phenomenon that is caused by abnormal warming (above 0.4°C) of the Pacific Ocean waters near the coasts of Ecuador and Peru, and it can even reach the central and southern Peruvian coast. As a result of the climatic phenomenon, the Aedes *aegypti* vector (which in turn is a vector of chikungunya and Zika fever) had been quickly installed in 448 districts of Peru, and emergency was declared in 10 regions, which reported 231,874 victims; 1,129,013 affected and 143 dead. It is necessary to know this, because the direct impact of the weather phenomena contributes to the dengue vector conditioning, facilitating its dissemination with ease. The geographical and climatic conditions of the cities most affected by the El Niño Costero phenomenon turned them into zones of epidemics; in these places, there is an important population growth, from urbanization to sectorization in young towns and urban slums, where in many there is no basic infrastructure and water supply is insufficient, which requires temporary water storage, as well as high temperatures, migratory movement, and beaches with influx of people, which make not only dengue proliferate but also other arbovirosis such as chikungunya.

Keywords: dengue, natural phenomenon, natural disaster, public health

1. Epidemiology of dengue and the coastal El Niño phenomenon in Peru and Ecuador

1.1 Epidemiological data

Coastal El Niño is a weather phenomenon that is caused by abnormal warming (above 0.4°C) of the Pacific Ocean waters near the coasts of Ecuador and Peru, and it can even reach the central and southern Peruvian coasts. As a result, it produces intense rains that, in turn, cause overflow of streams, floods, and allow the accumulation of stagnant waters, which forms the ideal scenario for the appearance of outbreaks of vector-borne diseases such as dengue (DENV), other arbovirosis, and zoonotics such as leptospirosis [1–4]. This phenomenon was presented more clearly in the summer of 2017; however, rains and floods have been reported for Peru even since December 2016 [5].

As a result of the climatic phenomenon, the *Aedes aegypti* vector (which in turn is a vector of chikungunya and Zika [ZIKV] fever) had been quickly installed in 448 districts of Peru, where more than 14 million people live, by July 2017 [6]. Thus, the Peruvian State in June 2017, declared emergency in 10 regions, which reported 231,874 victims; 1,129,013 affected and 143 dead. It is necessary to know this, because the direct impact of the weather phenomena contributes to the dengue vector conditioning, facilitating its dissemination with ease. Thus, the Peruvian Ministry of Health reported that at the end of 2017, the epidemiological surveillance system reported 76,093 cases of dengue (among probable and confirmed), marking an increase of up to three times more cases compared to 2016 (25,236 cases) (**Figure 1**) [7].

Among the most frequently reported forms were dengue without warning signs (88.6%), dengue with warning signs (11%), and severe dengue (0.3%). The cumulative national incidence for 2017 was 239.1 cases per 100,000 inhabitants and there were 93 deaths, of which 79 were confirmed cases and 14 were probable [8].

There was a marked increase in cases, in those places where there was a greater presence of rain and floods. Thus, for example, Piura concentrated 64% of dengue cases: this place being one of the most affected cities and even presented an overflow from its main river that crosses through the same city, the river Piura [9].

Do not forget that northern Peru is an endemic area due to climate, geography, and other factors that make it a vector-friendly ecosystem, being considered one of the countries with the greatest impact due to climate change [10].

1.2 Dengue and climate

Dengue transmission occurs through an insect vector, predominantly *Aedes aegytpi* but also *Aedes albopictus*. Environmental parameters, especially temperature and precipitation, affect the demography and behavior of these vectors, making dengue an obvious candidate to investigate the impact of climate on the disease. The incidence of dengue is very seasonal; this seasonality is the footprint of local meteorological variables, which also vary seasonally, and their impact on the demographics of mosquito vectors and transmission dynamics [11].

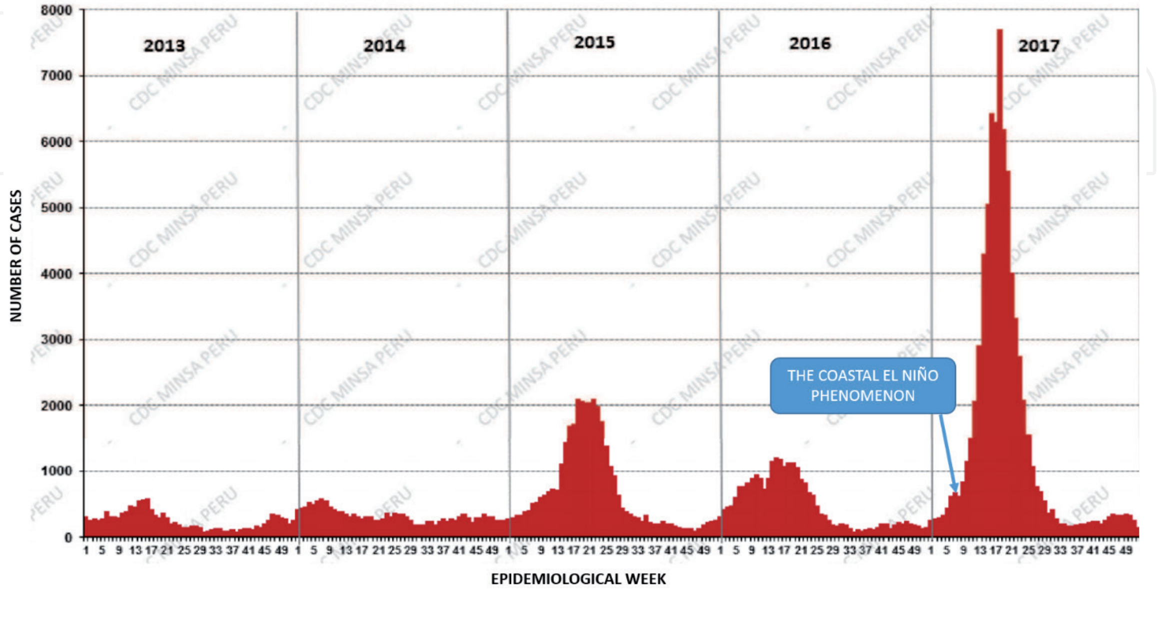

Figure 1.
Number of dengue cases, according to epidemiological weeks. Peru, 2013–2017. Taken from: Ministry of Health of Peru MINSA [12].

The geographical and climatic conditions of the cities most affected by the El Niño Costero phenomenon turned them into zones of epidemics; in these places, there is an important population growth, from urbanization to sectorization in young towns, urban slums, where in many there is no basic infrastructure and water supply is insufficient, which requires temporary water storage, as well as high temperatures, migratory movement, and beaches with influx of people, which make not only dengue proliferate but also other arbovirosis such as chikungunya [13].

1.3 Epidemiology of other metaxenic diseases

The propagation of the vector for decades is conditioned by the climatic changes. For example, in May 2004, heat waves and droughts were observed in the coastal areas of Kenya, toward Lamu and Mombasa, two large coastal cities. That period was also the beginning of a large chikungunya outbreak in these two cities (with reported attack rates of 75%) before its spread to the Indian Ocean [14]. Entomologists have explained how and why droughts can be associated with increases in diseases transmitted by *Aedes*, such as chikungunya, dengue, Zika, and yellow fever [15, 16]. During droughts, due to water scarcity, people store a greater amount of water outside or inside the home for longer periods of time, providing shelters to mosquito eggs and larvae [13].

