NEW INSIGHTS ON THE EMERGENCE OF CHOLERA IN LATIN AMERICA DURING 1991: THE PERUVIAN EXPERIENCE


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Abstract. After a century of absence, in late January 1991, Vibrio cholerae invaded the Western Hemisphere by way of Peru. Although a number of theories have been proposed, it is still not understood how that invasion took place. We reviewed the clinical records of persons attending hospital emergency departments in the major coastal cities of Peru from September through January of 1989/1990 and 1990/1991. We identified seven adults suffering from severe, watery diarrhea compatible with a clinical diagnosis of cholera during the four months preceding the cholera outbreak, but none during the previous year. The patients were scattered among five coastal cities along a 1,000 km coastline. We postulate that cholera vibrios, autochthonous to the aquatic environment, were present in multiple coastal locations, and resulted from environmental conditions that existed during an El Nino phenomenon. Once introduced into the coastal communities in concentrations large enough for human infection to occur, cholera spread by the well-known means of contaminated water and food.

INTRODUCTION

Cholera remains endemic in many parts of the developing world and continues to cause significant morbidity and mortality every year. Since 1990, more cases of cholera have been reported to the World Health Organization (WHO) than in the previous decade. More countries are reporting cholera cases and new continents are being affected as a consequence of the continuing spread of the current seventh cholera pandemic. Adding to this epidemic burden, cholera strains resistant to common antimicrobial agents are being reported from endemic areas, and a new serogroup of Vibrio cholerae, O139, has been responsible for large epidemics of clinical cholera in Asia.

While many aspects of cholera are well known such as its routes of transmission, diagnosis, pathophysiology, and therapy, some aspects of its epidemiology remain poorly understood, including both its pandemic nature, i.e., how cholera arises in continents where the disease was previously unre-ported for a century, and the reservoir of cholera vibrios between epidemic periods. The Latin American extension of the seventh cholera pandemic offers an opportunity to test a new hypothesis concerning its epidemiology. Some have proposed that a single point introduction of V. cholerae O1 occurred in Chimbote, a major Peruvian seaport, and in Lima, a coastal city with a nearby major seaport before the beginning of the epidemic in Latin America at the end of January 1991. According to this hypothesis, massive contamination of sea water along the coast occurred from excreta of cholera patients on a ship arriving from Asia. In the present study, we propose an alternate hypothesis based on clinical data obtained from the coastal areas of Peru prior to the onset of the epidemic. Our theory suggests there were multiple entry points of Vibrio cholerae along the Pacific coast of Peru.

MATERIALS AND METHODS

Patients. The study was conducted between February 1998 and February 1999. During that year, the emergency rooms of the main hospitals in seven cities along the Pacific northern coast of Peru from the North Health Region of Lima and including the following cities and seaports: Chancay, Huacho, Chimbote, Trujillo, Chiclayo, and Piura, were visited by two investigators (Figure 1). Hospitals included in the evaluation were the largest maintained by the government of Peru in these cities. All the hospitals provided medical care to people of low socioeconomic status, and had treated the majority of cholera patients in that region from the beginning of the 1991 cholera epidemic in Peru.

Of the nine hospitals visited, medical records were obtained from six emergency rooms; the National Hospital Cayetano Heredia in the North Health Region of Lima (the first hospital in Lima city to report cholera cases in 1991); one hospital in the port of Chancay located 60 km north of Lima; two hospitals in Chimbote, the second largest Peru seaport located 440 km north of Lima; and two hospitals in Trujillo, a city located 570 km north of Lima.

Lists of patients admitted to the emergency rooms over the five-month period (September–January) during 1989/1990 and 1990/1991 were reviewed. These time periods were selected as the highest risk time for diarrheal diseases, before the usual seasonal peak of common diarrhea which occurs from January to April each year. The search initially focused on both adults and children who were admitted to emergency rooms with an acute diarrhea diagnosis defined as three or more liquid stools per day for no longer than 3 days. Among the patients with acute diarrhea, particular attention was given to patients meeting the criteria for clinical cholera as defined by WHO—acute, watery diarrhea and evidence of severe dehydration in patients older than five years of age. Severe dehydration was defined as the presence of shock, generalized cramps, and signs of severe fluid loss, such as “washerwoman’s hands,” sunken eyes, hoarse voice, poor skin turgor, and oliguria.

Data extracted from clinical records included the date of onset of symptoms as described by patients; physical findings, including the evaluation of the degree of dehydration.
on admission, and therapy instituted, such as the necessity for intravenous fluids, including kind and volume. Information regarding the total number of patients evaluated in the emergency rooms, the number of patients with the diagnosis of diarrhea, and the number of patients meeting the criteria for cholera were recorded. The percentage of patients with diarrhea among all patients attending these emergency rooms was calculated and compared between the two periods (1989/1990 and 1990/1991) covered by the study.

