Dengue Reemergence in Argentina

G. Avilés,* G. Rangeón,† V. Vorndam,‡ A. Briones,§ P. Baroni,* D. Enria,* and M.S. Sabattini*

*Instituto Nacional de Enfermedades Virales Humanas (INEVH) "Dr. J.I. Maiztegui", Administración Nacional de Laboratorios e Institutos de Salud "Dr. C. Malbrán", Pergamino, Argentina; †Ministerio de Salud, Salta, Argentina; ‡Centers for Disease Control and Prevention, San Juan, Puerto Rico; and §Delegación Sanitaria Federal, Salta, Argentina

Aedes aegypti, eradicated from Argentina in 1963, has now reinfested the country as far south as Buenos Aires. In 1997, four persons with travel histories to Brazil, Ecuador, or Venezuela had confirmed dengue, and surveillance for indigenous transmission allowed the detection of 19 dengue cases in Salta Province. These cases of dengue are the first in Argentina since 1916 and represent a new southern extension of dengue virus.

Dengue History in Argentina

Several cases of dengue fever were reported in Argentina at the beginning of this century. Indigenous cases were reported in 1905, 1911, and 1916 in northern Argentina (Chaco, Corrientes, Formosa, and Misiones Provinces) (1). In February and March 1916, an epidemic with 15,000 reported cases occurred in Entre Rios Province along the Uruguay and Paraná Rivers in eastern Argentina. None of these patients had hemorrhagic symptoms. Since this epidemic, no indigenous cases had been reported until 1997 (1).

Aedes aegypti

In 1955, when the *Aedes aegypti* eradication campaign began in Argentina, an estimated 1,500,000-km^2 area was infested (Figure 1) (1). Santiago del Estero Province had the highest infestation rate, with *Ae. aegypti* found in 9.4% of localities and 5.3% of houses. This province is characterized by a warm summer and low socioeconomic conditions, with many houses lacking running water (1). The southern extension of *Ae. aegypti* distribution was 35 degrees south, the latitude of Buenos Aires (1). Buenos Aires was only minimally affected, with only 6 of 199,172 houses infested. By 1963, *Ae. aegypti* was considered eradicated from the country (1), but in 1986 the National Ministry of Health reported reinfestation in the north (2). The reinfested area is the area that was infested in 1955, including Salta Province. Buenos Aires Province was reinfested in 1991 and the Federal District in 1995 (2,3). In autumn 1997, high infestation levels (35% in 1996 and 18% in 1997) were found in houses in Buenos Aires Province and the Federal District (3). In Villa María, Córdoba Province (32 degrees south), *Ae. aegypti* was found in summer (February) of 1995, disappeared in winter, and reappeared in early

Figure 1. Geographic distribution of *Aedes aegypti,* 1955: Dengue risk area in Argentina.

Address for correspondence: G. Avilés, Instituto Nacional de Enfermedades Virales Humanas "Dr. Julio I. Maiztegui", Monteagudo 2510 (2700) Pergamino, Argentina; fax: 54-24-774-33045; e-mail: Gaby@inevh.sld.ar.

summer (December 1995) (4). The mosquito was also found in Buenos Aires Province (Zárate and Campana, 34.2 degrees and 34.4 degrees south, respectively) in February 1996 and October 1996 (early spring) (Avilés G, unpublished data). These findings indicate that *Ae. aegypti* may spend winter in refuges in temperate areas and may not necessarily be reintroduced during summer.

The presence of *Ae. aegypti* in most of the country and the reappearance of dengue fever in neighboring countries (Brazil, Paraguay, and Bolivia) increases the risk for dengue infection in Argentina. The Instituto Nacional de Enfermedades Virales Humanas "Dr. J.I. Maiztegui" is the National Reference Center of Dengue Diagnosis. This article summarizes the first dengue cases diagnosed in Argentina in recent years and documents the southernmost expansion of dengue in South America.

The Study

DEN 1 HAW, DEN 2 NGC, DEN 3 H87, and DEN 4 H241 strains were obtained from the Centers for Disease Control Laboratory, San Juan, Puerto Rico. Plaque reduction neutralization tests (PRNTs) were performed as described by Russel et al. (5), with an 80% plaque reduction endpoint. The enzyme-linked immunosorbent assay (ELISA) capture IgM test was done as described by Innis et al. (6) and Kuno et al. (7). Polymerase chain reaction (PCR) was done according to the protocol of Lanciotti et al. (8). The isolation attempts and immunofluorescence tests were done by injecting sera into C6/36 cells and using monoclonal antibodies against each of the serotypes (9).

Study Area

Salta Province is located in northwestern Argentina (Figure 2) in the subtropical area between 22° and 26°, 30 minutes south. A serosurvey was done in Orán, Salvador Mazza, and Guemes (Figure 2). Active surveillance was also conducted in Tartagal. Median temperatures in northern localities (Tartagal and Orán) are 26°C in summer and 19°C in winter. In Salta city the median temperatures are 22°C in summer and 15°C in winter.

