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# Clinical and Epidemiological Characterization of Cholera, Mexico 2013-2014

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## Abstract

**Background**: During Epidemiological Week 34 of 2013, the Mexican Epidemiological Surveillance System (SINAVE) identified two probable cases of cholera in Mexico City.

**Methods:** Both samples were processed by DNA sequencing and biochemical analyses at the Institute of Epidemiological Diagnosis and Reference "Dr. Manuel Martínez Báez" (InDRE) and compared with the circulating strain of the Caribbean.

**Results**: *V. cholerae* serogroup O1, serotype Ogawa, biotype El Tor, toxigenic, was confirmed positive, then a detailed study from September 2nd, 2013 to August 27th, 2014 was carried out where a total of 201 laboratory-confirmed cases of *V. cholerae* O1 toxigenic were reported in in seven states of Mexico; 50.7% were men. The average of the number of evacuations was 8 (range 0 to 48). The mean duration of diarrhoea was 2 days. The age range of the cases was from 3 months to 88 years. The 53.2% were identified without dehydration data, 21.9% with mild, 19.9% with moderate and 5.0% with severe dehydration; 65.0% received outpatient care, 24% hospitalization, and 11% in Observation or Emergency.

**Conclusion**: The timely detection of cases plays an important role in promotion, detection and control actions. The notification of probable cases in less than 24 h sharing the information obtained in the National Public Health Laboratory Network (RNLSP) evidenced an immediate response; triggering actions for the intentional search of cases, epidemiological surveillance, health promotion and prevention and control of diseases for adequate control of an epidemic.

**Keywords:** Cholerae; Epidemiological surveillance; Mexico

## Introduction

*V. cholerae* causes an acute intestinal disease known as cholera that is characterized by diarrhea and severe dehydration that can lead to death in less than 48 h without an adequate treatment. Transmission of the agent is through ingestion of water and/or food contaminated with intestinal secretions from infected subjects [1-4]. The transmission is linked to poor management of environmental determinants such as sanitary conditions, access to quality drinking water, population density and lack of hygiene. The areas at greatest risk are those lacking basic infrastructure where the minimum requirements for clean water and sanitation are not met [5,6]. In the genus Vibrio twelve of the 66 species are considered pathogenic for humans. Three of these are the major human pathogens, *V. vulnificus, V. parahaemolyticus and V. cholerae*. The two main virulence factors expressed by *V. cholerae* O1 and O139 are the thermo-labile cholera toxin (CT) responsible for aqueous diarrhea [7,8] and the pilus co-regulator of toxin, which modulates the formation of adhesion factors and is a regulator of intestinal colonization [9-11]. The simultaneous expression of both has serious damaging infectious effects [12].

Most *V. cholerae* O1 infections are asymptomatic, and moderate diarrhea may be indistinguishable from other causes of gastroenteritis [13]. Approximately 5% of infected patients develop a severe form of cholera [14]. Four clinical forms have been described: 1) asymptomatic, 2) mild, 3) moderate and 4) severe, the latter characterized by severe dehydration and/or hypovolemic shock [15,16]. Rehydration is the essential component of the treatment for the replacement of water and electrolytes [17]. To cut the transmission chain, the antibiotic treatment of choice with oral doxycycline or tetracycline is indicated for the sensitive strains and as an alternative trimethoprim-sulfamethoxazole, erythromycin, and furazolidone [2,18].

Natural disasters or anthropogenic phenomena can favor the risk of epidemics due to deficiencies in sanitary, hygienic and resource conditions. An example of this was the outbreak of cholera in the Rwandan refugee camp during 1994 with 48,000 cases and 23,800 deaths in just one month. In 1961 the World Health Organisation declared the seventh pandemic wave of cholera. This spread from Asia

to Europe and Africa, reaching the American continent in 1991, registering around 400,000 cases and 4,000 deaths in the region, which was free of cholera for more than a century [19].

On January 12, 2010, an earthquake of 7.0 degrees (Ritcher scale) struck the Island of Hispaniola, territory that make up the Dominican Republic and Haiti. However, the socioeconomic, developmental and infrastructure conditions in the distribution of water for human consumption, sewage and excreta disposal of the latter favored the appearance and rapid spread of an outbreak of cholera that registered until October of that year a total of 4722 cases and 303 deaths. The epidemiological investigation in that country identified Vibrio cholerae 01 Ogawa as the strain that caused the outbreak (http://www.who.int/csr/don/2010_10_28/en/).

