Venezuelan Hemorrhagic Fever: Clinical and Epidemiological Studies of 165 Cases

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Epidemiological and clinical data are presented on 165 cases of Venezuelan hemorrhagic fever (VHF), a newly emerging viral zoonosis caused by Guanarito virus (of the family Arenaviridae). The disease is endemic in a relatively circumscribed area of central Venezuela. Since its first recognition in 1989, the incidence of VHF has peaked each year between November and January, during the period of major agricultural activity in the region of endemicity. The majority of cases have involved male agricultural workers. Principal symptoms among the patients with VHF included fever, malaise, headache, arthralgia, sore throat, vomiting, abdominal pain, diarrhea, convulsions, and a variety of hemorrhagic manifestations. The majority of patients also had leukopenia and thrombocytopenia. The overall fatality rate among the 165 cases was 33.3%, despite hospitalization and vigorous supportive care.

In September 1989 an outbreak of severe hemorrhagic illness was first recognized by physicians in the municipalities of Guanarito and Guanare in the state of Portuguesa in central Venezuela [1]. The outbreak initially was thought to be dengue hemorrhagic fever, but following the isolation of a new arenavirus (Guanarito virus) [2] in two fatal cases, the disease was named Venezuelan hemorrhagic fever (VHF). Since its initial recognition, sporadic cases of VHF have continued to occur within a relatively circumscribed region of central Venezuela. In order to learn more about this newly emerged rodent-associated disease, we attempted to collect clinical and epidemiological data on all reported VHF cases that occurred during the past 7 years. This paper summarizes the results of studies of 165 VHF cases observed between September 1989 and January 1997.

Materials and Methods

Study area. The currently recognized area of VHF endemicity occupies ~9,000 km^2 in the southern and southwestern portions of Portuguesa State and adjacent regions of Barinas State in the central plains (llanos) of Venezuela (figure 1). The climate of the region is tropical, with a mean annual temperature of 28°C and a mean precipitation of ~1,300 mm/y. Rainfall within the region tends to be seasonal, with heavy rainfall between May and mid-November and a pronounced dry period from December until the end of April.

The human population of the region of VHF endemicity is ~300,000, with ~150,000 people living in Guanare, the state capital, and another 8,000 living in the town of Guanarito (figure 1). The remainder of the population (~142,000) live in rural areas; most of these people are involved in agriculture and/or cattle raising. However, many of the residents of Guanare and Guanarito own or work on farms in the surrounding countryside, so they also potentially have contact with the rodent reservoirs of Guanarito virus [3]. Principal crops of the region are corn, sorghum, cotton, rice, sunflowers, sugarcane, melons, and beans. During the planting and harvest seasons, a large number of temporary agricultural workers come into the area from nearby regions of Venezuela and Colombia.

Study population. All except one of the 165 patients with VHF included in our study were treated in Guanare at the Miguel Oraa Hospital, a 200-bed public hospital that is operated by the Ministry of Health and Social Assistance and serves most of the population of this region. The single patient treated elsewhere was an adult female resident of Guanarito who received medical care in Caracas. Patients admitted to Miguel Oraa Hospital with a clinical illness compatible with VHF were interviewed by a nurse. The patients' hospital records were also reviewed. On the basis of information obtained from the interview and hospital records, a 3-page epidemiological questionnaire was completed for each suspected VHF patient; this

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Figure 1. *Upper left,* map of Venezuela showing the locations (shaded) of the states of Portuguesa and Barinas. *Lower right,* enlarged map of the same two states, showing the approximate locality of residence (△) of all patients with Venezuelan hemorrhagic fever (VHF; $n = 42$) who were reported in 1996.

document contained clinical and demographic data as well as results of selected laboratory tests.

Whenever possible, an acute-phase blood sample was obtained shortly after hospital admission for virus isolation attempts and serology. Three to 5 weeks later, a second (convalescent) blood sample was obtained from patients who survived and could be relocated. The acute-phase blood sample was stored in a liquid nitrogen refrigerator, and the convalescent serum was held at −20°C in Guanare until transport to Caracas or Atlanta for testing.

Case definition. On the basis of an analysis of the epidemiological questionnaire and the results of laboratory tests, VHF cases were classified as probable or confirmed. A probable case was defined as an acute febrile illness characterized by most or all of the following: weakness, headache, myalgia, sore throat, vomiting and/or diarrhea, hemorrhagic manifestations of any type, leukopenia, and thrombocytopenia, occurring in a previously healthy person living in or having recent contact with rural areas within the VHF-endemicity zone. A confirmed VHF case was defined by the symptomatology noted above, plus laboratory confirmation of recent Guanarito virus infection, either by actual virus isolation or demonstration of seroconversion to Guanarito viral antigen in acute and convalescent blood samples.