RESULTS

A total of 3,640 charts of patients with diarrhea who attended the emergency rooms in these six hospitals between September and January of 1989/1990 and 1990/1991 were reviewed. Seven persons from the 1990–1991 records were identified who fit the clinical definition of cholera, none from 1989/1990.

The earliest case of clinical cholera was detected in Hospital Belen, Trujillo, on October 23, 1990, almost four months before the cholera epidemic was officially declared in Peru. After this case occurred, six additional patients with acute, watery diarrhea and severe dehydration were seen during December 1990 and the first three weeks of January 1991 in Trujillo, Chimbote, Chancay and Lima (Figure 1). The epidemiological and clinical characteristics of these seven cholera patients are presented in Table 1. All of the patients required intravenous fluids for rehydration, but the amount given was not recorded. None of the patients died; all were discharged after a short period of hospitalization, mainly to the observation rooms in the emergency wards.

About one week later on January 23, 1991, the cholera epidemic began: four patients were admitted to the emergency room at Hospital Chancay with watery diarrhea and shock. One day later, the Hospital La Caleta in Chimbote also admitted four adult patients with acute, watery diarrhea resulting in severe dehydration and shock. Shortly thereafter, an increasing number of patients with similar symptoms were seen daily in each of the hospitals visited. Therefore, according to our evaluation, the cholera epidemic in Peru began on January 23, 1991. A few days later, on January 28, the Hospital Cayetano Heredia in Piura managed its first case of clinical cholera (Figure 1).

Data on the percentages of patients with diarrhea among all patients admitted to the emergency rooms of three of the hospitals included in this study, from September to March 1989/1990 and 1990/1991, are presented in Table 2. No difference in the percentage with diarrhea was noted during September to January of 1990/1991, but the percentage of patients with diarrhea in February and March 1991 (following the onset of the epidemic) was significantly higher than in 1990.

DISCUSSION

The largest epidemic of cholera during the last decade of the Twentieth Century occurred unexpectedly in Latin America in 1991. Peru was the first country to report cases
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TABLE 1
Epidemiological and clinical characteristics of patients who fulfilled the definition of cholera before the third week of January 1991

<table>
<thead>
<tr>
<th>Place of origin</th>
<th>Date of onset of symptoms</th>
<th>Age/gender</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trujillo-Hospital Belen</td>
<td>23 October 1990</td>
<td>60/M</td>
<td>Watery diarrhea, generalized cramps</td>
</tr>
<tr>
<td>Chimbote-Hospital Regional</td>
<td>11 December 1990</td>
<td>Adult, NA</td>
<td>Watery diarrhea, vomiting, generalized cramps, shock</td>
</tr>
<tr>
<td>Trujillo-Hospital Belen</td>
<td>24 December 1990</td>
<td>48/M</td>
<td>Watery diarrhea, generalized cramps</td>
</tr>
<tr>
<td>Chancay-Hospital Chancay</td>
<td>26 December 1990</td>
<td>32/F</td>
<td>Watery diarrhea, severe dehydration, somnolence</td>
</tr>
<tr>
<td>Chancay-Hospital Chancay</td>
<td>29 December 1990</td>
<td>15/M</td>
<td>Watery diarrhea, generalized cramps</td>
</tr>
<tr>
<td>Lima-Hospital Cayetano Heredia</td>
<td>13 January 1991</td>
<td>63/M</td>
<td>Watery diarrhea, vomiting, acute renal failure</td>
</tr>
<tr>
<td>Chancay-Hospital Chancay</td>
<td>16 January 1991</td>
<td>60/M</td>
<td>Watery diarrhea, hypovolemic shock</td>
</tr>
</tbody>
</table>

* NA = not available. M = male, F = female.

of cholera and also the country most severely affected by the epidemic, not only in terms of numbers (almost 300,000 cases during the first year of the epidemic, and approximately 45,000 cases per week during the first few weeks), but also in terms of the significant impact that the epidemic had on its impoverished economy.\(^8,9\) Nine years later, the origin of the epidemic has yet to be determined.

