

HANTAVIRUS ANTIBODIES IN RODENTS AND HUMAN CASES WITH PULMONARY SYNDROME, RIO NEGRO, ARGENTINA

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Abstract In Río Negro Province, Argentina, human cases of hantavirus pulmonary syndrome (HPS) appeared in the region of subantarctic forests. The Andes virus (ANDV) has been identified in the region both in *Oligoryzomys longicaudatus* rodents and in humans, with the main transmission being from rodents to humans but also showing the possibility of human to human transmission. Between 1996 and 2004, in 40 campaigns, 29960 night-traps for capturing live rodents were set up. Blood samples were obtained from the rodents and processed using enzyme immunoassay with recombinant antigens made from ANDV. A total of 1767 rodents were captured, with a capture success of 5.9% and an antibody prevalence of 2.1%. Important differences were observed among the species captured from Andes and Steppe regions. Seropositive *Oligoryzomys longicaudatus*, *Abrothrix olivaceus*, *Abrothrix xanthothinus* and *Loxodontomys microtus* were captured. During the 1993-2004 period, 40 HPS cases were registered.

Key words: hantavirus, epidemiology, rodents, pulmonary syndrome, Andes virus

Resumen *Anticuerpos contra hantavirus en roedores y casos humanos con síndrome pulmonar, Río Negro, Argentina.* En la Provincia de Río Negro, Argentina, se presentaron casos humanos de síndrome pulmonar por hantavirus (SPH) en la región de los bosques subantárticos. El virus Andes (AND) fue identificado en la región, tanto en el roedor *Oligoryzomys longicaudatus* como en seres humanos, demostrándose la transmisión principalmente del roedor al hombre y la posibilidad de la transmisión de persona a persona. Para ello, se procedió a la colocación de 29960 trampas para captura viva de roedores, tipo Sherman, en 40 operativos efectuados desde 1996 hasta 2004. Se obtuvieron muestras de sangre de los roedores, las que fueron procesadas mediante enzimoimmunoensayo con antígenos recombinantes elaborados a partir de virus AND. Fueron capturados 1767 roedores, con un éxito de trapeo del 5.9% y una prevalencia de anticuerpos contra hantavirus del 2.1%. Se observaron importantes diferencias en las especies capturadas en cada una de las regiones. Se capturaron *O. longicaudatus*, *Abrothrix olivaceus* y *Abrothrix xanthothinus* y *Loxodontomys microtus* seropositivos. Se registraron 40 casos humanos en el período 1993-2004.

Palabras clave: hantavirus, epidemiología, roedores, síndrome pulmonar, virus Andes

The prototype of the genus *Hantavirus*, Bunyaviridae family, was isolated in Korea in the 1970 decade and was called Hantaan virus. All related viruses are known as hantavirus and have been associated with two clinical syndromes: hemorrhagic fever with renal syndrome (FHRS), predominant in Asia and Europe and hantavirus pulmonary syndrome (HPS), described in 1993 and present exclusively in America¹.

The first identified reservoir for HPS was the wild rodent, *Peromyscus maniculatus*, in the USA in 1994. Later other reservoirs such as *Sigmodon hispidus*, *Oryzomys*

palustris and *Peromyscus leucopus*, were identified. In Argentina initially *Oligoryzomys longicaudatus*, *O. flavescens* and *O. chacoensis* have been identified as reservoirs, while in the rest of America the list of identified reservoirs becomes longer each day (*Calomys laucha* in Paraguay and Bolivia, *O. microtis* in Peru, *O. fulvescens* in Panama, *O. fornesi* and *Holochilus sciureus* in Brasil, *O. flavescens* in Uruguay, etc.). All of them belong to the Muridae family, Sigmodontinae subfamily²⁻⁷.

In the USA and in several countries of South America, especially in Brazil, Chile and Argentina, increasing numbers of cases have been observed.

During the period 1996-2001 the Argentine Health Ministry, reported 324 cases of human hantavirus infections. Of these, 138 came from provinces of the North (Salta, Jujuy), 124 were from the Central region (Buenos

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Aires, Santa Fe) and 62 from the South of the country (Chubut, Neuquen, Rio Negro). Mortality rate reached 30% between 1996 and 2001. The cases were associated with any one of the six genotypes of Andes Hantavirus: AND Nort Oran, AND Nort Bermejo, AND Sout, AND Cent Lec, AND Cent Buenos Aires and AND Cent Plata⁵.