In Peru, the consequence of this weather phenomenon allowed the dissemination of the *Aedes* vector and consequently led to the increase in cases of emerging diseases, such as Zika and chikungunya (**Figure 2**). Thus, from 2016 to 2018, 1113 gestating women entered the surveillance system for Zika, of which 61% were notified in 2017. Of the total number of pregnant women notified, 31% had laboratory confirmation for Zika virus through molecular tests like polymerase chain reaction-reverse transcription (RT-PCR) [7].

1.4 Dengue and coinfections

The fluvial precipitations that the phenomenon of the coastal El Niño brought with it during 2017 triggered the collapse of the sewerage system, generating floods and the exposure of wastewater, which together with the rains gave an adequate

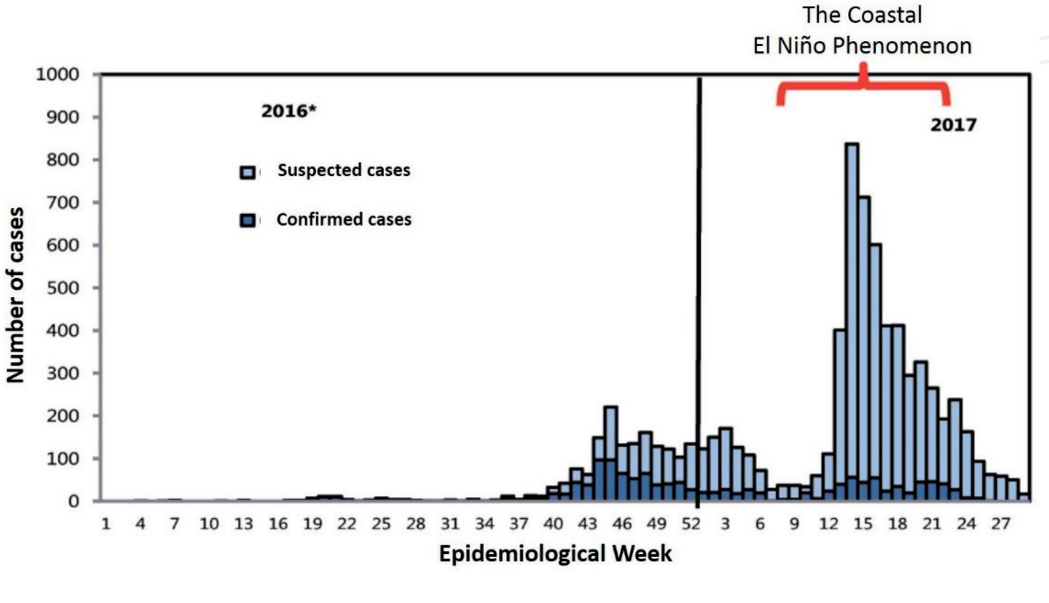

Figure 2.
Distribution of indigenous cases of Zika by onset of symptoms. Peru 2016–2017. Taken from: Ministry of Health of Peru MINSA [17].

environment for the transmission of leptospirosis in urban areas of the Lambayeque region. It was even possible to demonstrate that during this period, laboratory findings compatible with dengue and leptospirosis were reported simultaneously. While it is true that many of the immunoglobulin can remain for years in the patient and do not necessarily require an acute infection, the similarity of clinical symptoms between dengue and leptospirosis makes both pathologies confusing to health personnel, even more so during the appearance of a weather phenomenon where there is an outbreak [18].

1.5 Dengue and seasonality

Dengue in Ecuador fluctuates with a very similar seasonality. The season is an important determinant of infectious disease rates, including mosquito-propagated arboviruses, such as dengue, chikungunya, and Zika. Seasonal disease patterns are driven by a combination of climatic or environmental factors, such as temperature or rainfall, and trends in human behavior time, such as school year schedules, vacations, and weekend patterns. These factors affect both disease rates and medical care-seeking behavior. The seasonality of dengue fever has been studied in the context of climatic factors. Thus, between 2009 and 2016, a predictive model of dengue detection was studied using data from the same patients in rural areas in Ecuador. Thus, compared to the average of every day, cases were more likely to be diagnosed on Tuesdays (relative risk [RR]: 1.26; 95% confidence interval [CI]: 1.05–1.51) and Thursdays (RR: 1.25; 95% CI: 1.02–1.53), and were less likely to be diagnosed on Saturdays (RR: 0.81; 95% CI: 0.65–1.01) and Sundays (RR: 0.74; 95% CI: 0.58–0.95). The holidays were not significant predictors of dengue diagnoses, except for an increase in diagnoses the day after Christmas (RR: 2.77; 95% CI: 1.46–5.24) [19].

From the political sphere, the coastal El Niño phenomenon caused the Ministry of Health and the Ministry of Defense of Ecuador to take into account the declaration of emergency for the Peruvian city of Piura, issued by the Ministry of Health of that country. This is because that city is close to the border of Ecuador, and the trade between the two countries is very high, which makes it necessary to work in a multisectoral way to eradicate the vector [20].

1.6 Impact on the epidemiological surveillance system

It is very necessary to maintain entomological surveillance, especially in those cities where the phenomenon left vector presence. Migration and population increase, in addition to raising awareness and educating the population about the risk factors of dengue occurrence, should always be taken into account to avoid a disease that was installed in the Americas decades ago, precisely because of migration from other areas. The consequences of climate change must be learned as it not only destroys our habitat but directly interferes with our health [21]. Health authorities have the responsibility to plan strategies and evaluate their impact progressively. Many times it is not enough to plan, but to change strategies to avoid having the same results.

2. Clinical behavior of dengue

2.1 Definitions

Classically, the disease presents with an incubation period of 3–14 days; after that a febrile phase (1–4 days); viremia, the critical phase from 4 to 7 days; and a recovery phase from day 7 onward [22]. This disease course depends on the virus serotype and whether or not the individual has previously had a dengue infection. In this spectrum of disease, one can have:

- Dengue without warning signs: Person with a fever of 7 or less days, with at least two of the following symptoms such as eye pain, myalgia, headache, arthralgia, low back pain, rash, and nausea [23, 24].

- Dengue with warning signs: Person with a probable case of dengue with one or more of the clinical signs such as severe abdominal pain, dyspnea, serous effusion, persistent vomiting, hypothermia, mucosal bleeding, altered mental status, increased hematocrit, and hepatomegaly [23, 24].

- Severe dengue: A probable case with or without warning signs presenting one of the following signs such as signs of hypovolemic shock, severe bleeding, respiratory distress syndrome due to plasma extravasation, and severe organ involvement (encephalitis, hepatitis, and myocarditis) [25].

2.2 Signs and symptoms

It is known that the cross-immunity of dengue serotypes is limited, which increases the possibility of reinfections and with them more florid clinical pictures [25, 26].