In Mexico, during the 7$^{th}$ pandemic, cholera was reintroduced. In 1991, the first confirmed case was identified, later, a total of 2,690 cases of cholera were detected and 34 deaths in 16 states were recorded [20]. Although there were epidemic cholera peaks during the following years, the mortality rate was low. Between 1991 and 2001, through the Institute of Epidemiological Diagnosis and Reference "Dr. Manuel Martínez Báez" (InDRE), the National System of Epidemiological Surveillance (SINAVE) confirmed 45,977 cases of cholera in 97% of the Mexican territory with a lethality rate of 1.2% [4,16]. The last case of cholera reported from the 1991 outbreak was in September 2001. Until 2010, one case was again confirmed in the town of Navolato, in the northeastern state of Sinaloa [21]. Since then, sporadic cases of *V. cholerae* serogroup 01 have been reported, one case was identified in 2011 and two in 2012, all cases in the same state of Sinaloa [22]. In the light of the devastating effects of an epidemic of *Vibrio cholerae*, immediate detection and control actions are required to prevent outbreaks. This manuscript describes the actions taken to react to such an event.

## Methods

### Data collection

The samples were identified by the Special Cholera Epidemiological Surveillance System when complying with the operational definition of the current case in Mexico. Notifying the General Directorate of Epidemiology in the first 24 h after the detection, undertaking the actions established in the current Standardized Manual of Epidemiological Surveillance of Cholera for the study of outbreak and contacts. The diagnostic samples were sent to the National Public Health Laboratory Network (RNLSP) for processing and further confirmation. Once the positive confirmation was made, an epidemiological warning was issued through the national epidemiological surveillance committee to the whole country to intensify the intentional search of cases in the national territory. This provided an opportunity in the early detection of cases in the state of Hidalgo, as well as the implementation of actions for its control.

The study included cases according to the operational definition of a confirmed cholera case after its reintroduction during 2013 and at the end of 2014 in Mexico. All the information was obtained from the SINAVE, specifically from the platform of the Special Surveillance System of Cholerae confirmed by the RNLSP.

### Operational definitions

**Confirmed case of cholera**: Any probable case in which the presence of toxigenic *V. cholerae O1* or *V. cholerae O139* in fecal matter or gastrointestinal content is isolated or demonstrated [5].

**Diagnostic algorithm**: Processing of rectal or faecal swab specimens processed by the RNLSP following the Laboratory Surveillance Guidelines for Acute Diarrheal Bacterial Disease.

The final identification of the *V. cholerae* strains and their toxigenicity was carried out at the InDRE. Agglutination tests were performed to distinguish between *V. parahaemolyticus* or *V. cholerae* to samples received in the laboratory. After this step, samples were sent to the InDRE for the toxigenicity and antibiotic susceptibility tests.

## Results

During September 2013 in the 34$^{th}$ epidemiological week (EW), SINAVE identified two cases of cholera in Mexico City [23]. Initial strains analyses by pulsed field electrophoresis (PFGE) and PCR amplification of the virulence genes suggested that both strains were identical to each other but different from those previously circulated in the country during the 1990s. During the following EW, four additional cases were identified in Huejutla de Reyes, Hidalgo, 121 km northeast of Mexico City. Thereafter, a cholera epidemic began in the region of La Huasteca, which spread over the states of Veracruz, San Luis Potosí and the State of Mexico (Figure 1). By the end of 2013, a total of 187 cases were reported (159 in Hidalgo, 9 in the State of Mexico, 13 in Veracruz, 2 in San Luis Potosí, 3 in Mexico City and 1 in Sinaloa). During 2014, only 14 further cases were identified (13 in Hidalgo and one in Queretaro), total of 201 cases during the period of study. All of cases were confirmed by the InDRE, undistinguishable to those isolates in Mexico City during 2013 and identical from the strain described in the outbreak of Haiti.

Figure 1 describes the number of cholera confirmed cases from the EW33 in 2013 to the EW35 of 2014 and the geographical location of the states affected by the outbreak (Inset). The first two cases were recorded by date of onset of symptoms in Mexico City during EW34 and EW35. In Hidalgo State, they started from EW36. The EW39 2013 had the largest number of cases registered with 89 (Hidalgo, 78; State of Mexico, 8; San Luis Potosí, 1; and Veracruz, 2).