In the province of Río Negro, all cases occurred in the region of subantarctic forests and were associated to AND virus (genotype AND Sout) transmitted by infected *O. longicaudatus* rodents⁹ or from person-to-person^{9,10}. Successive studies have been carried out in this particular region to define reservoirs^{8,11}, evaluate risk factors¹², evaluate clinical aspects¹³ and antibody prevalence for Hantavirus in rodents^{8,14}.

The first objective of this study was to present new information on the species of rodents potentially harboring hantavirus in the subantarctic forest region of the province of Río Negro, Argentina, and rodent seroprevalence as well as the relationship between human cases and both the size of rodent populations and rodent seroprevalence. The second objective was to identify differences in rodent population and in the prevalence of antibodies against hantavirus in this region, according to whether they were captured in areas related or not to HPS. Additionally, results from studies on rodents carried out in the steppe region of the province of Río Negro are presented.

Materials and Methods

The first area under study was Subantarctic forest: Bariloche Department, to the west of Rio Negro, Argentina (latitude/longitude S41.79/W71.31 to S41.04/ W71.10) and in neighbouring areas of La Angostura (North, Neuquen) and Lago Puelo (South, Chubut). The climate is cold and humid, with

800 to 1000 mm rain fall. Vegetation is lush, with dense forests coexisting with areas of shrub vegetation (*Rose rubiginosa*, *Rubus idaneus*, among others). Farming systems include mushrooms, strawberries, hops and fine fruits. The stable population reaches 142 000 inhabitants, a number which greatly increases during the winter and summer tourist periods (Fig. 1).

The second area was Steppe region: Departments of Pilcaniyeu to the East of Río Negro, General Roca and 25 de Mayo in the center, and Valcheta and San Antonio to the West (latitude/longitude S41.08/W70.50 to S40.40/ W66.09). The climate is cold in winter and hot in summer, with 200-400 mm rainfall. Vegetation is scarce, with a predominance of shrub and xerophilous species and a minimum of herbaceous stratum.

Sherman type traps were used to capture live rodents, using oats as bait. Traps were set 2 m apart, and each line (consisting of 10-25 traps) were set out in such a way to cover the widest variety possible of shrub and herbaceous stratum, water courses and around rural buildings, favouring the presence of rodents. Standardized procedures were used for setting the traps-night and for caring for the operators' bio safety¹⁵.

In the period 1996-2004, a total of 29 960 traps-night were set as follows:

- Subantarctic forests: A total of 4311 traps-night were set in nine campaigns, carried out in homes and sites of exposure to disease, where 24 cases had been detected, and other twenty campaigns unrelated to cases of disease, with a total of 18 625 traps-night set. It was not possible to carry out this type of study during the years 2000 and 2003.

- Steppe: In the period 2001-2005 eight campaigns were carried out, setting a total of 7024 traps-night.

Captured rodents were anesthetized using either ether or methoxifluorane, and blood samples were obtained using cardiac puncture. After this, the animals were sacrificed by cervical dislocation and necropsy was carried out to obtain the liver, lungs, spleen and kidney. All samples were kept in liquid nitrogen until they were processed at the National Institute of Infectious Diseases INEI-ANLIS Dr. C. G. Malbrán laboratory.

The province of Río Negro maintains a vigilance system that includes a register of the cases occurred during the 1993-2004 period and epidemiological studies to identify sites of exposure.