Figure 2. Surveillance for dengue virus infections in Salta Province: Localities with cases.

Study Participants

Blood samples were collected at regional hospitals from patients seeking treatment for any illness.

Surveillance of Imported Cases

During the epidemiologic surveillance of the cases compatible with dengue, from January to November 1997 our laboratory received 16 samples from returning travelers who had suspected dengue (Table 1). Sera of four patients, returning from Brazil, Ecuador, and Venezuela, were positive by IgM-capture-ELISA. Cases from Ecuador and Venezuela were positive by PRNT, but the serotype could not be determined because of cross-reactions, possibly indicating secondary flavivirus infections.

Table 1. Imported dengue cases-Argentina, 1997

Patient no.	Travel history	Onset of symptoms	MAC-ELISA	Plaque reduction neutralization tests D1	D2	D3	D4
1	Brazil	02/14/97	Pos	---	---	---	---
2	Ecuador	unknown/97	Pos	1,280	1,280	80	<20
3	Venezuela	11/16/97	Pos	---	---	---	---
4	Venezuela	unknown/97	Pos	>1,280	>1,280	>1,280	>1,280

---Not done

Surveillance of Cases in Salta Province

A total of 404 sera were studied from Orán, Salvador Mazza, Santa Victoria, Tartagal, General Mosconi, Salta city, Junta del San Antonio, Aguaray, and Guemes during April through November 1997. Nineteen serologically positive samples were detected from four of these locations (Orán, Salvador Mazza, Tartagal, and Guemes) (Table 2). Twelve samples were positive by MAC-ELISA, indicating current or recent infections, and three of these had PRNT titers indicating primary DEN 2 infections. Three other samples had cross-reactive antibody patterns indicative of secondary flavivirus infections. Seven other samples were immunoglobulin (Ig)M negative, but positive by PRNT. Three of these showed PRNT titers indicating DEN 2 infections. Six additional samples were positive by PRNT, but the serotype could not be determined. Virus isolation attempts on 36 acute-phase samples had negative results, but one sample was diagnosed as dengue 2 by reverse transcriptase-PCR.

Epidemiologic and Clinical Data

We obtained epidemiologic and clinical information from nine patients. One, a man from Salvador Mazza, had fever, retroocular pain, malaise, muscle pain, and arthralgias and had traveled to Santa Cruz de la Sierra, Bolivia, before onset of symptoms. Seven other patients reported symptoms including headache, muscle pain, abdominal pain, arthralgias, rash, pharyngitis, and epistaxis. No hemorrhagic manifestations were reported. Six of these patients reported no travel history and must have become infected in Orán or Tartagal. Travel histories were not available from the other two patients.

Conclusions

Laboratory results show that imported cases of dengue arrived in Argentina during 1997, enabling local transmission in cities like Rosario and Buenos Aires. In northern Argentina, there is continuous traffic with Bolivia, Paraguay, and Brazil, where dengue is known to occur. We report early evidence of DEN 2 virus circulating in northern Argentina, where indigenous cases

Table 2. Surveillance for dengue virus infections, Salta Province, Argentina

Locality*	positive/ tested	Onset	ELISA IgM	PRNT D1	D2	D3	D4
Orán	6/161	--	Pos	20	320	80	<20
		--	Neg	80	80	160	20
		04/22/97**	--	<20	80	<20	<20
		04/28/97	--	20	>160	20	40
		05/16/97	Pos	640	1,280	640	80
		11/16/97	Pos	--	--	--	--
Salvador Mazza	7/113	--	Pos	<20	20	<20	<20
		--	Pos	<20	80	20	<20
		--	Pos	160	>640	>640	20
		--	Neg	<20	80	40	<20
		--	Neg	--	80	80	20
		--	Neg	20	40	--	<20
		--	Pos	<20	<20	<20	<20
Tartagal	3/7	08/30/97	Pos	80	>160	>160	<20
		10/26/97	Pos	<20	160	<20	<20
		11/23/97	Pos	640	>1,280	640	40
Guemes	1/100	--	Neg	<20	40	<20	<20
Unknown	2/6	--	Pos	<20	<20	<20	<20
			Pos	40	>160	80	<20

*Samples from the following localities were negative by IgM capture -enzyme-linked immunosorbent assay: Santa Victoria (2), General Mosconi (2), Salta city (11), Junta del San Antonio (1) and Aguaray (1).
**An acute-phase sample from this case was positive for DEN 2 by RT-PCR.

have occurred in Orán, Tartagal, Guemes, and Salvador Mazza. These cities are generally located along a highway going north into Bolivia, where DEN is endemic. Clinically, all cases were classic dengue fever. High PRNT antibody titers in the acute-phase samples indicated that dengue or other flavivirus infections had probably been present but had gone undetected. Only sporadic cases were found in the area under active surveillance, as in Texas in 1995 when isolated cases of indigenous transmission were detected (10).

