**Article /** Artículo
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# Symptomatology associated with confirmed diagnosis of dengue: secondary analysis of surveillance data from Mexico

## Sintomatología asociada al diagnóstico confirmado de dengue: análisis secundario de los datos de vigilancia de México

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## ABSTRACT

**Objective** The complexity of dengue symptomatology makes accurate clinical diagnosis difficult. This study aimed at identifying signs and symptoms associated with laboratory-confirmed dengue among febrile patients suspected of having a vector-born infection.
**Methods** This was a secondary analysis of surveillance data collected for a period of six years by the Mexican Ministry of Health in the north-central state of San Luis Potosí. All health facilities reported clinical data and obtained blood samples for any patient with a febrile condition of unknown origin, and who also presented at least two of the following symptoms: headache, myalgia, arthralgia, and exanthema. The final sample of 23,983 individuals was analyzed using multinomial logistic regression to compute crude and adjusted odds ratios with 95% confidence intervals (OR; 95% CI). The dependent variable was the outcome of final laboratory diagnosis: dengue fever (DF), dengue hemorrhagic fever (DHF), and no dengue as reference category.
**Results** Eleven variables were statistically significant in crude analyses, but only 7 remained in the final adjusted model; four were positively associated with both DF and DHF: Exanthema (DF 2.92; 2.38-3.58, DHF 1.71; 0.72-4.03), retro-ocular pain (DF 1.24; 1.13-1.36, DHF 1.58; 1.09-2.28), being non-indigenous (DF 1.50; 1.25-1.80, DHF 5.69; 1.74-18.5) and adulthood (DF 1.44; 1.31-1.59, DHF 2.73; 1.75-4.26). Hemorrhage (79.3; 48.3-129.7), abdominal pain (2.50; 1.35-4.63) and arthralgia (3.23; 1.53-6.79) were also predictive, but only for DHF.
**Conclusion** We recommend health authorities worldwide to consider these findings when producing guidelines for clinical diagnosis to reduce over- and underdiagnosis.

**Key Words:** Dengue fever; clinical diagnosis; hemorrhagic dengue; Mexico; symptomatology (*source: MeSH, NLM*).

## RESUMEN

**Objetivo** La complejidad sintomatológica del dengue dificulta el diagnóstico clínico preciso. Este estudio buscó identificar signos y síntomas asociados al dengue confirmado por laboratorio en pacientes febriles con sospecha de infección transmitida por vector.
**Métodos** Análisis secundario de datos de vigilancia recolectados en un periodo de seis años por la Secretaría de Salud de México en el estado norcentral de San Luis Potosí. Todos los establecimientos de salud reportaron datos clínicos y obtuvieron muestras de sangre de pacientes con fiebre de origen desconocido que presentaron al menos dos de los siguientes signos/síntomas: cefalea, mialgia, artralgia y exantema. La muestra final de 23983 personas se analizó con regresión logística multinomial para calcular razones de momios (RM) crudas y ajustadas con intervalos de confianza (IC) de 95%. La variable dependiente fue el diagnóstico por laboratorio: fiebre de dengue (FD), dengue hemorrágico (DH), y no dengue como referencia.
**Resultados** Once variables fueron estadísticamente significativas en los análisis crudos, pero solo siete permanecieron en el modelo ajustado; cuatro se asociaron positivamente

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con FD y DH: exantema (FD 2,92; 2,38-3,58, DH 1,71; 0,72-4,03), dolor retroocular (FD 1,24; 1,13-1,36, DH 1,58; 1,09-2,28), ser no indígena (FD 1,50; 1,25-1,80, DH 5,69; 1,74-18,5) y ser adulto (FD 1,44; 1,31-1,59, DH 2,73; 1,75-4,26). La hemorragia (79,3; 48,3-129,7), el dolor abdominal (2,50; 1,35-4,63) y las artralgias (3,23; 1,53-6,79) también fueron predictoras, pero solo de DH.

**Conclusión** Se recomienda a las autoridades sanitarias tener en cuenta estos hallazgos al elaborar directrices para el diagnóstico clínico con el fin de reducir el sobre e infradiagnóstico.