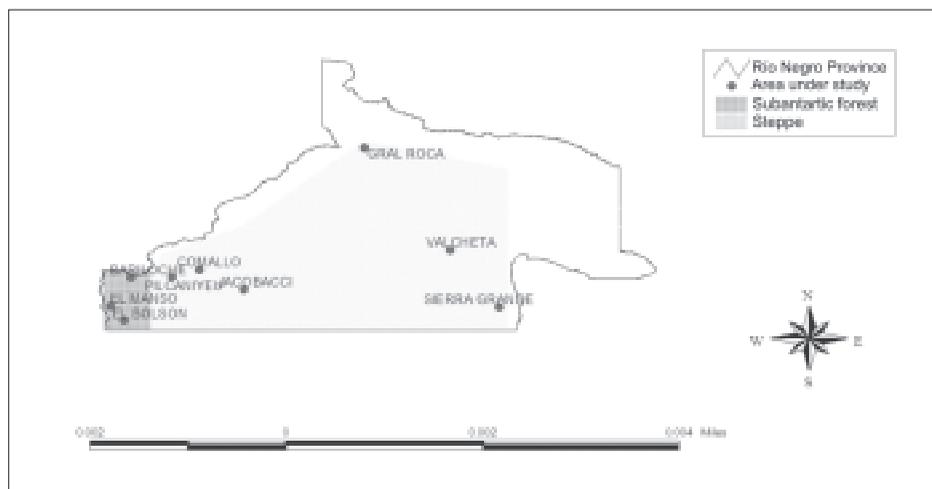


Fig. 1

In 2004, a serological screening was carried out in the rural human population over 18 years of age, in the area of El Manso (subantarctic forests, (latitude/longitude S41.35/W71.44), where a 50% of the existing population was studied (490 people).

Blood samples from both rodents and humans were processed using enzyme immunoassay (ELISA) with recombinant antigens produced from AND virus¹⁶.

The relationships between rodent population (expressed as the success of trapping or the percentage of rodents captured every 100 traps set), antibody prevalence against hantavirus in rodents and human cases occurrence, were analysed using Pearson's coefficient of correlation. Supposing the distribution of the variables was normal, *BMDP* (*SPSS*, Chicago, IL) software was used for the analysis.

Odds ratio (OR), Z-test, Chi square test of association and confidence intervals (CI) of 95% were estimated using *Epidat 3.0* (Xunta de Galicia, Spain).

Results

In the subantarctic forest region, campaigns associated with homes and probable sites of exposure to virus, captured 138 rodents (trapping success rate of 3.2%; CI 95% 2.6-3.7) with an AND seroprevalence of 2.9% (CI 95% 0.8-7.2) (Table 1).

In campaigns unrelated to disease cases, a significantly higher number of rodents was found (1410 rodents; 7.6% trapping success rate; CI95% 7.2-7.9; p: 0.0000; OR 0.4) with a lower, non significant difference in the prevalence of antibodies against AND virus (2.4% prevalence; CI 95% 1.5-3.1; p: 0.6398) (Table 2).

The range of trapping success rate in studies unrelated to disease cases varied from 1.9% to 15.4% in summer, 2.9% to 88.4% in spring, 3.3% to 38.0% in fall and 2.7% to 16.0% in winter (Table 2).

The species most often captured were *Oligoryzomys longicaudatus* (39.1% related to disease cases, 48% unrelated to disease cases) with no significant differences being observed (p: 0.2204), compared with campaigns associated with homes and probable sites of exposure to virus, *Abrothrix longipilis* (34.1%, 40.1%) and *Abrothrix olivaceus* (18.1%, 5.8%) (Table 4).

Among rodents captured in places associated to disease cases, 7.4% of *O. longicaudatus* were found reactive for AND and from captures unrelated to disease cases, seropositive *O. longicaudatus*, *Loxodontomys microtus* and *A. longipilis* were respectively 4.4%, 8.3% and 0.2% (Table 4). Differences between the presence of seropositive *O. longicaudatus* from places related (7.4%) and unrelated (4.4%) to disease cases were not significant (p: 0.2873). The majority of seropositive *O. longicaudatus*, 70% (23), were adult males (Table 4).

Among captures unrelated to disease cases, Pearson's correlation was negative for trapping success of *O. longicaudatus* and for seroprevalence (p: 0.1990).

Considering all captures carried out, seasonal success of trapping was 8.9% in spring, 4.8% in summer, 8.3% in autumn and 6.1% in winter. Significant differences were observed between spring and winter (p: 0.0000) and spring and summer (p: 0.0000) with no significant differ-

Table 1.— Rodents' captures in sites of exposure to 24 hantavirus in different seasons of the year in the subantarctic forests region, positivity for Andes virus (AND) antibodies (percentage), and *Oligoryzomys longicaudatus* specimens captured. Río Negro, Argentina, 1996-2004.