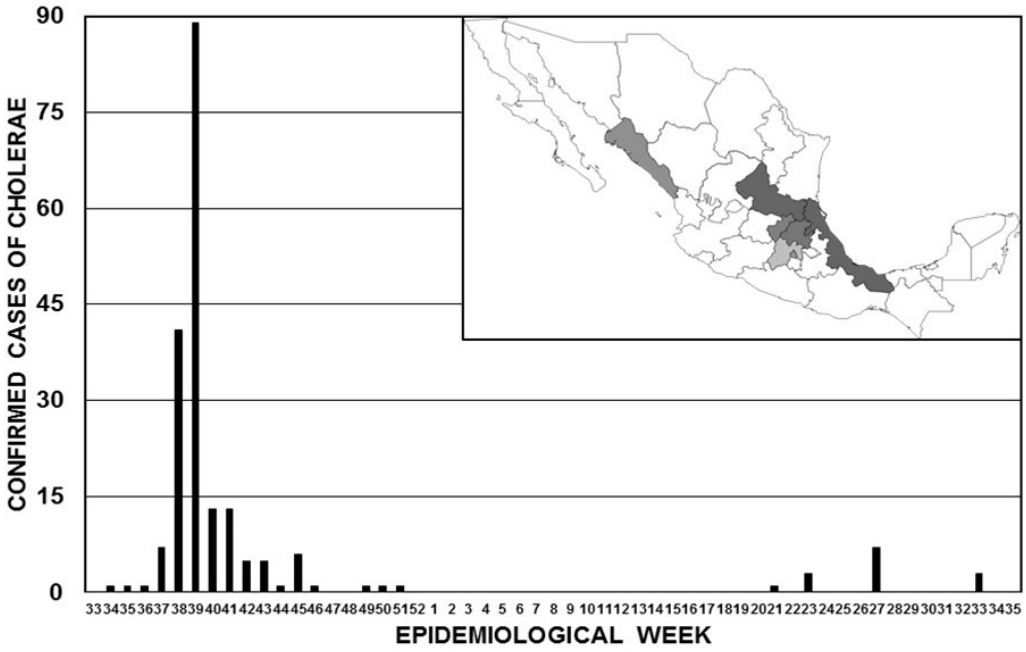


**Figure 1:** Confirmed cases of *V. cholerae* 01toxigenic ordered by date of the onset of symptoms.From September 2, 2013(EW33).

The initial clinical characterization showed a difference in the severity reported between the cases of this outbreak and the Caribbean epidemic. The mean number of bowel movements in 24 h was 8 events (range 0 to 48). The duration of diarrhea was 2 days on average. Regarding gender, the duration was longer in women with 2 days of average (range 1 to 5) and men one day of average duration with the same time range. Regarding the characteristics of bowel movements, 25.3% were liquid or in "rice water", 13.0% with mucus, 1.5% with mucus and blood, while in the remaining 60.2% of the patients did not present these types of evacuations, according to the recorded data. 92.6% of the cases presented stools of liquid consistency and pasty stools in 7.4% (Table 1).

| Variable | AVG (Range) Total | AVG (Range) Women | AVG (Range) Men |
|---|---|---|---|
| Bowel movements in 24 h | 8 (0-48) | 8 (1-33) | 8 (0-48) |
| Length in days | 2 (1-5) | 2 (1-5) | 1 (1-5) |
| Age in years | 33 (0-88) | 34 (1-88) | 31 (0-82) |
| **A. Characteristics of bowel movements** | | | |
| | Total n (%) | Women n (%) | Men n (%) |
| Rice water | 51 (25.3) | 20 (20.2) | 31 (30.4) |
| With mucus | 26 (13.0) | 15 (15.1) | 11 (10.7) |
| Mucus and blood | 3 (1.5) | 1 (1.0) | 2 (2.0) |
| None | 121 (60.2) | 63 (63.7) | 58 (56.9) |
| Total | 201 | 99 | 102 |
| **B. Consistency of evacuations** | | | |
| Liquid | 186 (92.6) | 91 (91.9) | 95 (93.1) |
| Pasty stool | 15 (7.4) | 8 (8.1) | 7 (6.9) |
| Total | 201 | 99 | 102 |
| **C. Hydration status** | | | |
| None | 107 (53.2) | 53 (53.7) | 54 (53.0) |
| Mild | 44 (21.9) | 25 (25.2) | 19 (18.5) |
| Moderate | 40 (19.9) | 14 (14.1) | 26 (25.5) |
| severe dehydration/ shock | 10 (5.0) | 7 (7.0) | 3 (3.0) |
| Total | 201 | 99 | 102 |
| **D. Other signs and symptoms** | | | |
| Cramps | 13 (6.5) | 8 (8.0) | 5 (4.9) |
| Cramps and vomiting | 25 (12.4) | 10 (10.1) | 15 (14.7) |
| Vomiting | 77 (38.3) | 36 (36.4) | 41 (40.2) |
| None | 86 (42.8) | 45 (45.5) | 41 (40.2) |
| Total | 201 | 99 | 102 |
| **E. Type of care** | | | |
| Ambulatory | 131 (65.0) | 66 (66.7) | 65 (63.7) |
| Hospitable | 48 (24.0) | 21 (21.2) | 27 (26.5) |