Laboratory tests. All laboratory tests done on clinical or autopsy samples from patients suspected of having VHF were carried out in a biosafety-level-3 (BSL-3) laboratory at the Instituto Nacional de Higiene in Caracas or in the maximum-

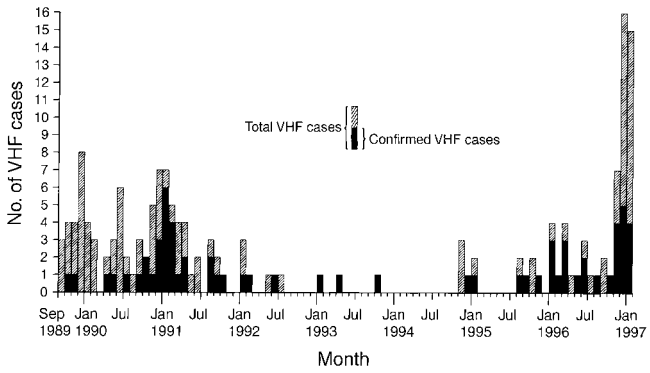

Figure 2. Incidence of Venezuelan hemorrhagic fever (VHF; probable [▨] and confirmed [■] cases) during the period of September 1989 through January 1997, by month.

containment facility at the Special Pathogens Branch, Centers for Disease Control and Prevention, in Atlanta. Blood and tissue samples from suspected VHF patients were assayed for Guanarito virus in cultures of Vero E-6 cells, as described previously [3]. Most of these acute-phase samples were also assayed for the presence of dengue and yellow fever viruses by culture in mosquito cells [4]. Acute and convalescent serum samples from surviving patients were screened for the presence of Guanarito virus antibodies by indirect fluorescent antibody test and/or by IgM ELISA, as described before [1].

Statistical methods. Comparison of sample means was by one-way analysis of variance (ANOVA). Testing of the homogeneity of sample variances was by Bartlett's test. The acceptable type 1 error (α) in all statistical tests was 0.05.

Results

Seasonal incidence. Figure 2 and table 1 show the total number of reported VHF cases by month from 1 September

Table 1. Incidence of Venezuelan hemorrhagic fever (VHF), by month, during the period of September 1989 through January 1997.

	No. of cases of VHF		
Month	Confirmed	Probable	Total
January	16	20	36
February	6	4	10
March	4	4	8
April	4	4	8
May	2	4	6
June	3	9	12
July	1	3	4
August	4	3	7
September	3	8	11
October	6	5	11
November	7	13	20
December	10	22	32
Total	66	99	165

Table 2. Prevalence of presenting symptoms and signs among 55 confirmed cases of Venezuelan hemorrhagic fever.

Symptom or sign	Prevalence (% of cases)
Fever	92.7
Malaise	74.5
Headache	58.2
Bleeding gums	52.7
Arthralgia	52.7
Sore throat	36.4
Vomiting	34.5
Abdominal pain	30.9
Myalgia	30.9
Dehydration	29.1
Diarrhea	27.3
Lymphadenopathy	23.6
Melena	20.0
Cough	20.0
Convulsions	18.2
Hematemesis	16.4
Petechiae	16.4
Conjunctivitis	14.5
Nausea	13.4
Tonsilar exudate	12.7
Epistaxis	12.7
Pharyngitis	12.7
Somnolence/stupor	10.9
Rectal bleeding	9.1
Hepatomegaly	5.6
Splenomegaly	1.8

1989 through 31 January 1997. A total of 165 VHF cases were recognized during this period. Of the total, 66 cases (40%) were confirmed by virus isolation and/or demonstration of seroconversion; the other 99 (60%) were classified as probable cases on the basis of the diagnostic criteria noted above. Fifteen of the 66 confirmed cases were described previously in a preliminary publication [1].

We were unable to get acute-phase blood specimens or to isolate virus in the probable VHF cases; in addition, some of these patients died or were lost to follow-up, so a convalescent blood sample was not obtained from them. Nonetheless, as discussed below, the two categories of cases (probable and confirmed) were similar in all respects. For this reason, the data given in figures 1 and 2 and table 1 include information on all VHF cases (probable and confirmed) observed during the aforementioned period, while tables 2–4 give data only on confirmed VHF cases.