Period	Study	Area	Trap-nights	Captures (trap success rate %)	Positive (%; CI 95%)	<i>O. longicaudatus</i> (trap success rate %)	Positive (%)
Cases							
Spring 1996*	5	El Bolsón	965	70 (7.3)	0	21 (2.2)	0
Summer 1996	10	El Bolsón	1896	6 (0.3)	0	3 (0.2)	0
Summer 1996	3	Bariloche	486	0	0	0	0
Fall 1997*	1	El Bolsón	200	2 (1.0)	0	0	0
Summer 1997*	1	Bariloche	120	12 (10.0)	2 (16.7)	6 (5.0)	2 (33.3)
Fall 1999	1	Bariloche	134	2 (1.5)	0	2 (1.5)	0
Fall 2000	1	Bariloche	185	9 (4.9)	0	7 (3.8)	0
Spring 2000	1	Bariloche	205	28 (13.7)	2 (7.1)	12 (5.9)	2 (16.7)
Spring 2003	1	Valle Encantado	120	9 (7.5)	0	3 (2.5)	0
Total	24		4311	138 (3.2, CI 95%, 2.6-3.7)	4 (2.9, CI 95%, 0.8-7.2)	54 (1.3, CI 95%, 0.9-1.6)	4 (7.4, CI 95%, 2.1-17.9)

*: Cantoni et al, 2001¹¹

Spring 96 to Fall 97: outbreak 1996 study

Table 2.— Rodents' captures in places unrelated to disease cases, in different seasons of the year in the subantartic forests region, Río Negro, Argentina, 1996-2004

Period	Area	Trap-nights	Captures (trap success rate %)	Positive (%)	<i>O. longicaudatus</i> (trap success rate %)	Positive (%)
Summer 1995*	El Bolsón	300	43 (14.3)	0	9 (3.0)	0
Spring 1996**	Lago Puelo	120	37 (30.8)	7 (18.9)	29 (24.2)	7 (24.1)
Summer 1996*	El Bolsón	2205	42 (1.9)	1 (2.4)	18 (0.8)	1 (5.6)
Summer 1996*	Bariloche	964	29 (3.0)	2 (6.9)	11 (1.1)	2 (18.2)
Summer 1996*	Lago Puelo	774	119 (15.4)	9 (7.6)	79 (10.2)	8 (10.1)
Fall 1997*	El Bolsón	1762	92 (5.2)	0	40 (2.3)	0
Fall 1997*	Bariloche	1000	98 (9.8)	1 (1.0)	39 (3.9)	0
Fall 1997*	Lago Puelo	200	76 (38.0)	2 (2.6)	61 (30.5)	2 (3.3)
Winter 1997*	El Bolsón	850	42 (4.9)	0	15 (1.8)	0
Winter 1997*	Bariloche	700	75 (10.7)	0	48 (6.9)	0
Winter 1997*	Lago Puelo	200	32 (16.0)	2 (6.3)	22 (11.0)	2 (9.1)
Spring 1997*	Angostura	250	221 (88.4)	5 (2.3)	130 (52.0)	4 (3.1)
Spring 2001	Bariloche	1300	45 (3.5)	0	6 (0.5)	0
Spring 2001	El Bolsón	900	24 (2.7)	0	4 (0.4)	0
Summer 2002	Bariloche	1300	112 (8.6)	0	34 (2.6)	0
Summer 2002	El Bolsón	900	68 (7.6)	0	21 (2.3)	0
Fall 2002	Bariloche	700	74 (10.6)	3 (4.1)	28 (4.0)	3 (10.7)
Fall 2002	El Bolsón	600	57 (9.5)	0	26 (4.3)	0
Winter 2002	Bariloche	1300	35 (2.7)	0	16 (1.2)	0
Winter 2002	El Bolsón	600	40 (6.7)	0	22 (3.7)	0
Spring 2004	Villegas	1000	31 (3.1)	0	18 (1.8)	0
Spring 2004	El Manso	400	8 (2.9)	0	0	0
Fall 2005	El Manso	300	10 (3.3)	0	1 (0.3)	0
Total		18625	1410 (7.6, CI 95%, 7.3-7.9)	32 (0.2, CI 95%, 0.15-3.1)	677 (3.6, CI 95%, 3.3-3.9)	29 (4.4, CI 95%, 2.7-6.0)

*: *Cantoni et al, 2001*¹; ** *Cantoni et al, 1997*⁸; *Levis et al, 1998*¹²

Table 3.— Rodents' captures in places unrelated to disease cases, in different seasons of the year in the steppe region, Río Negro, Argentina, 1996-2004