The data presented here suggest that *V. cholerae* was present in Peru for at least several months before the recognized onset of the cholera epidemic. Seven patients were identified who had symptoms typical of cholera (as defined by WHO) at least four months prior to the recognition of the cholera epidemic in Peru. Since it is known that severe clinical cases of cholera account for only 1–2% of infections with *V. cholerae* in endemic areas\(^10\) and infection occurs in many asymptomatic persons in newly-infected areas,\(^11\) we may assume that these microorganisms were already widespread in the environment by the time these cases occurred. Furthermore, the occurrence of clinical cholera cases along the northern coast of Peru substantiates the wide dispersion of vibrios into the environment. Almost certainly once the epidemic was under way, it was amplified from city-to-city by contaminated water and food, particularly fish and shellfish.\(^3\) Its spread was also facilitated by poor sanitary conditions and hygienic practices prevailing in low socioeconomic groups in Peruvian coastal cities at that time.\(^8,11\)

Clearly, a major limitation of this study is the lack of microbiological confirmation of the clinical diagnoses. It is possible that these cases of severe, dehydrating, watery diarrhea were due to causes other than *V. cholerae* O1. Diarrheagenic organisms, such as enterotoxigenic *Escherichia coli*, *Salmonella*, and *V. cholerae* non-O1, have all been known to produce severe cholera-like diarrhea in adults.\(^12-14\)

Other non-infectious possibilities include arsenic and antimony poisonings\(^15\) or insecticides.\(^16\) All of these other etiologies seem unlikely, however, since no similar cases were identified during the same period in the previous year. Note that this clinical picture of cholera had not been seen previously by Peruvian physicians (Leon-Barua R and Sease C, unpublished data); it was clearly recognized as a new, previously undescribed illness in Peruvian adults.

If we assume that these patients did indeed have cholera, then the obvious questions are from where did the vibrios originate? and how did they become so widely dispersed? There are several possibilities, most of which have already been postulated: 1) Passengers or crew aboard ships from cholera-infected areas introduced vibrios into the sea at large cities with nearby ports, such as Lima and Chimbote;\(^3\) 2)

TABLE 2
Patients with diarrhea among all patients attending the emergency rooms of 3 hospitals in Peru. September to March 1989/1990 and 1990/1991

<table>
<thead>
<tr>
<th>Hospital-city/year</th>
<th>September</th>
<th>October</th>
<th>November</th>
<th>December</th>
<th>January</th>
<th>February</th>
<th>March</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cayetano Heredia-Lima</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>194 (7.2)</td>
<td>219 (7.1)</td>
<td>188 (6.3)</td>
<td>NA</td>
</tr>
<tr>
<td>1989/1990</td>
<td>NA</td>
<td>73 (3.1)*</td>
<td>68 (3.1)</td>
<td>146 (6.2)</td>
<td>175 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990/1991</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional-Chimbote</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1989/1990</td>
<td>33 (5)</td>
<td>67 (9.0)</td>
<td>56 (9.0)</td>
<td>96 (12.0)</td>
<td>107 (10.0)</td>
<td>75 (10.0)</td>
<td>51 (7.0)</td>
</tr>
<tr>
<td>1990/1991</td>
<td>63 (9)</td>
<td>71 (8.0)</td>
<td>88 (10.0)</td>
<td>79 (8.0)</td>
<td>141 (12.0)</td>
<td>553 (58.0)</td>
<td>141 (34.0)</td>
</tr>
<tr>
<td>Belen-Trujillo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1989/1990</td>
<td>84 (9.3)</td>
<td>96 (9.1)</td>
<td>108 (9.9)</td>
<td>94 (8.5)</td>
<td>115 (9.8)</td>
<td>125 (10.3)</td>
<td>114 (8.6)</td>
</tr>
<tr>
<td>1990/1991</td>
<td>104 (13.8)</td>
<td>80 (10.3)</td>
<td>75 (8.7)</td>
<td>138 (11.6)</td>
<td>145 (13.8)</td>
<td>719 (50.8)</td>
<td>171 (15.1)</td>
</tr>
</tbody>
</table>

* Figures are number of patients with diarrhea (% of all patients attending the emergency room). NA = not available.
Bilge water containing vibrios was emptied into the ocean from sea-going vessels as has been shown in the Gulf of Mexico.\(^3\) Vibrios other than toxigenic *V. cholerae* (either non-toxigenic *V. cholerae* O1 or *V. cholerae* of other serogroups present in sea water that acquired virulence genes through phage infection) were responsible;\(^18\) and 4) Toxigenic *V. cholerae* O1 was already present in the coastal waters, either as viable, but nonculturable organisms associated with plankton or in very low concentrations as culturable organisms that could not readily be recovered. Environmental factors such as increased temperature due to El Nino or changes in salinity and/or nutrient concentrations may have enabled the indigenous population of vibrios to increase and be transmitted to humans in infectious doses through the ingestion of riverine water along the coast and the consumption of seafood or other foods contaminated with seawater.\(^19\)