**Palabras Clave:** Dengue hemorrágico; diagnóstico clínico; fiebre por dengue; México; sintomatología (*fuente: DeCS, BIREME*).

Dengue is a mosquito-borne viral disease mainly transmitted via the species Aedes aegypti, whose prime breeding grounds are in tropical/subtropical regions; it is a member of the Flavivirus genus and is closely related to the yellow fever and the Japanese encephalitis viruses (1). Most often, an infection is asymptomatic or can lead to the less serious and self-limiting dengue fever (DF). However, some cases can evolve into the more severe dengue hemorrhagic fever (DHF), which in turn can lead to the dangerous dengue shock syndrome, both entities associated with fatality rates of 1-10% or higher if untreated (2). There are four serotypes; infection from one gives immunity to that serotype, but any subsequent infections from one of the others increases the risk of developing severe dengue complications through a mechanism known as antibody dependent enhancement (3,4). Previous research suggests that there are some differences in the clinical manifestations of the serotypes, although this is not yet clear (5).

For being a neglected tropical disease, dengue's global relevance to public health has gained traction over the last decades, as it has continued to acquire an ever-increasing share of the global disease burden (1,6,7), and of all mosquito-borne viral diseases it is spreading the fastest (8). With ~2.5 billion people living in dengue endemic areas around the world (8), there are an estimated 390 million infections every year, of which ~25% result in clinical manifestations (1,9). Annually, ~500,000 people develop DHF worldwide, resulting in death in ~2.5% of them (10). Besides the risk of dying, dengue also poses a great burden in terms of costs due to hospitalization and/or inability to work. For many low- and middle-income countries (LMIC), it also poses a financial strain in terms of medical interventions, vector-control programs, and loss of tourism (2).

Prior to the 1970s, severe epidemics had only been present in 9 countries, but today, it is endemic in over 100 throughout Asia, Africa, Latin America, and the Western Pacific regions (8). Since the 90s, the World Health Organization began compiling data and has since then produced reports on cases of DF and DHF (11). With this data, the presence of all four serotypes was confirmed in the Latin American and Caribbean region (12). While the reported incidence rates for Mexico have shown a downward trend during the last few years, coinciding with the overall decrease experienced throughout the region (13), the burden of this disease have caused major concern in most of the world for the last decades (14). A systematic review from 2013 with studies from 44 countries in the Americas looking at the burden of disease between 1995 and 2010 reported a pooled estimate for the incidence of classic DF of 72.1 cases per 100,000 person-years (12).

Early and accurate diagnosis is then crucial, especially with respect to DHF, where if properly treated, reduces the death rate to less than 1% (1). However, since many health care settings in LMIC lack laboratory facilities, treating physicians have to rely on clinical symptomatology to establish a diagnosis; this is an area where there is still room for improvement. Hence, this study aimed at identifying relevant clinical symptomatology associated with the diagnosis of DF and DHF among febrile patients to increase the accuracy of presumptive clinical diagnoses.

## METHODOLOGY

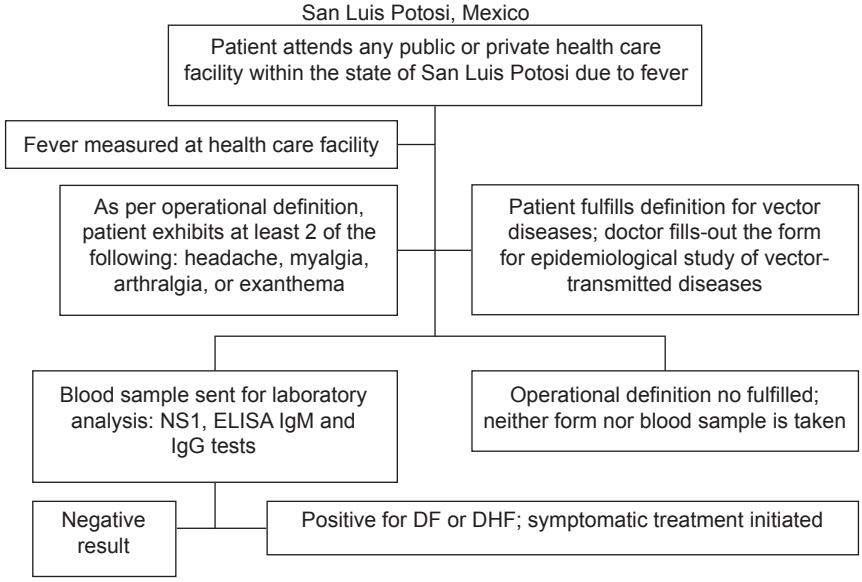
### Study design

This was a secondary analysis of surveillance data collected by the Mexican Ministry of Health in the north-central state of San Luis Potosí (SLP) for a period of six consecutive years (through 2019).