Period	Area	Trap-nights	Captures (trap success rate %)	Positive (%)	<i>O. longicaudatus</i> (trap success rate %)	Positive (%)
Spring 2001	Pilcaniyeu	200	46 (23.0)	1 (2.2)	3 (1.5)	0
Spring 2004	Pilcaniyeu	400	25 (6.3)	0	12 (3.0)	0
Fall 2005	Pilcaniyeu	400	33 (8.3)	0	11 (2.8)	0
Spring 2001	Comallo	672	6 (0.9)	0	0	0
Spring 2002	Jacobacci	1390	53 (3.8)	0	0	0
Summer 2003	Gral. Roca	1112	14 (1.3)	0	0	0
Spring 2003	Valcheta	1200	22 (1.8)	0	0	0
Fall 2001	Sierra Grande	1650	20 (1.2)	0	0	0
Total		7024	219 (3.1, CI 95%, 2.7-3.5)	1 (0.5, CI 95%, 0.01-2.5)	26 (0.4, CI 95%, 0.2-0.5)	0.0 CI 95% 2.7-6.0)

*: West to East of Río Negro Province

Table 4.— Different rodent species captured and the prevalence of antibodies against hantavirus in the subantartic forests and the steppe regions, Río Negro, Argentina, 1996-2004

Rodent species	Subantartic forest		Related disease cases		Steppe area without cases	
	rodent (%)	positive (%)	rodent (%)	positive (%)	rodent (%)	positive (%)
<i>Abrothrix olivaceus</i>	82 (5.8)	—	25 (18.1)	—	42 (19.2)	1 (2.4)
<i>Abrothrix longipilis</i>	566 (40.1)	1 (0.2)	47 (34.1)	—	5 (2.3)	
<i>Abrothrix xanthorhinus</i>	28 (2.0)	—	0	—	83 (37.9)	—
<i>Oligoryzomys longicaudatus</i>	677 (48.0)	29 (4.4)	54 (39.1)	4 (7.4)	26 (11.9)	—
<i>Eligmodontia morgani</i>	16 (1.1)	—	1 (0.7)	—	18 (8.2)	—
<i>Loxodontomys microtus</i>	12 (0.9)	1 (8.3)	1 (0.7)	—	0	—
<i>Reithrodon auritus</i>	0	—	0	—	6 (2.7)	—
<i>Phyllotis xanthopygus</i>	0	—	0	—	4 (1.8)	—
<i>Akodon iniscatus</i>	5 (0.4)	—	0	—	0	—
<i>Mus</i> spp and <i>Rattus</i> spp	20 (1.4)	—	10 (7.2)	—	33 (15.1)	
<i>Geoxus valdivianus</i>	1 (0.1)	—	—	—	—	—
Species not identified	2 (0.1)	1 (50)	—	—	2 (0.9)	—
Total	1410 (100)	32 (2.4, CI 95%,1.5-3.1)	138 (100)	4 (2.9, CI 95%, 0.8-15.1)	219 (100)	1 (0.5, CI 95%, 0.01-2.5)

Table 5.— Cases and deaths by hantavirus pulmonary syndrome in Río Negro, Argentina, 1993-2004

Year	Cases	Death (%)
1993	1	0 (0)
1994	2	1 (50)
1995	4	2 (50)
1996	19	10 (52.6)
1997	1	0 (0)
1998	2	0 (0)
1999	1	0 (0)
2000	3	1 (33.3)
2001	1	0 (0)
2002	2	0 (0)
2003	4	4 (100)
2004	0	0 (0)
Total	40	18 (43.9)

Font: Ministry of Health, Río Negro, Argentina

ences observed between spring and autumn ($p: 0.2280$). Reactive antibodies for Andes virus were 3.2%, 3.2%, 1.4% and 0.9% respectively, with no significant differences observed between spring and the rest of the seasons ($p: 0.2428$).

In the Steppe region a total of 219 rodents were captured (3.1% trapping success; CI95% 2.7-3.5) with a 0.5% prevalence of antibodies against Andes virus (Table 3). The most frequently captured species were: *Abrothrix xanthorhinus* (37.9%), *A. olivaceus* (19.2%) and *O.*

longicaudatus (11.9%). From the West of the region (latitude/longitude S41.08/W70.50), in the transition zone with subantartic forests, a seropositive *A. olivaceus* (2.4%) was captured (Table 4).