Figure 2 and table 1 illustrate two interesting characteristics about the incidence of VHF. First, the disease appears to be endemic, with cases occurring throughout the year. Cases of VHF were reported in every month, but there was a definite seasonal trend, with more than half (53%) of the 165 cases occurring during the months of November, December, and January (table 1).

The second implication of the incidence data (figure 2) is that there are cyclic periods of VHF activity on a multiyear scale. After the disease was first recognized in September 1989, there was almost continuous activity until about August 1992 (a 35-month period). Then, from September 1992 until August 1996, there was little disease activity; a total of only nine cases occurred during this second 36-month period. Beginning in September 1996, however, the monthly incidence of VHF increased again, and as of May 1997, cases were still occurring. Although not shown in figure 2, 9 VHF cases (7 confirmed) occurred in February, 10 (6 confirmed) in March, and 5 in April 1997.

Table 3. Hematologic findings in 49 confirmed cases of Venezuelan hemorrhagic fever at the time of hospitalization.

Parameter	Mean	SD	Range
Hematocrit (%)	34.2	8.1	7.4–45.0
Hemoglobin (g/dL)	11.2	2.6	2.4–15.0
WBCs ($\times 10^9$/L)	2.5	1.5	0.8–6.6
Platelets ($\times 10^9$/L)	63.2	31.9	10–140

Geographic distribution. To date, all of the probable and confirmed cases of VHF have occurred among people residing in the southern and southwestern portions of Portuguesa State and in adjacent areas of Barinas State (figure 1) or have involved persons who lived elsewhere but had recent contact with the region of VHF endemicity. The focal distribution of the disease is illustrated by the lower map in figure 1, which shows the approximate locality of the 42 VHF cases reported in 1996. This geographic pattern of infection has not changed significantly since 1989. It also closely correlates with our isolations of Guanarito virus from wild rodents (*Sigmodon alstoni* and *Zygodontomys brevicauda*) collected during field studies in central Venezuela ([3] and unpublished data).

Demographic data. VHF occurs predominately in males; of the 66 confirmed VHF cases, 47 (71.2%) involved males and 19 (28.8%) involved females. A similar sex difference was

Table 4. Clinical diagnoses in 56 confirmed cases of Venezuelan hemorrhagic fever at time of patients' hospitalization.

Diagnosis	No. of confirmed cases of VHF
Viral syndrome	16
Classic dengue fever	11
No diagnosis	7
Venezuelan hemorrhagic fever	6
Hemorrhagic virosis	5
Dengue hemorrhagic fever	4
Tonsillitis/pharyngitis	2
Convulsive syndrome	1
Bronchopneumonia	1
Gastrointestinal hemorrhage	1
Sepsis	1
Febrile syndrome	1

noted in the 99 probable VHF cases; 70 (70.7%) were in males and 29 (29.3%) were in females.

The 66 patients with confirmed VHF ranged in age from 5 to 79 years (mean age, 27.6 years; SD, ±15.7). The age distribution among males and females in the confirmed group was not significantly different: the mean age of males was 28.3 years (SD, ± 14.6; range, 6–57 years), and that of females was 26.1 years (SD, ± 18.2; range, 5–79 years).

Clinical and laboratory findings. Table 2 shows the prevalence of symptoms and signs among 55 patients with confirmed VHF when first admitted to the hospital. Most patients reported a history of fever (92.7%) and progressive onset of symptoms. VHF usually begins as a mild, nonspecific febrile illness that progresses in severity over the next 5–7 days. At that point the illness is usually so severe that hospitalization is required. Among 53 confirmed cases of the disease in which a complete history was recorded, the mean time from the onset of symptoms until hospitalization (mean onset) was 6.4 days (SD, ± 3.6; range, 1–23 days). For 34 surviving patients in this group, the mean onset was 5.7 days (SD, ± 2.6; range, 1–12 days); in 19 fatal cases, the mean onset was 7.6 days (SD, ± 4.6, range, 3–23 days).

Table 3 summarizes the hematologic findings in 49 confirmed VHF cases at the time of initial hospitalization. All of these patients had thrombocytopenia ($<150 \times 10^9$ platelets per liter), and 85.7% had leukopenia ($<5 \times 10^9$ WBCs per liter). Subsequent hematologic values were not recorded, since many of the patients received blood transfusions and platelets during their hospitalization. Chemical studies of electrolytes as well as tests of liver and renal function were done on a few patients, but the results are not included here. In general, these latter tests were done only on patients with the gravest illnesses, most of whom died.