Previous studies observed the outbreaks from 2010 onward, observing that dengue cases occurred in a greater proportion due to DENV-2, the most frequent clinical symptom being retro-ocular pain, myalgias associated with a 7-day fever [27]. Also, it was observed that in dengue cases, many of them were reinfections and DENV-2 continued to prevail, which was one of the worst at presenting cross-immunity (**Figure 3**).

A study conducted in the north coast of Peru found that, among the referred symptoms, 82% reported fever, being less than half quantified (values from 37to 41°C), followed by headache (75.6%), arthralgias (69.7%), myalgias (62.4%), retroocular pain (55.5%), lumbar pain (44.7%), and only 24.4% presenting rash. The presence of platelet decrease (78.4%) was the most frequent among cases with alarm signs [28] (**Figure 4**).

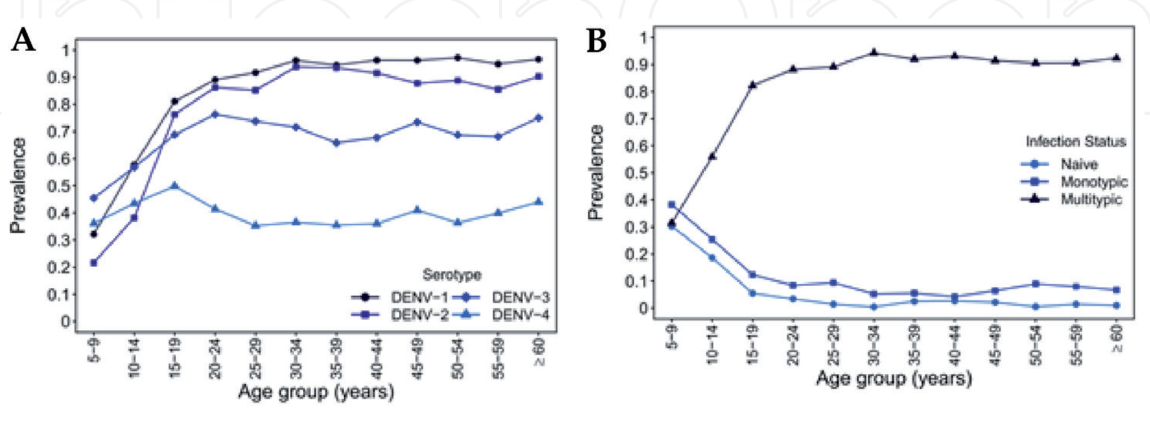

Figure 3.
Age distribution of DENV-neutralizing antibodies in 2010. Samples were collected between March and June 2010, approximately 6 months prior to a large dengue epidemic largely caused by American/Asian genotype DENV-2. Panel A: Age distribution of serotype-specific DENV-neutralizing antibodies. Panel B: Age distribution of number of prior DENV infections. Naive indicates absence of detectable DENV-neutralizing antibodies against any serotype, monotypic indicates DENV-neutralizing antibodies against one serotype, and multitypic indicates DENV-neutralizing antibodies against two or more serotypes. Taken from: Forshey et al. [29].

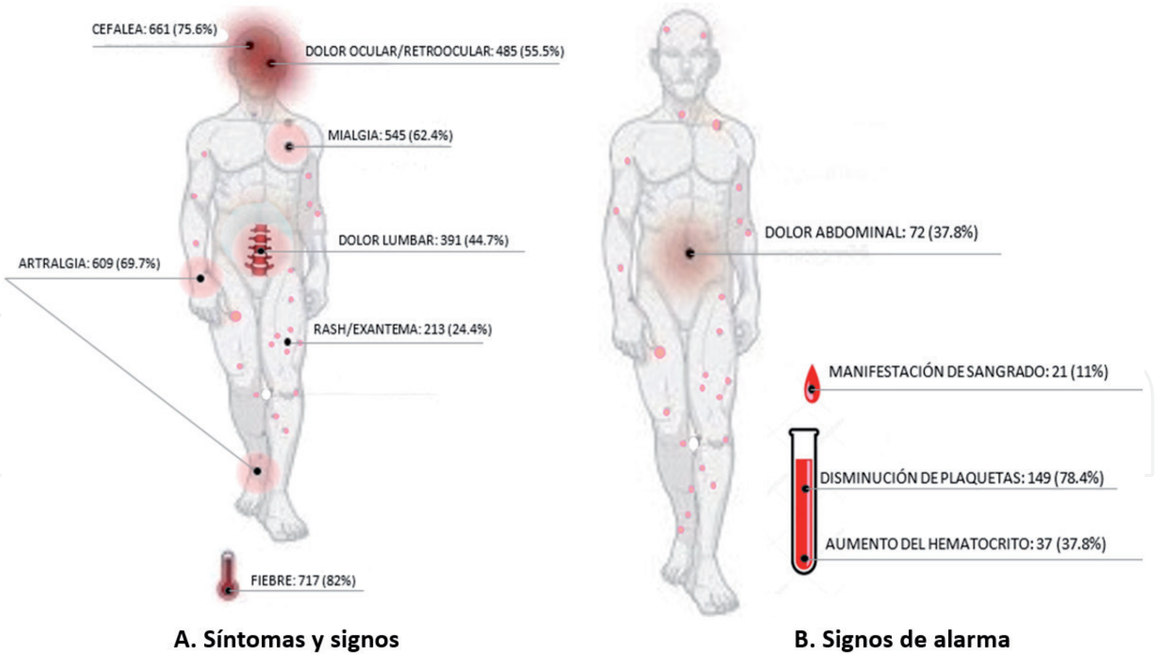

Figure 4.
Symptomatology of patients diagnosed with dengue. (A) Symptoms and signs. (B) Warning signs. Taken from: Perales-Carrasco et al. [28].

2.3 Signs and symptoms in coinfections

In recent years, new viruses such as chikungunya (CHIKV) and Zika (ZIKV) have also been introduced. In recent years after the ZIKV epidemic, cases of ZIKV infection have continued to be observed, and in children, according to Salgado et al. [30], there were found patients with encephalitis with coinfection of DENV and ZIKV.

Another study, also conducted in Peru, showed that the circulating serotypes during the coastal El Niño phenomenon were DENV-2 and DENV-3, as well as confirmed cases of CHIKV and ZIKV, even in high Andean areas; concomitantly, the study revealed that the main symptoms of dengue were headaches, arthralgias, and back pain associated with fever (**Table 1**) [27].

Taken from: Forshey et al. [29].

In Peru, there could be a subdiagnosis or overdiagnosis of dengue and therefore of the clinical variability, on the one hand; the amount of arbovirosis that can give a similar clinical presentation is wide, and within these viruses is oropuche, which can be confused with dengue during the endemic months [31]. The contrary occurs in patients with a second dengue virus infection in which the diagnostic methods have a lower sensitivity of 60%, as is the case of non-structural (NS1), a test widely used in our environment [26].