### Surveillance data

The Mexican Ministry of Health sets the national procedures and guidelines for collecting and reporting health data through the National Epidemiological Surveillance System, to which all state-level health authorities, services, and organizations report (15). This system gathers weekly data for over 100 diseases, with ~50 million cases registered every year (16,17). The procedure used for collecting dengue surveillance data is shown in (Figure 1).

**Figure 1.** Flowchart of the dengue surveillance system in San Luis Potosi, Mexico




**Data management and variable definition**

Data was retrieved in excel format and converted into SPSS format for management and analysis. The original dataset contained 24,225 observations, but after eligibility, the final sample size for analysis was 23,983. There were three inclusion criteria for cases to be considered for analysis: presence of fever (reported or confirmed at clinic), final diagnosis (i. e., DF, DHF, no dengue), and that the case originated in SLP; 68 and 174 cases were excluded, as final diagnosis was missing and the state of origin was other than SLP, respectively.

While the original dataset consisted of 180 variables, most were irrelevant for the purpose of the study (e.g., geographic/administrative data) and were therefore excluded, resulting in 30 variables useful for analyses. The variables serotype, pleural effusion, and tourniquet tests would have been kept if it had not been for the very large proportion of missing values (>90%).

Most signs and symptoms recorded were coded dichotomously. Some variables were also recoded and/or re-categorized as needed. For instance, age was computed from the date of birth and the consultation date, but was later categorized into age groups, as dengue has been positively associated with age (18). For the main analysis, age was dichotomized as <18 and ≥18 years, because the risk increased in adulthood.

**Statistical analysis**

Analyses included binary and multinomial logistic regression. Odds ratios (OR) and 95% confidence intervals (CI) were computed using SPSS v.24. The outcome variable in the binary model was coded as any dengue (DF/DHF) vs. no dengue. In the multinomial model the dependent variable was kept in three categories as DF, DHF, and no dengue with the latter used as reference.

Exposure variables included signs/symptoms and basic demographic data such as sex, age, and ethnicity. Variables with crude ORs with a $p<0.10$ were entered in the full models, but only those that were statistically significant ($p<0.05$) remained in the final adjusted model. Signs/symptoms were coded dichotomously with the absence of the clinical feature used as reference.

Written permission to use, analyze, and publish the data was given by the Ministry of Health of SLP (ID 6S.2/34638). Informed consent was not obtained, as this was surveillance data; yet complete anonymity was maintained throughout the analysis and reporting process.

## RESULTS

A total of 23,983 individuals of all ages (mean 27.5 years) presenting with a febrile condition were suspected of having dengue in SLP during a period of six consecutive years. Out of these, 3,225 (13.4%) were confirmed cases of DF with 7.3% (n=237) of them having DHF.

Among patients with DF, 54.6% were women and 45.4% men, two thirds were aged ≥18 and one third <18 years. While sex was not associated with DF, age showed an inverted U-shape reaching the highest adjusted odds at 25-34 years (adj. OR 1.77; 95% CI 1.49-2.10). The indigenous population represented a small proportion of all cases (8%) and dengue diagnoses (6.5%); non-indigenous had an adjusted OR for having any dengue of 1.31 (1.13-1.53) compared with the indigenous population. A total of 18 signs and symptoms were present among confirmed cases; 6 had the highest occurrence: headache (96.7%), myalgia

(90.3%), arthralgia (79.8%), retro-ocular pain (50.5%), petechiae (67%), and gingivitis (54.1%). Arthralgia, persistent vomiting and abdominal pain were marginally significant in the crude, but not in the adjusted model. Only exanthema (2.55; 2.14-3.03), hemorrhage (4.06; 2.90-5.67), and retroocular pain (1.16; 1.07-1.25) remained statistically significant in the adjusted analysis (Table 1).