Initial clinical diagnoses. Table 4 shows the attending physician's clinical impression (diagnosis) as noted in the hospital records of 56 patients with confirmed VHF upon admission. The most common admitting diagnosis was viral syndrome (16 of 56, or 28.6%). Classical dengue or dengue hemorrhagic fever was initially diagnosed in another 26.8% of the confirmed VHF cases. A specific diagnosis of VHF was made in only six (10.7%) of the 56 confirmed cases on admission.

Treatment. No specific antiviral therapy was given to any of the patients with VHF. Treatment was supportive and varied considerably, depending upon the patients' clinical status. For this reason, we were unable to evaluate the efficacy of specific therapeutic measures.

Outcome and duration of hospitalization. Twenty-two (33.3%) of the 66 patients with confirmed VHF died; the fatality rate in the 99 probable cases was also 33.3% (33/99). The mean time from initial hospitalization until death among the 22 confirmed VHF fatalities was 4.6 days (SD, ± 6.9; range, 1–33). Among the 44 patients with confirmed VHF who survived, the mean duration of hospitalization was 10.6 days (SD, ± 5.4; range, 1–23 days).

Discussion

To date, five arenaviruses (Lassa, Junin, Machupo, Guanarito, and Sabia) have been associated with hemorrhagic fever in humans [5]. Although each of these viruses and the diseases that they cause (Lassa fever, Argentine hemorrhagic fever, Bolivian hemorrhagic fever, VHF, and Sao Paulo hemorrhagic fever, respectively) have a unique geographic distribution and ecology [5, 6], the clinical manifestations of human infection with these agents are very similar. The presenting symptoms and signs of the 55 confirmed VHF cases in this study (table 2) were not very different from clinical descriptions of the four other arenaviral hemorrhagic fevers [5–17]. Likewise, the initial hematologic findings in the confirmed VHF cases (table 3) were similar to those reported for the other arenaviral hemorrhagic fevers.

Thrombocytopenia was the most consistent hematologic finding; in 127 (96.9%) of 131 probable and confirmed VHF cases in which initial platelet counts were determined, there were $<150 \times 10^9$ platelets per liter on admission. However, the initial platelet count appeared to have no relation to the outcome of the case. The initial mean platelet count among 44 survivors of confirmed VHF was 66.2×10^9/L (SD, ± 33.3; range, $23–140 \times 10^9$/L), and in 22 confirmed fatal cases it was 58.2×10^9/L (SD, ± 29.7; range, $10–133 \times 10^9$/L).

In contrast, for VHF patients entering the hospital with active convulsions or a history of recent convulsions, the prognosis was poor. Overall, 22 (15.7%) of 140 patients with probable or confirmed VHF whose medical records were complete had a history of convulsions just before or at the time of hospital admission. Sixteen of these 22 patients (72.7%) ultimately died, compared with an overall VHF fatality rate of 33.3%. CNS manifestations, including encephalitis and convulsions, also have been reported to occur in cases of Lassa fever [18, 19] and Argentine hemorrhagic fever [5]; they carry a poor prognosis in these diseases as well.

VHF, like the other arenaviral hemorrhagic fevers [5–17], is insidious in onset and initially is difficult to differentiate from a variety of other febrile illnesses. This is illustrated by the data given in table 4, which summarizes the clinical diagnoses noted in the medical records of 56 patients with confirmed VHF at the time of their initial hospitalization. Despite the fact that VHF is endemic in the region and that local physicians are aware of the disease, only six of 56 confirmed cases (10.7%) were initially diagnosed as VHF. Another five patients (8.9%) were admitted to the hospital with a diagnosis of hemorrhagic virosis, which is compatible with a diagnosis of VHF. The most frequent diagnoses were viral syndrome (28.6%) and classic dengue/dengue hemorrhagic fever (26.8%).

Dengue is common in Venezuela, especially in urban areas, where it occurs in both endemic and epidemic forms. During the first few days of dengue fever, before the appearance of the characteristic maculopapular rash, this disease really cannot be differentiated clinically from VHF [20]. Furthermore, many

patients with dengue also have leukopenia, thrombocytopenia, and mild hemorrhagic manifestations (i.e., epistaxis, petechiae, and purpura), further confounding the differential diagnosis [20]. It is only after observation of the patient for a number of days that the differentiation between dengue and VHF can be made clinically (i.e., by the absence of rash and by fever lasting 8–12 days in VHF).