The Huánuco region, located in the center of Peru, was one of the cities that presented an increase in dengue cases, where about 90% of patients presented with myalgia, headache, and rash; being in these patients a diagnostic confirmation of 92% by PCR. This being an area with low endemicity, but as a result of coastal El Niño, it could mean a majority of primary infection, and therefore this high rate of clinical diagnostic correlation [26]. In addition, it is important to know the behavior in children under 5 years of age, in which many of them have antigens from mothers in endemic areas, which leads to more severe manifestations being possible in this particular age group [32].

Finally, it can be observed that, in the years before the dengue virus infection, the agent (DENV-2) and the clinical manifestations were similar, with the difference in the number of cases and the increase in coinfections of the new circulating

Clinical symptoms	Total n = 496 (%)	PCR real-time confirmed cases		
		DENV (n = 170)	ZIKV (n = 39)	CHIKV (n = 23)
		n (%)	n (%)	n (%)
Chills	3 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)
Headache	444 (89.5)	152 (89.4)	34 (87.2)	20 (87.0)
Dizziness	1 (0.2)	0 (0.0)	1 (2.6)	0 (0.0)
Cough	1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)
Sore throat	184 (37.1)	50 (29.4)	11 (28.2)	11 (47.8)
Nausea and/or vomits	251 (50.6)	86 (50.6)	20 (51.3)	13 (56.5)
Loss of appetite	312 (62.9)	104 (61.2)	23 (59.0)	18 (78.3)
Back pain	270 (54.4)	105 (61.8)	23 (59.0)	17 (73.9)
Dysuria	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	419 (84.5)	147 (86.5)	35 (89.7)	17 (73.9)
Arthralgia	396 (79.8)	143 (84.1)	32 (82.1)	19 (82.6)
Retro-ocular pain	337 (67.9)	118 (69.4)	27 (69.2)	17 (73.9)
Rash	89 (17.9)	26 (15.3)	8 (20.5)	6 (26.1)
Melena	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal bleeding	9 (1.8)	3 (1.8)	1 (2.6)	1 (4.3)
Gums bleeding	3 (0.6)	2 (1.2)	1 (2.6)	0 (0.0)
Petechiae	11 (2.2)	3 (1.8)	0 (0.0)	1 (4.3)
Ecchymosis	2 (0.4)	1 (0.6)	1 (2.6)	0 (0.0)
Blood-tinged sputum	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	22 (4.4)	7 (4.1)	1 (2.6)	1 (4.3)
Thoracic pain	5 (1.0)	2 (1.2)	0 (0.0)	0 (0.0)
Fatigue	3 (0.6)	0 (0.0)	1 (2.6)	0 (0.0)
Altered mental status	1 (0.2)	1 (0.6)	0 (0.0)	1 (4.3)

Table 1.
Clinical symptoms in patients with positive samples for DENV, ZIKV, and CHIKV.

viruses; this should make the health staff reflect on making proper use of diagnostic tests to provide better care and avoid fatal outcomes, as it was in some cases discussed above in the last phenomenon of the coastal El Niño (**Table 2**).

3. Laboratory in the diagnosis of dengue

Today, there are guidelines established by international organizations for the rational use of dengue diagnostic tests. The World Health Organization (WHO) recommends the use of polymerase chain reaction (PCR) for the early detection of dengue and its complementation with other tests such as immunoglobulin M (IgM), immunoglobulin G (IgG), and NS1 [33]; however, the use according to the clinical picture and the time of the disease will favor the optimal use of the different tests.

The sensitivity and specificity of the NS1 antigen test can range from 49 to 59% and from 93 to 99%, respectively, while that of the IgM antibody test is from 71 to

Characteristics	Crude analysis		Risks for dengue	
	Chikungunya	Dengue	p-value	Adjusted odds ratio (95% CI)*
Clinical				
Diarrhea, n (%)	3/37 (8)	13/57 (23)	0.064	2.13 (0.29–15.66)
Ascites, n (%)	0/37 (0)	1/57 (2)	1.000**	N.E.
Pleural effusion, n (%)	0/37 (0)	2/56 (4)	0.516	N.E.
Laboratory				
Hemoglobin (mg/dl) median (interquartile range (IQR)) [n]	10.5 (10–12) [35]	10.5 (10–12) [36]	0.910	
Decrease for age, n (%)	26/36 (72)	25/53 (47)	0.019	1.33 (0.26–6.87)
Increase for age, n (%)	0/36 (0)	1/53 (2)	1.000**	N.E.
Hematocrit (%) median (IQR) [n]	30.9 (29–34) [33]	31.5 (30–35) [37]	a. 0.510	
Decrease for age, n (%)	24/33 (73)	30/52 (58)	0.160	1.04 (0.26–4.19)
Increase for age, n (%)	0/33 (0)	1/52 (2)	1.000**	N.E.
White blood cells (1000 cells/ml) Median (IQR) [n]	6.4 (5–10) [33]	7.4 (5–12) [36]	0.220	
Decrease for age, n (%)	17/33 (52)	16/53 (30)	0.048	0.28 (0.07–1.08)
Increase for age, n (%)	4/33 (12)	5/53 (9)	0.728	1.97 (0.27–14.17)

Note: N.E.: Not estimable. Taken from: Paternina-Caicedo et al. [32].
**Adjusted by age, days with symptoms, and sex.*
***Fisher's exact test.*
****Best fit was the natural logarithm of the exposure variable.*

Table 2.
Clinical and laboratory characteristics of chikungunya and dengue and their relative adjusted risks among children <24 months of age in Colombia.

80% and 46 to 90%, respectively, considering a median of 5 days of fever before the collection of the samples (interquartile range of 3–7 days) for the two tests mentioned. The diagnostic accuracy for the detection of IgM increases for late acute infection (5 days after the onset of symptoms) compared to the early one. The NS1 antigen is an early marker of acute infection, and its combined use with IgM detection can provide a definitive diagnosis of 96.9–100% for samples obtained after 3 days of illness [33]. The reported sensitivity and specificity of IgG for dengue are 92.0 and 100%, respectively [34].

The patient usually has an incubation period of 4–5 days after the bite by mosquitoes of the *Aedes* genus, then presents a clinical picture with variable signs and symptoms for a period of 4–5 days, a period in which he presents the virus of the dengue circulating in the bloodstream and can transmit the disease to other patients through new bites by the aforementioned vector, so techniques based on virus isolation, through cultures, or the detection of genomic material, such as PCR, require samples taken during this time. The end of the patient's clinical picture is usually manifested by a generalized maculopapular rash, which indicates recovery and can guide the use of serological tests, such as the detection of IgM and IgM antibodies, since the viral load values in the patient have disappeared or significantly reduced, which would make the use of molecular tests or culture inefficient. Leukopenia can be found at this stage with normal platelet and transaminase counts [3].

We can summarize the diagnostic tests used for dengue in four groups: (i) virus isolation and characterization, (ii) detection of the genomic sequence through a nucleic acid amplification test, (iii) detection of specific antibodies against the virus, and (iv) identification of dengue virus (glycoprotein) antigens. Isolation of the virus is achieved by cell culture that gives the most specific result, and the sera are usually collected in the first 3–5 days after the fever starts. Virus isolation is highly dependent on viral load, which limits the period during which the virus can be successfully isolated in the patient's serum. In addition, its high cost makes this test little accessible to most laboratories [3]. Viral identification can also be done using dengue-specific monoclonal antibodies by immunofluorescence and reverse transcription-PCR (RT-PCR) [3].