Results from the multinomial model are presented in Table 2. A total of 11 variables were significant in crude analyses, but only 7 remained significant once adjusted; four of them were positively associated with both DF and DHF: exanthema (DF 2.92; 2.38-3.58, DHF 1.71; 0.72-4.03), retro-ocular pain (DF 1.24; 1.13-1.36, DHF 1.58; 1.09-2.28), being non-indigenous (DF 1.50; 1.25-1.80, DHF 5.69; 1.74-18.5) and adulthood (DF 1.44; 1.31-1.59, DHF 2.73; 1.75- 4.26). Hemorrhage (79.3; 48.3-129.7), abdominal pain (2.50; 1.35-4.63) and arthralgia (3.23; 1.53-6.79) were also predictive, but only for DHF (Table 2).

**Table 1**. Crude and adjusted odds ratios from binary logistic regression for the probability of having dengue fever, San Luis Potosi, Mexico

| Clinical characteristics and risk factors | | Confirmed dengue, n (%) Positive n=3225 | Negative n=20758 | Crude OR [95% CI] | Adjusted* OR [95% CI] | P-value |
|---|---|---|---|---|---|---|
| Exanthema | | 199 (6.2) | 534 (2.6) | 2.49 [2.10-2.94] | 2.55 [2.14-3.03] | <0.01 |
| Bruised skin | | 4 (3.9) | 3 (2.8) | 1.42 [0.31-6.53] | | |
| Gingivitis | | 33 (54.1) | 40 (45.5) | 1.41 [0.73-2.72] | | |
| Petechia | | 69 (67.0) | 76 (69.7) | 0.88 [0.49-1.57] | | |
| Ecchymosis | | 17 (16.5) | 20 (18.3) | 0.88 [0.43-1.79] | | |
| Hematomas | | 14 (13.6) | 23 (21.1) | 0.58 [0.28-1.21] | | |
| Edema | | 4 (3.9) | 7 (6.4) | 0.58 [0.16-2.07] | | |
| Ascites | | 2 (1.9) | 5 (4.6) | 0.41 [0.07-2.17] | | |
| Hemorrhage | | 61 (1.9) | 88 (0.4) | 4.53 [3.26-6.30] | 4.06 [2.90-5.67] | <0.01 |
| Persistent vomiting | | 88 (3.7) | 419 (2.9) | 1.26 [0.99-1.59] | | |
| Hematemesis | | 8 (13.1) | 10 (11.4) | 1.17 [0.43-3.17] | | |
| Melena | | 4 (6.6) | 5 (5.7) | 1.16 [0.30-4.52] | | |
| Epistaxis | | 18 (29.5) | 41 (46.6) | 0.48 [0.24-0.95] | | |
| Retro-ocular pain | | 1629 (50.5) | 9263 (44.6) | 1.26 [1.17-1.36] | 1.16 [1.07-1.25] | <0.01 |
| Abdominal pain | | 89 (3.8) | 435 (3.1) | 1.22 [0.97-1.54] | | |
| Arthralgia | | 2573 (79.8) | 16224 (78.2) | 1.10 [1.00-1.20] | | |
| Myalgia | | 2911 (90.3) | 18764 (90.4) | 0.98 [0.86-1.11] | | |
| Headache | | 3119 (96.7) | 20094 (96.8) | 0.96 [0.78-1.18] | | |
| Non-Indigenous | | 3014 (93.5) | 19066 (91.8) | 1.26 [1.09-1.47] | 1.31 [1.13-1.53] | <0.01 |
| Sex | Female | 1762 (54.6) | 11404 (54.9) | 1.00 | | |
| | Male | 1463 (45.4) | 9354 (45.1) | 1.01 [0.94-1.09] | | |
| Age | 0-4 | 223 (6.9) | 2066 (10.0) | 1.00 | 1.00 | 0.27 |
| | 5-9 | 269 (8.3) | 2806 (13.5) | 0.88 [0.73-1.07] | 0.90 [0.74-1.08] | 0.04 |
| | 10-14 | 366 (11.4) | 2788 (13.4) | 1.21 [1.02-1.45] | 1.20 [1.00-1.44] | <0.01 |
| | 14-24 | 712 (22.1) | 3849 (18.5) | 1.71 [1.46-2.01] | 1.69 [1.44-1.99] | <0.01 |
| | 25-34 | 520 (16.1) | 2696 (13.0) | 1.78 [1.51-2.11] | 1.77 [1.49-2.10] | <0.01 |
| | 35-44 | 400 (12.4) | 2231 (10.8) | 1.66 [1.39-1.97] | 1.66 [1.38-1.98] | <0.01 |
| | 45-54 | 305 (9.5) | 1853 (8.9) | 1.52 [1.26-1.83] | 1.55 [1.28-1.87] | <0.01 |
| | 55+ | 429 (13.3) | 2469 (11.9) | 1.61 [1.35-1.91] | 1.66 [1.39-1.98] | <0.01 |