The results of our study, however, contradict the single introduction hypotheses. It was not the hospitals in Chimbote and Lima, but the hospital in Trujillo, almost 130 km north of Chimbote that first diagnosed cholera cases. In fact, the first case was seen in Trujillo in October 1990, followed by six other cases that occurred along the northern coast of Peru between early December 1990 and the third week of January 1991. These six cases were distributed along the 1,000 km coastline of northern Peru. By the third week of January, additional cases of cholera occurred along almost all of the northern coast of Peru. Thus, an alternate hypothesis to that of a single introduction of cholera into the continent is required to explain the findings of multiple cases throughout the north coast of Peru.\(^20\) Furthermore, the disease was presumably not present before October 1990 because no clinical cases were identified during the comparable time period in 1989, nor were any diarrhea epidemics previously reported. The absence of recognizable clinical cholera in South America for a century prior to 1991 is interpreted as the absence of *Vibrio cholerae* El Tor, the *V. cholerae* O1 biotype that caused the 7th cholera pandemic.\(^5\) Previous isolations of both non-toxigenic *V. cholerae* O1 and *V. cholerae* non-O1, however, had been made in this region several years prior to the epidemic. In Peru (1984)\(^21\) and Mexico (1987),\(^22\) *V. cholerae* non-O1 was isolated from clinical specimens. Non-toxigenic *V. cholerae* O1 El Tor had been isolated from sewage in Brazil (1982)\(^23\) and from two patients with diarrhea in Lima, Peru (1988).\(^24\) These findings suggest that although both O1 and non-O1 *V. cholerae* had previously been cultured in this area of the world, the possibilities that these strains might be resident vibrios which acquired virulence genes through phage infection on a massive scale seems less likely.

The vibrios responsible for the Latin American epidemic are genetically similar, but not identical to cholera vibrios responsible for the seventh cholera pandemic.\(^25\) One could conclude that the vibrios were imported from an endemic area, possibly from Asia or Africa. But this still begs the question of how the vibrios could have occurred in several places at the same time along the Pacific northern region of Peru. A strong possibility, and one that would fit the known observations, is the association of *Vibrio cholerae* and marine plankton recently elucidated by Colwell.\(^19\)

*Vibrio cholerae* was shown as early as 1969 to be an autotrophic inhabitant of brackish water and estuarine ecosystems\(^26\) and a seasonal inhabitant of bays and estuaries, e.g., the Chesapeake Bay.\(^27-29\) Pathogenic vibrios are known to be associated with zooplankton such as coppepods with chitin exoskeletons and with shellfish, including crabs, shrimp, and crayfish. *Vibrio cholerae* is part of the natural flora of the gut of these animals and has a powerful chitinase that enhances its growth on the surfaces of plankton and shellfish.\(^30\) *Vibrio cholerae* will survive in seawater for months or years\(^31\) and thus, the bacterium can be transported by ocean currents over very long distances. Work done with phytoplankton,\(^32\) including blue-green algae, suggests that pathogenic vibrios may survive on both zooplankton and phytoplankton in the aquatic environment, but zooplankton act as amplifiers, increasing the numbers to those sufficient to trigger an epidemic.\(^33,34\)

Thus, the evidence presented here suggests that toxigenic *V. cholerae* O1 El Tor was, indeed, present all along the Pacific northern coast of Peru, at least since October 1990, causing sporadic cases in the region until January 1991 when the epidemic began in full force. The dissemination of vibrios in coastal seawater was most probably associated with selected plankton populations whose abundance was related to the El Nino phenomenon of 1991. City-to-city dissemination is a less likely explanation for the beginning of this epidemic. Therefore, we hypothesize a multiple-point introduction of *V. cholerae* from seawater, via its plankton host rather than a single point entry. Recent analyses of other parameters, such as sea surface temperature and sea surface height in the Bay of Bengal, have shown good correlation with the cholera epidemic patterns in Bangladesh.\(^19\)

Taking into account the viable but nonculturable phenomenon manifested by *V. cholerae*,\(^34\) it is possible to detect *V. cholerae* on plankton by means of molecular genetic techniques.\(^35\) Thus, it is more probable that the cholera epidemic of 1990 was triggered from a large oceanic and riverine source, notably the *V. cholerae* autotrophic to plankton in the natural aquatic environment. Unfortunately, direct data, including phytoplankton or zooplankton analyses from that period of time are not available. Work is now in progress (Gil AI and others, unpublished data), however, that demonstrates a relationship between plankton and *Vibrio cholerae* in Peruvian waters. From August 1997 to September 1999, viable but nonculturable forms of *V. cholerae* O1 have been found in sea water and plankton along the coast of Lima, Trujillo, and Arequipa, and culturable forms along the coast of Lima.

The early recognition of cholera epidemics may be made possible by using data from different disciplines such as marine biology, satellite imagery, and clinical surveillance to provide an early warning that will permit full implementation of public health measures in order to prevent an outbreak. The link between cholera and marine ecology has potential long-term health implications as climates change and sea levels fluctuate.\(^36\)

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