On the other hand, serological tests are relatively inexpensive and easy to perform. These characteristics make them the most used tests for dengue infection. IgM levels begin to rise on the third day of a primary infection and peak at 2 weeks after the onset of fever (**Figure 5**). IgG is detectable at the end of the first week of illness and may persist for life. Enzyme-linked immunosorbent assay (ELISA) tests can analyze the levels of IgM and IgG, and the IgM/IgG ratio is useful to distinguish primary from secondary infections. The IgM/IgG ratio greater than 1.4 is indicative of primary dengue infection, while the IgM/IgG ratio lesser than 1.2 is indicative of secondary dengue infection. The potential cross-reactivity of dengue virus with other flaviviridae when using serological assays remains a significant limitation for its use. Prior vaccination against yellow fever can also lead to a false positive serological test for dengue virus. The prolonged period of seroconversion also results in false negatives [3]. All flaviviruses produce a glycoprotein called NS1 and tests such as antigen capture ELISA and quick tests based on immunochromatography can be used to identify it in the bloodstream; it is detectable from days 0 to 9 after the onset of symptoms, although detection appears to be higher in the samples collected up to 3 days after the onset of symptoms. Quick tests are now available and provide results in 15 min. Rapid tests for NS1 have been estimated to have a significantly higher sensitivity for primary infections (94.7%) than for secondary infections (67.1%; $p < 0.001$) and now appear to be a potential alternative to culture, PCR, and serology [38].

The Brazilian Ministry of Health recommends that samples of patients with suspected dengue fever taken up to 8 days (preferably 5) after the onset of symptoms should be processed using ELISA for the detection of NS1 and qRT PCR for the detection of the DENV genome and the serotype. At 8–15 days after the onset of symptoms, the samples are analyzed for IgM detection using ELISA. After 15 days,

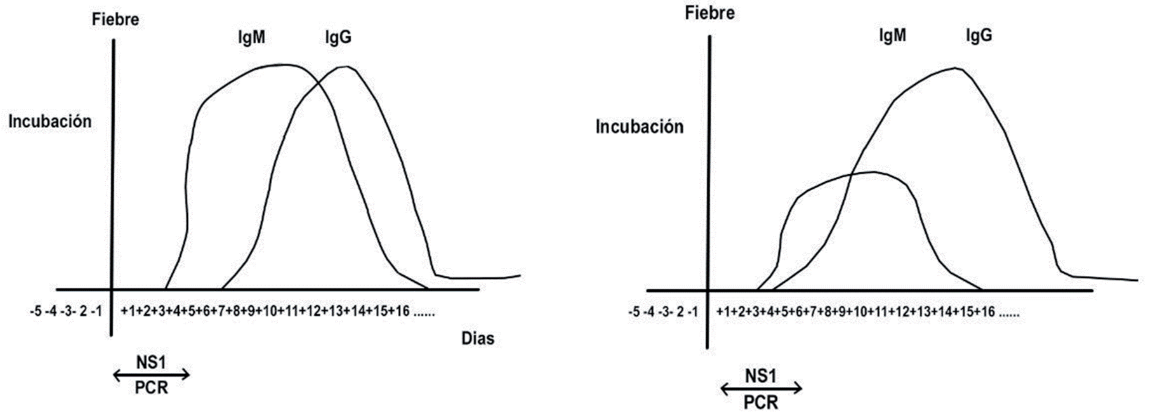

Figure 5.
(A) Primary infection by dengue. (B) Secondary infection by dengue. Source: Clinical Pathology Department, Almanzor Aguinaga Asenjo, Hospital, Essalud.

the sera are selected for IgG using ELISA. Dengue infection cannot be excluded in samples that are negative for the NS1 antigen and must be confirmed by IgM/IgG detection [35].

Cases of DENV-2 had a higher proportion of severe dengue than among those of DENV-1 and DENV-4 [39]. Nevertheless, the secondary infection was not a predictor of severe clinical manifestation in adults, who were primarily infected with serotype DENV-3 [40]; on the other hand, the dengue in children have suggested that infection with secondary DENV-2 is more likely to result in severe disease compared with other serotypes [41].

The fifth variant DENV-5 has been isolated in October 2013. This serotype follows the sylvatic cycle unlike the other four serotypes which follow the human cycle. The likely cause of emergence of the new serotype could be genetic recombination, natural selection, and genetic bottlenecks [42].

4. Diagnosis of dengue and other arbovirosis in the context of the Guillain Barre syndrome epidemic

During the months of June–July of 2019, 35 cases were registered and diagnosed as the Guillain-Barre Syndrome, at the Almanzor Aguinaga Asenjo National Hospital of Chiclayo in Peru, of which 22 had electrophysiology results compatible with the said syndrome, two had a normal result, and 11 were not evaluated with the mentioned diagnostic test. Three cases had IgG for flavivirus, three cases had IgG for flavivirus and IgG for chikungunya concomitantly, four cases had IgG for chikungunya, and one case had IgM for chikungunya. In other words, there were 11 cases of patients with a history of flavivirus or chikungunya infections in the context of the presentation of Guillain-Barre syndrome [43]. These patients were evaluated with the recomLine Tropical Fever IgG and IgM tests, immunoblot of German origin that has a sensitivity for IgG of 100% for primary infection by Zika, 100% for secondary infection for dengue or Zika, and 98.6% for primary infection by dengue; also the IgM has a sensitivity of 72.7% for dengue or Zika, and both tests have a specificity of 96–100%. On the other hand, the mentioned test describes a sensitivity and specificity of 100% for both IgM and IgG for chikungunya's diagnosis [44].

In the literature, there is the case of a dengue patient who developed Guillain-Barre syndrome, who presented the NS1 antigen on the second day of symptoms with subsequent IgM and IgG positive on the sixth day of evolution [45]. There is also another case described with similar laboratory findings, but that developed the syndrome approximately 2 weeks after the onset of dengue symptoms [46]. Therefore, this syndrome could develop early or late in relation to the onset of symptoms due to infection. In our cases, we did not have positive IgM and we did not have the opportunity to evaluate the NS1 antigen, but it is noteworthy that all cases detected with flavivirus antibodies only had positive IgG in their results. The previous cases described in the existing literature may represent primary cases of dengue since they raised IgM values early.

In our cases, the majority of patients did not show joint pain during the diagnosis of Guillain-Barre syndrome, which could suggest that these are non-acute cases, but as described in the case cited, this syndrome may occur during convalescence of the dengue; on the other hand, in an endemic area such as Lambayeque-Peru, the presence of cases with secondary infection that usually have low IgM values and not even increase it (**Figure 5**) should not attract attention [47]. In addition, Ramabhatta et al. [48] conducted a study on a sample of 568 cases diagnosed of dengue and showed that IgG-positive patients were more prone to complications than IgM-positive patients, therefore, the etiological association between dengue and Guillain-Barre syndrome in the Lambayeque region could not be ruled out.