* Adjusted for those variables with statistically significant crude ORs.

**Table 2**. Crude and adjusted odds ratios from multinomial logistic regression for the probability of having dengue fever and dengue hemorrhagic fever, San Luis Potosi, Mexico

| Clinical characteristics and risk factors | | Odds ratios [95% CI] Dengue Fever | | Dengue hemorrhagic fever | |
|---|---|---|---|---|---|
| | | Crude | Adjusted* | Crude | Adjusted* |
| Exanthema | | 2.48 [2.09-2.95] | 2.92 [2.38-3.58] | 2.55 [1.50-4.34] | 1.71 [0.72-4.03] |
| Bruised skin | | 3.21 [0.30-33.5] | - | 1.20 [0.23-6.11] | - |
| Gingivitis | | 0.90 [0.19-4.26] | - | 1.50 [0.75-2.96] | - |
| Petechia | | 0.60 [0.18-2.05] | - | 0.92 [0.50-1.69] | - |
| Ecchymosis | | 0.89 [0.18-4.38] | - | 0.87 [0.42-1.83] | - |
| Hematomas | | 1.24 [0.31-4.98] | - | 0.51 [0.23-1.12] | - |
| Edema | | 2.91 [0.53-15.9] | - | 0.32 [0.06-1.61] | - |
| Ascites | | ** | - | 0.46 [0.08-2.46] | - |
| Hemorrhage | | 0.55 [0.25-1.19] | 0.52 [0.20-1.31] | 69.0 [47.7-99.8] | 79.3 [48.5-129] |
| Retroocular pain | | 1.24 [1.15-1.34] | 1.24 [1.13-1.36] | 1.50 [1.16-1.94] | 1.58 [1.09-2.28] |
| Persist. vomiting | | 1.12 [0.87-1.44] | - | 3.55 [2.03-6.22] | - |
| Abdominal pain | | 1.03 [0.80-1.33] | 0.99 [0.77-1.29] | 4.48 [2.71-7.42] | 2.50 [1.35-4.63] |
| Hematemesis | | ** | - | 1.35 [0.50-3.68] | - |
| Melena | | ** | - | 1.32 [0.34-5.17] | - |
| Arthralgia | | 1.04 [0.94-1.14] | 0.99 [0.88-1.11] | 3.20 [2.00-5.12] | 3.23 [1.53-6.79] |
| Myalgia | | 0.93 [0.82-1.05] | - | 3.03 [1.49-6.14] | - |
| Headache | | 0.95 [0.77-1.18] | - | 1.07 [0.50-2.28] | - |
| Epistaxis | | 2.86 [0.52-15.5] | - | 0.36 [0.17-0.77] | - |
| Non-Indigenous | | 1.25 [1.07-1.45] | 1.50 [1.25-1.80] | 1.52 [0.87-2.68] | 5.69 [1.74-18.5] |
| Sex | Female | 1.00 | - | 1.00 | - |
| | Male | 0.99 [0.92-1.07] | - | 1.20 [0.93-1.56] | - |
| Age | <18 | 1.00 | 1.00 | 1.00 | 1.00 |
| | ≥18 | 1.42 [1.31-1.54] | 1.44 [1.31-1.59] | 4.16 [2.93-5.89] | 2.73 [1.75-4.26] |

* Adjusted for those variables with statistically significant crude ORs; ** Unable to compute due to small sample size.