Among the 165 VHF patients included in this study, there was only one person who might have been a secondary or contact case. This individual was a 30-year-old housewife who developed a fatal illness, compatible clinically and histopathologically with VHF, 19 days after her husband was hospitalized with a nonfatal confirmed Guanarito virus infection. The husband remained in the hospital for 7 days and then returned home. His wife became ill 12 days later. Unfortunately, we were unable to isolate virus from her acute blood sample, and she died before a convalescent serum could be obtained.

A number of other examples of presumed person-to-person transmission of arenaviruses (Lassa, Junin, and Machupo) from one spouse to another have been reported [21]. No nosocomial infections were observed among any of the hospital personnel or other patients in contact with the 165 patients with VHF. Because of the diagnostic problems noted above, many of the VHF patients were initially admitted to open wards with minimal isolation precautions. Nosocomial infections have been reported among persons in contact with patients with Lassa fever and Bolivian hemorrhagic fever [5, 9, 16, 21].

As noted previously, the majority of people living in the study area are involved in some type of agricultural activity; thus, it was not possible to estimate the risk of VHF infection by occupation. Most of the male patients interviewed gave their occupation as farmer or agricultural worker, whereas most of the females gave their occupation as homemaker. This presumed difference in occupational exposure to potentially infected rodents might partly explain the preponderance of males (70.9%) among the 165 total VHF cases. On the other hand, women living in rural areas in this region often work in the fields during the harvest season (e.g., picking cotton), so they do have some exposure to potentially infected rodents.

The two rodent species (*S. alstoni* and *Z. brevicauda*) that have been incriminated as reservoirs of Guanarito virus are most abundant in tall grass along roadsides and fence lines, on the edges of cultivated fields, and in the naturally occurring savanna that dominates the landscape of this region [3]. During 4 years of rodent-trapping in the region of VHF endemicity, we have never collected *S. alstoni* or *Z. brevicauda* within houses or farm buildings. Presumably, human infection occurs outdoors. Thus one might expect persons having frequent contact with rodent-infested grassland habitats to be at higher risk of contracting VHF.

The seasonal occurrence of VHF also supports the concept that humans acquire Guanarito virus infection by contact with infected rodents outdoors in rural areas. As shown in table 1, 53.3% of the 165 VHF cases occurred during the months of November, December, and January. This 3-month period corresponds with the end of the rains and the beginning of the dry season; it is a time of intense agricultural activity in the region, as crops are harvested and the land is cleared and tilled in preparation for the next planting. Consequently, there is probably more human contact with the soil and with potential rodent vectors during this period than at other times of the year. A similar epidemiological pattern has been observed with Argentine hemorrhagic fever; that disease is four times more prevalent in males than in females, and peak activity occurs in the fall (May) among agricultural workers harvesting corn [13].

Another interesting finding about VHF is its focal distribution. As shown in figure 1, all VHF cases to date have been restricted to a relatively small region in southern Portuguesa State and adjacent areas of Barinas. The few cases that have occurred among nonresidents of the areas of endemicity have involved persons who had recently visited or worked in rural areas within that zone. This pattern has not changed since the first recognition of VHF in September 1989.

Since 1992 we have been actively trapping rodents, principally *S. alstoni* and *Z. brevicauda,* at many different localities in central Venezuela, both within and outside of the region of VHF endemicity. The objectives of this study are to monitor the seasonal abundance of the two suspected rodent reservoirs, to determine the prevalence of natural infection among them, and to delineate the geographic distribution of Guanarito virus. Although both *S. alstoni* and *Z. brevicauda* have a wide distribution in Venezuela [22], to date we have not isolated Guanarito virus from rodents captured outside of the area where VHF has been detected in humans.

During our sampling of wild rodents from central Venezuela, a second new arenavirus, designated Pirital [23], was isolated from both *S. alstoni* and *Z. brevicauda.* Pirital virus infection is common in *S. alstoni* within the area of VHF-endemicity, but it also occurs outside of the area and has a much wider geographic distribution in central Venezuela than does Guanarito virus. To date, we have not isolated Pirital virus in any VHF cases. It is interesting that virus studies among rodents in Argentina and Bolivia have also shown the coexistence of two different arenaviruses, one pathogenic for humans and the other apparently not, within those respective hemorrhagic fever zones. Junin and Oliveros viruses are sympatric within the Argentine hemorrhagic fever zone [24]; Machupo and Latino viruses both occur in the hemorrhagic fever region of Bolivia [25]. Much remains to be learned about the ecology, virus-host interactions, and pathogenesis of the arenaviruses.

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