5. Dengue lethality

5.1 Lethality in the context of Peru and Latin America

In 2014, according to WHO and Pan American Health Organization (PAHO), the average fatality rate for the Americas is 0.04%, being among the countries with the highest rate, followed by Dominican Republic with 1.54%, Peru with 0.12%, compared to Guatemala and Colombia that have 0.07% [49]. In Colombia and Peru, the most frequent serotype 2 prevailed, and in the Dominican Republic serotype 4 prevailed [50].

Nationally, the Center for Epidemiology, Prevention and Control of Diseases of the Ministry of Health, reported in 2017, 76,093 cases of dengue in the country (3.03 times more cases in relation to 2016, and the largest number of cases reported in the last 5 years [9, 51] and 92 reports of deaths by dengue, the highest number reported in the last 10 years) (**Figure 6**).

About 43.6% came from Piura, 17.1% from Loreto, 9.9% from Madre de Dios, 8.8% from Ucayali, 4.2% from San Martín, and the remaining 16.4% from other regions; all the age groups were affected, but with a greater proportion in people over 65 (37%) and young adults (21.7%) [9].

In the Piura Healthcare Network, 30 deaths associated with dengue virus were confirmed by laboratory, and occurred between epidemiological weeks Nos. 08 and 35, over 8 months; a similar panorama reported by the Lambayeque Healthcare Network, which reported the death of six dengue-associated patients, until epidemiological week No. 20 [13, 52]; although this information could be underestimated, because in many cases it is attributed to pneumonia, and actually the cases of dengue are not properly diagnosed, causing figures not approximate to reality [53].

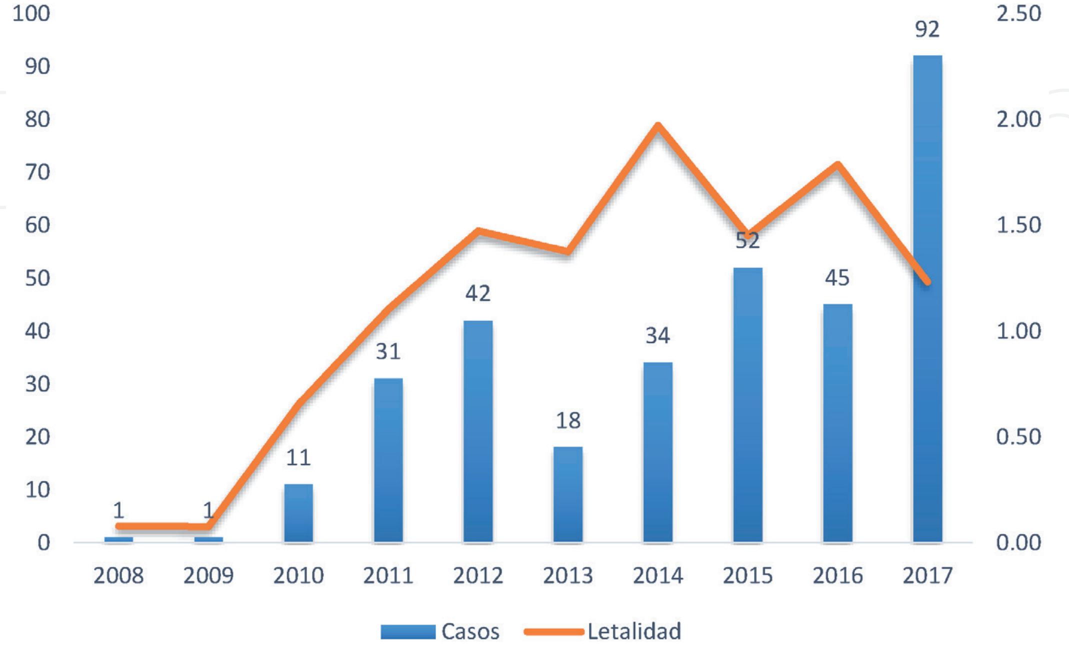

Figure 6.
Death toll and dengue lethality in Peru, 2008–2017. Source: Metaxenic disease surveillance system of the Center for Epidemiology, Disease Prevention and Control of the Ministry of Health (CDC-Perú).

In the departments of the north coast of Peru, such as Piura and Lambayeque, there are several conditions that favor the presence of epidemics, rainfall, and flooding due to the occurrence of the Coastal El Niño phenomenon, population growth at risk (young People, Urban Marginal Neighborhoods, etc) that is associated with the non-existence of basic infrastructure, insufficient water supply that leads to temporary water storage, constant circulation of *Aedes aegypti*, high temperatures and humidity, and poor community empowerment in the integrated control of vector control. Also in the Peruvian jungle, such as Loreto, Madre de Dios, Ucayali, and San Martin, they have a high incidence of death and lethality due to their diverse climatic and sanitary conditions, in addition to their population growth [13].

In the Healthcare Network of Piura, 22,562 cases of dengue were notified, 88 of which were severe dengue and 30 died, with 1.3% of lethality in general and 34.1% of lethality of severe cases; in Lambayeque there were 1384 cases; 13 being cases of severe dengue and nine deaths due to dengue, which makes 9.4% lethality in general and 43.3% lethality of severe cases, showing differences with national figures [37] (**Table 3**).

Although serotypes 2 and 3 were isolated in 94% of the positive cases; in Piura and Lambayeque, it was serotype 3 that was isolated in 90% of the cases and in almost all the deceased cases.

5.2 Delays in the process of health care as a method to identify the causes of mortality

The "delays" proposed by Thaddeus et al. in 1993, considered as the time between the appearance of a complication and its appropriate treatment and

Country	Serotype	N° dengue cases	N° severe cases	Deceased	General lethality (×1000)	Severe cases lethality (×100)
South America		387,669	1476	318	0.8	21.5%
Argentina	DEN 1,3	557	0	0	0.0	0.0%
Bolivia	DEN 1,4	10,842	66	15	1.4	22.7%
Colombia	DEN 1,2,3	26,279	286	15	0.6	5.2%
Chile	DEN 1,3	10	0	0	0.0	0.0%
Ecuador	—	11,387	18	4	0.4	22.2%
Brazil	DEN 1,2,3,4	252,054	378	133	0.5	35.2%
Venezuela	DEN 1	8615	359	16	1.9	4.5%
Paraguay	DEN 1,2	1832	0	0	0.0	0.0%
Uruguay	—	0	0	0	0.0	0.0%
Peru	DEN 2,3	74,648	251	92	1.2	36.7%
Essalud Piura*	DEN 2,3	22,562	88	30	1.3	34.1%
Essalud Lambayeque*	DEN 2,3	1384	30	13	9.4	43.3%

Taken and adapted: Díaz-Vélez et al. [37, 50].

Table 3.
General lethality and severe cases lethality of dengue reported by Social Security of Piura and Lambayeque compared to countries of South America, 2017.

resolution, initiating these concepts in the framework of care for severe maternal mortality and morbidity evaluating them as autonomy factors for the search for medical care, distance, and health services [36]. The use of this approach is considered, since it would allow to identify and classify the barriers and situations related to the search for medical care in patients affected by dengue, which are part of a chain of delays or delays that would hinder risk prevention, limit the access to quality health services, and would result in the lack of timely attention to the complication and, consequently, in death [54].