The reestablishment of dengue in Argentina is of concern because of the following risk factors (11): 1) the presence of *Ae. aegypti* vector in high densities in several places (3); 2) the low levels of immunity in the human population in all areas that have been studied (1); 3) endemic virus in neighboring countries (12); and 4) the widespread presence of substandard living conditions, including the lack of running water, in areas where the virus is most likely to be introduced. Air conditioning is uncommon throughout the country, and the climate is subtropical in the north and temperate in the central region, where conditions are suitable for dengue transmission in summer. Surveillance should be continued and expanded in the most susceptible areas to monitor introduction and spread of this reemerging disease.

Acknowledgments

The authors thank Robert Shope and Elsa Segura for revising this manuscript; Liliana Canini, Nora M. Mellano, Milton Bejarano, José A. Rodriguez, Silvia Gonzalez Ayala, and Roque Brun, who attended patients and provided samples; and Cristina C. Bono and Maria Luisa Cacase, who also provided samples.

Dr. Avilés is a biologist in charge of the Arbovirus Laboratory, National Reference Center of Dengue Diagnosis, Collaborative Center PAHO/WHO, Instituto Nacional de Enfermedades Virales Humanas "Dr. J.I. Maiztegui"-Administracion Nacional de Laboratorios e Institutos de Salud, Pergamino, Argentina. Her areas of expertise are arbovirology and medical entomology (mosquitoes). Her research interests include arboviruses (in humans and vertebrates), DEN, YF, WEE, EEE, VEE, and the competence of mosquitoes as vectors for arboviruses.

References

1. Sabattini MS, Avilés G, Monath TP. Historical, epidemiological and ecological aspects of arboviruses in Argentina: Flaviviridae, Bunyaviridae and Rhabdoviridae. In: An overview of arbovirology in Brazil and neighboring countries. Travassos da Rosa APA, Vasconcelos PFC, Travassos da Rosa JFS, editors. Belem, Brazil: Instituto Evandro Chagas; 1998. p. 113-34.
2. Boffi R. Programa de prevención del dengue y control del *Aedes aegypti*. In: Temas de zoonosis y enfermedades emergentes. 2do Congreso Argentino de Zoonosis, 1er Congreso Argentino y Latinoamericano de Enfermedades Emergentes y Asociación Argentina de Zoonosis, editors. 1998;413-419, Buenos Aires.
3. Schweigmann N, Boffi R. *Aedes aegypti* y *Aedes albopictus*: situación entomológica en la región. In: Temas de zoonosis y enfermedades emergentes. 2do Congreso Argentino de Zoonosis, 1er Congreso Argentino y Latinoamericano de Enfermedades Emergentes y Asociación Argentina de Zoonosis (eds.) 1998;259-263, Buenos Aires.
4. Avilés G, Cecchini R, Harrington ME, Cichero J, Asis R, Rios C. *Aedes aegypti* in Córdoba Province, Argentina. J Am Mosq Control Assoc 1997;13:255-8.
5. Russel PK, Nisalak A, Sukhavachana P, Vivona S. A plaque reduction test for dengue virus neutralizing antibodies. J Immunol 1967;99:291-6.
6. Innis BL, Nisalak A, Nimmannitya S, Kusalerdchariya S, Chongwasdi V, Suntayakorn S, et al. An enzyme-linked immunosorbent assay to characterize dengue infections where dengue and Japanese encephalitis co-circulate. Am J Trop Med Hyg 1989;40:418-27.
7. Kuno G, Gómez I, Gubler DJ. An ELISA procedure for the diagnosis of dengue infections. J Virol Methods 1991;33:101-13.
8. Lanciotti RS, Calisher CH, Gubler DJ, Chang GJ, Vorndam AV. Rapid detection and typing of dengue viruses from clinical samples by using reverse transcriptase-polymerase chain reaction. J Clin Microbiol 1992;30:545-51.
9. Gubler DJ, Kuno G, Sather GE, Velez M, Oliver A. Mosquito cell cultures and specific monoclonal antibodies in surveillance for dengue viruses. Am J Trop Med Hyg 1984;33:158-65.
10. Centers for Disease Control and Prevention. Dengue fever at the U.S.—Mexico border, 1995-1996. MMWR Morb Mortal Wkly Rep 1996;45:841-4.
11. Gubler DJ. Dengue. In: The arboviruses: epidemiology and ecology. Monath TP, editor. II. Boca Raton, FL: CRC Press; 1988. p. 223-60.
12. Pan American Health Organization. Dengue and dengue hemorrhagic fever in the Americas: guidelines for prevention and control. Washington, D.C. 1994; Scientific publication No. 548.