| | | | |
|---|---|---|---|
| Emergency | 22 (11.0) | 12 (12.1) | 10 (9.8) |
| Total | 201 | 99 | 102 |
| **F. Percentage of cases that met the operational definition of probable cholera case** | | | |
| Yes | 125 (62.2) | 63 (63.6) | 62(60.8) |
| Total | 201 | 99 | 102 |
| Source: SINAVE/DGE/SALUD/MEXICO. | | | |

**Table 1**: Clinical characteristics of cases by gender.

Regarding the hydration status of the patients, 53.2% were identified without dehydration, 21.9% with mild dehydration, 19.9% with moderate dehydration and 5.0% with severe dehydration/ shock. The type of care given to the patients had a predominance of ambulatory care with 65.17% (131 cases) followed by 24.0% (48) with hospital care and 11.0% (22) in observation or Emergency Room (ER).

The distribution of the associated factors in confirmed cases of cholera showed that in 87% (174 cases) no association was found with any factor. On the other hand, 2% of the cases were found to be associated with malnutrition; 4% with diabetes; 1% with pregnandy; 4% with hypertension; 2% with other associated factors. Finally, a case of acute renal failure, a case of probable keto acidosis and a case of neurological sequelae were associated with cholera. During the epidemic, only one death was registered that was determined for a cause other than an infection. It is noteworthy that there were no gender-based statistical differences in the clinical characteristics.

## Discussion

The availability of critical information, obtained in a timely manner, allowed the design of epidemiological surveillance strategies, prevention and control actions that resulted in the control of the outbreak during the first 13 weeks from the identification of the index case. In this way, the necessary activities were triggered for the intentional search of cases from the detection of the cases in Mexico City and the implementation of actions in epidemiological surveillance, health promotion and disease prevention. The coordination at federal and local level by the areas of epidemiological surveillance, laboratory, health promotion and the preventive program allowed an adequate control of the outbreak. It was not possible to identify a positive sample of *V. cholerae O1*, toxigenic *via* Spira or Moore swabs in white or residual waters. There was no evidence of the possible primary source of infection, nor was it possible to identify the microorganism in white waters for human consumption and use, or in the water sources of the network that supplied the population. The signs and symptoms identified in cases of Mexico were of less seriousness compared to the cases recorded in the cholera outbreak in Haiti, despite being the same strain identified (Figure 2). The early use of molecular epidemiology tools, both the complete identification of the virulence genes and the PFGE pattern, as well as the sequencing and analysis of the genome of the bacterium, undoubtedly identified that it was the same strain which caused the outbreaks in Haiti, the Dominican Republic and Cuba.

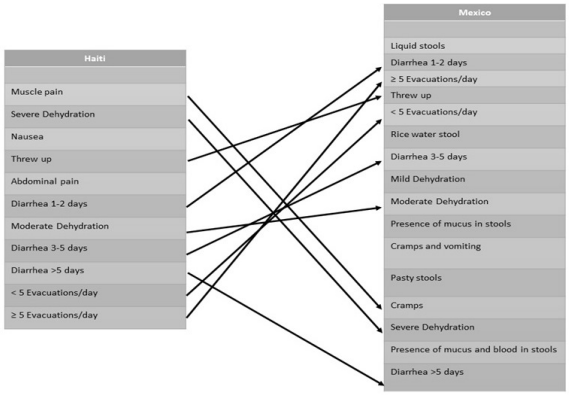


**Figure 2.** Comparative analysis of clinical signs and symptoms based on the frequency found in Haiti (left) and Mexico (right).

This demonstrates that molecular epidemiology is a very powerful tool for monitoring diseases of importance to public health. In fact, Mexico bears a well-structured epidemiological surveillance system that includes all the institutions of the National Health System and a network of regional public health laboratories that use standardized methods to quickly confirm the diagnosis of cholera. This allows prevention and control actions to quickly control the outbreak of cholera in Mexico, situation that did not occur in other countries such as Dominican Republic or Haiti.

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