5.2.1 Delay in the recognition of the health problem

Poor recognition of a clinical disorder is one of the factors that cause the delay in seeking attention. It includes deficiencies in health education for communities and families, which makes it difficult to recognize warning signs (signs and symptoms) in conditions that can be life-threatening [36].

5.2.2 Delay in deciding to get attention

This delay is usually caused by limitations in the understanding of what medical care implies and could lead to a large number of patients arriving at health facilities in poor conditions, including factors such as information on dengue and institutional recognition, social and environmental situation, onset of symptoms, self-medication, gender and initial care, and motivations to make decisions [36, 55].

5.2.3 Delay in arriving at health services

It involves the difficulty of arriving at a health facility, either because of the difficult access to services or because it takes too long to reach the place of care, which can discourage the patient from seeking care, even when he has decided to seek care opportunely. It is generally the result of the lack of access to health services and economic, organizational, and sociocultural barriers which control the use of services. It is also possible to mention travel time, transport system used, and the socioeconomic impact of the delay [36, 55].

5.2.4 Delay in receiving the appropriate treatment

The cumulative effect of the first and second delays helps increase the risk of arrival at the health facility in serious conditions. Some never arrive at the hospital, and even if they do, it is possible that the treatment given to them is not adequate and poor surveillance or administrative procedures hinder the care. Other studies have shown more causes for inadequate treatment: chronic lack of trained personnel and essential supplies. Other factors mentioned are: failures in the operation of the public network, which determines waiting, reconsultation, and family movements between institutions; poor staff training and high emergency saturation [36, 55].

In relation to the first delay, aspects such as the delay in recognizing the health problem, absence of preventive-promotional talks, and lack of recognition of risk situations are described as the main ones, similar to studies that describe the population ignorance about the possibility of disease severity [56]. This last point reflects the poor knowledge by the population of less frequent dengue symptoms that in turn are associated with severity [57]. In the second delay, there are cases that went to non-health personnel and even self-medicating that are associated with delay as an explanation of serious or fatal cases [55, 58, 59] (**Figure 7**).

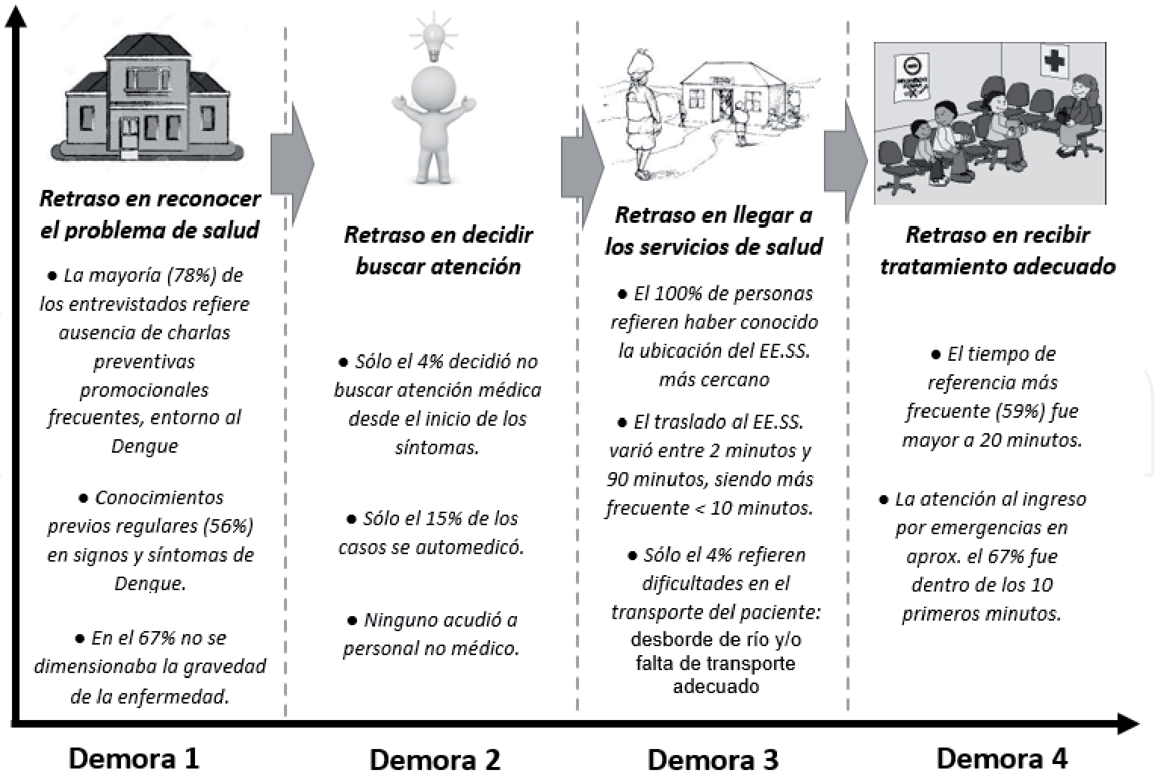

Figure 7.
Timeline of delays in the process of care of lethal cases care of dengue in two hospitals of EsSalud, in the Departments of Piura and Lambayeque, during 2017. Taken from: Burga-Cueva et al. Analysis of Lethality by Dengue in two Essalud Hospitals, in the Departments of Piura and Lambayeque. 2017. [64].

In the third delay, limitations for access to health services are evidenced, and some are given references, but lack of economic resources or available transportation is evidenced, thus also describing the distance of health facilities (to go to the nearest one) [60]. Finally, the fourth delay involves aspects such as the time of transfer to establishments of greater resolving capacity and the waiting time of cases upon arrival in emergencies, as mentioned by Ardila et al. [55], who describe the feeling of discomfort generated by a new interrogation and the waiting time that involves admission to a health facility of greater complexity (**Figure 7**).

6. Preventive measures against dengue

A study conducted in a population with a recent dengue outbreak showed that the level of knowledge was low in 76.2% of the population, 45% did not recognize the bite of the vector as the form of disease transmission, and 34% did not recognize the etiologic agent; of the most recognized clinical manifestations were fever, followed by headache, and musculoskeletal pain. Overall, 74.9% have a low level of knowledge about warning signs and about 93% were intermediate/low in prevention, and 43% of them are unaware of the reproduction of the vector, and 71% are unaware of the role of abate; results that show that the population despite having been exposed still does not know the prevention measures [61].

PAHO has planned to cooperate with member countries to stimulate the search for concrete solutions through a communication methodology to impact behavior (COMBI) [62, 63]. It should be noted that, since the introduction of dengue in America, attempts have been made to propose some integrated programs, with a community approach to the control of *Aedes aegypti*. This approach has been to educate the community about dengue disease and how to prevent transmission by controlling the *Aedes aegypti* vector in the domestic and community environments; in this context, it has been documented that many of these programs were successful in educating the community about dengue and its prevention [65].