## DISCUSSION

The research aimed at investigating signs and symptoms associated with confirmed dengue in patients with fever of unknown origin and suspected of having a vector-borne disease. Exanthema and retro-ocular pain had the strongest association for DF, and hemorrhage was pathognomonic for DHF. Retro-ocular and abdominal pain, and arthralgia were also significantly associated with DHF. Adults showed increased risks for both diagnoses irrespective of sex, and non-indigenous individuals also had increased odds.

Two previous studies found that exanthema was associated with dengue; one reported increased odds (3.02; 1.48-6.16) from a sample of 182 individuals (19), and the other found a significant difference in frequencies between ELISA-IgM positive and negative tests from 127 acute phase patients (20); however, since this test is mostly used to detect the hemorrhagic stage, such finding does not quite correspond to the reported here, as exanthema was only significant for DF. The first study referred (19) also found significant ORs for conjunctival redness (3.10; 1.53-6.29) and lymph node enlargement (3.98; 1.86-8.53), findings that were not replicated here.

A study from the Philippines with 2,103 individuals aged ≤18 years, hospitalized for suspicion of dengue, found that myalgia, abdominal pain, flushing and signs of circulatory collapse were more common in confirmed cases of dengue (21). While the latter two were not included in our original data, precluding comparisons, results for myalgia showed no increased adjusted OR for either form of dengue. For abdominal pain we did find an increased risk, but only for DHF. Hemorrhage, our strongest indicator for DHF, was not significant in that study, even though positive tourniquet and petechiae were significantly more common.

A review article from 2014 produced a meta-analysis that included 16 papers to investigate symptomatology predictive of severe dengue in DF patients (22); findings can be compared with the results presented here for DHF. Such, the meta-analysis included 11 characteristics that were assessed here, 5 matching and 6 unsupportive of our results. The two report that hemorrhage and abdominal pain were significant, and that sex, gingivitis, and epistaxis were not predictors for DHF. Yet, the review found that nausea/vomiting, skin rashes, hematemesis, melena, headache, and hepatomegaly (not present in our study) were predictive, which we did not, and unlike the review, we found that retro-ocular pain was associated with DHF.

The most recent study on dengue symptomatology included 700 randomly selected patients out of 2,607 confirmed cases presented at a Malaysian Hospital in 2014. In this cross-sectional study, common warning signs for severe dengue were persistent vomiting (55.9%) and abdominal pain (52.9%), with the later achieving a sensitivity of 59%; persistent vomiting and mucosal bleeding showed adjusted ORs of 2.41 (1.16-4.99) and 4.73 (2.09-10.69), respectively (23), similar to the reported here in patients with DHF, especially for hemorrhage and abdominal pain.

The main limitations of this study concern the original surveillance data. There were relevant variables not analyzed due to missing data such as the serotype that would have shed light on to what extent clinical manifestations might differ. Also, other important signs and symptoms were not collected at all (e.g., hepatomegaly). Information about previous infection was also lacking. Future studies could also investigate why indigenous populations might be better protected against dengue. On the other hand, the main strengths include the good data quality, the study period that spanned over 6 years, and the large sample studied. In fact, there is no research published of similar nature using such as large a sample encompassing an entire state. These strengths provide good grounds for generalizing the results to similar populations in the region.

As no fully operational dengue vaccine is available, outcomes still rely on early detection and adequate treatment. Therefore, identifying signs and symptoms that improve diagnostic accuracy is crucial in LMIC. This would lead to less over- and underdiagnoses ultimately curtailing morbidity and mortality outcomes.

In conclusion, a febrile patient with either exanthema and/or retro-ocular pain is at higher odds of having DF compared with a febrile patient without these symptoms. While retro-ocular pain, abdominal pain, and arthralgia are all telltales of DHF, the most critical sign to look for is hemorrhage.

We recommend that health authorities consider modifying the existing operational definitions used for dengue. Of the four signs and symptoms currently used by doctors, we suggest keeping exanthema, but probably remove headache, myalgia and arthralgia, and replace them with retro-ocular pain. In such case, the requirement that the patient exhibits at least two of the symptoms should be changed to only one ♦

**Conflicts of interest:** None.

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