Nevertheless, this improvement of the cognitive level related to the disease has not resulted in the action of preventing the disease. In this sense, even though people in a region with dengue endemicity are very well versed in the disease, they do not implement these measures that they know control vector proliferation and therefore the transmission of dengue; therefore, it is essential to reorient educational programs focused on the behavioral change of the population [66].

Likewise, historically in the region, efforts to control dengue vectors resulted in the elimination of populations of *Aedes aegypti* in many of the tropical and subtropical countries by the 1970s. However, vector populations were reintroduced through the emergence of new serotypes [67]. Therefore, currently, the main purpose of most programs is to reduce the densities of vector populations as much as possible and keep them at low levels. When feasible, efforts should also be made to reduce the longevity of adult female mosquitoes through the use of insecticidal methods in order to reduce the risk of virus transmission [65].

It should be noted that keeping infestation with *A. aegypti* low carries significant economic costs to society; however, when an outbreak of dengue occurs, the cost increases considerably in vector control and patient care; so, from this perspective, effectiveness and profitability could be maximized by intervening in the vector habitat (potential hatcheries) through promotion and prevention actions [68–70]. Although the concept of vector control is reasonable, control should be early in an outbreak or applied strategically during periods between epidemics to avoid escalation in transmission [71].

Another preventive measure to control the rapid spread of an outbreak is to manage the infected human host and prevent it from infecting *Aedes* mosquitoes, this in turn would reduce the amount of new infections to humans, breaking the epidemiological chain of dengue transmission [72]. So, meanwhile, there is no vaccine with proven efficacy for dengue prevention in all population groups, and the main strategy to prevent transmission and disease is vector control through the elimination of larval habitats (elimination of potential hatcheries) and prevention of mosquito-human contact [73]. Some well-documented successes indicate that rigorously applied vector control can reduce the transmission of DENV and the disease [74].

In that sense, success in reducing the burden of dengue on public health will require an integrated multiple approach; although the concept of integrated intervention for dengue prevention is gaining increasing acceptance, to date, no consensus has been reached regarding the details of how and what combination of approaches can be implemented most effectively to control the disease [75].

Integrated vector management, the strategic method promoted by WHO, is defined as, “a rational decision-making process for the optimal use of resources for vector control,” which includes lobbying, social mobilization, and legislation; planning and delegated decision-making at the lowest possible administrative level; guaranteeing the rational use of available resources; adaptation of strategies and interventions based on vector habitat, epidemiology, and local resources; and development of an essential infrastructure for integrated vector management based on the situation analysis [67].

However, the discipline of vector control has been strongly influenced by the theory developed by Ronald Ross and George Macdonald (i.e., the Ross-Macdonald model), which states that the potential for transmission of mosquito-borne pathogens depends largely on the abundance of adult vector mosquitoes, survival through the incubation period of the pathogen, and the rate of human infection [76].

Therefore, with this approach, interventions that reduce the population density of adult mosquitoes, the daily probability of survival, and the contact of the mosquito with humans are expected to have the greatest impact on decreasing virus transmission. It should be noted, however, that the Ross-Macdonald model was not formulated to specifically explore larval mosquito control. Recent quantitative assessments indicate that, under certain circumstances, control of the larvae may lead to greater than expected reductions in the transmission of pathogens [77]. In the context of larval control of *Aedes aegypti*, there should be the large-scale elimination of potential hatcheries.

In this context, taking into account that there is limited efficacy and intensity of the interventions used for dengue vector control, other alternatives to combat dengue endemic persistence are explored. Sustainable community participation and school-based health education interventions have finally evolved as an effective tool in reducing the larval source over other interventions [78], since children have inherent curiosity and enthusiasm to learn new things. Therefore, they can serve as an effective change agent to achieve a change in behavior in the family and community.

Methods for vector control include elimination or management of larval habitats, eliminating larvae with insecticides, the use of biological agents, and the application of adulticides; being for our conviction the elimination and management of larval habitats. Habitats are eliminated by preventing the access of mosquitoes to these containers or by emptying and cleaning them frequently, eliminating the evolutionary stages with the use of insecticides or biological control agents, eliminating adult mosquitoes with insecticides, or by combining these methods [79].

Habitat management seeks to change the environment in order to prevent or minimize the propagation of vectors and human contact with the vector pathogen, destroying, altering (proper conservation of disused material), and eliminating or recycling nonessential containers that serve as larval habitats. Efforts to reduce solid waste should be directed against disposable or nonessential containers [78].

However, the main method of *Aedes* control (and, generally, the only one) used in many countries, remains the spatial application of ultralow volume insecticides (ULVs) for the control of adult mosquitoes [63]. This strategy has to be repeated constantly, its cost is high, and its effectiveness is limited. *Aedes aegypti* prefers to stay inside the houses, therefore, the insecticide aerial application or from trucks simply does not reach the mosquitoes that stay in hidden places, such as wardrobes. There have been several cases of homeowners in various countries who have not allowed the entry of home spraying equipment or have closed windows and doors well to prevent outside fog produced by the insecticide from entering their homes, reducing in this way the effectiveness of the intervention [65] (**Table 4**).

Due to inadequate dengue surveillance systems, spraying does not arrive in time to prevent epidemic transmission, and adult mosquito populations return quickly after spraying. Public confidence and complacency regarding such an ineffective approach have only made the challenge of explaining the need for community participation in hatchery control greater [79].

Therefore, our approach, which is the most cost-effective measure to control the transmission of dengue, would be based on the design and execution of activities aimed at eradicating vector proliferation through the elimination of favorable habitats (potential hatcheries: tires, bottles, and buckets) for oviposition and allowing the development of the aquatic stages of the vector; with a participatory methodology based on the sociocultural characteristics of the population under study, with the local schools as main actors; for which, at first, the level of knowledge, attitude, and practice of dengue prevention measures of the population must be determined and from which it will design and carry out promotional, prevention interventions, with emphasis on behavioral changes.

	***Aedes* mosquito breeding prevention**	**Prevention of exposure to *Aedes* mosquito bites**	**Search for medical attention**
Individuals and households	• Water storage practices • Home plant care • Animal care • Garbage disposal • Storage of daytime materials in the yard	• Use of insecticides and spray repellents • Placing wire mesh on windows and doors • Sleep protected by a mosquito net during naps	• Disease recognition • Home treatment • Search for medical attention
Communities, community groups, schools, NGOs	• Communication with behavioral impact • Community cleaning • Promotion or organization of essential services: water, garbage collection • Promotion of the recycling of tires, cans, bottles, etc.	• Housing improvement	• Facilitation of patient transport to health facilities

Table 4.
Comprehensive behavioral monitoring of mobilization and social communication for dengue prevention and control.

Finally, the need for a good understanding and emphasis on behaviors related to the management of *Aedes aegypti* hatcheries, the main dengue vector; it should be the promotion and prevention approach at the community level, divided into individual and collective activities for the prevention of *Aedes aegypti* reproduction, prevention of exposure to *Aedes* mosquitoes, and seeking medical attention.

Taken from: Parks W, Lloyd L. COMBI. Planning social mobilization and communication for the prevention and control of dengue. Ginebra; 2004 [65].

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