Trapping success was significantly greater in the subantartic forests region (7.6%) than in the Steppe region (3.1%) ($p: 0.0000$; OR 2.7).

During the 1993-1995 period, 7 human cases were recorded and during the 1996-1998 period, 22 cases. Of the latter, 16 corresponded to a single outbreak in 1996, which included one index case and 15 cases in which inter-human transmission was demonstrated by genetic evidence¹⁰, for the rest of the cases in that period the source of transmission was not identified. The 1999-2001 period registered 5 cases and the 2002-2004 period, 6 cases, giving rise to a total of 40 cases with 43.9% lethality rate (Table 5).

Eleven out of 24 cases with rodent-transmission, (45.8%) occurred in spring, 2 (8.3%) in summer, 7 (29.2%) in autumn and 4 (16.7%) in winter, with significant differences being found between spring and the other seasons ($Z: 65$, $p: 0.0000$). Fifteen cases with inter-human transmission occurred in spring¹⁰.

Capture of rodents related to homes and sites of exposure to disease, allowed identification of infected rodents in only 4 of 24 cases (16.7%) (Table 1). The latter were the only samples where the AND seroprevalence in *O. longicaudatus* was equal or superior to 15% (Table 2). This prevalence in studies unrelated to cases of the disease was only observed in the spring and summer of 1996 (the year with a maximum number of cases).

Of the 243 blood samples obtained from adult inhabitants (range 18-83 years old) 3 were positive (1.2%, CI 95% 0.25-3.6), 26, 32 and 36 years old and without antecedent of SPH.

Discussion

This study reinforces the importance of *O. longicaudatus* as a possible reservoir for hantavirus in the region of subantarctic forests^{8,11,12,17}. Animals with antibodies against AND virus were captured on both the Northern and Southern borders of Río Negro, in the localities of El Bolsón and San Carlos de Bariloche, in different natural environments and related to homes and sites of exposure to human cases to hantavirus. The rates of rodent capture, 3.2% and 7.6% respectively, related or unrelated to disease cases showed extreme variability according to seasonality.

The greater number of rodents and human cases in spring and fall suggested the possible role of the increased rodent population as a risk factor for man, and spring and fall as the seasons with the highest risk of transmission. In previous studies in the neighbouring province of Neuquén¹⁷ and in North of Argentina¹⁸ also a greater number of rodents was found in spring than in other seasons.

Overall the proportion of infected rodents found in this study was low, and comparable to the reported in other regional studies^{5, 11, 17}. However prevalence close to or higher than 10% was observed during the four seasons of the year, when the captures of infected rodents were from places related to human cases. Nevertheless, no coincidence was found between seasonal prevalence in rodents and human outbreaks, and between trapping success rate and seroprevalence in *O. longicaudatus*.

In only 16.7% of studies in homes and sites of exposure to disease cases positive rodents were captured. In the North of Argentina, positive rodents were captured in only 1 out of 9 (11%) sites of exposure to disease cases¹⁹. This is indicative of the existing difficulties and limitations to reveal and precisely identify sites of infection and risk activities for man.

Previous studies have shown increased infection rates in *O. longicaudatus* males⁸. Local environmental conditions could generate increased rodent prevalence and gender distribution. According to this study, the potential role of *Abrothrix* spp and of other species as hantavirus reservoirs in the subantarctic forests region is extremely limited, either because of their low seroprevalence (*A. longipilis*, 0.2%) or their low number (*L. microtus*, 0.9%).

Seroprevalence for hantavirus found in the adult human rural population of the subantarctic forests region was also low (1.2%) and closer with the low seroprevalence

found in rodents (2.9% and 2.4% respectively related or unrelated to disease cases). Studies carried out in the North of Argentina identified higher human prevalence (6.3%) associated with an equally high rodent seroprevalence (5.8%)¹⁸.

In the Steppe region, successful capture of *O. longicaudatus* occurred only in transition zones with subantarctic forests (Pilcaniyeu) and in small numbers. Nevertheless, in the neighbouring province of Neuquén, to the North of Río Negro, the presence of *O. longicaudatus* with antibodies against hantavirus has been notified¹⁷, which raises the need to maintain vigilance systems in this region.

Abrothrix xanththorimus was the predominant species in this study (37.9%) but until now this species has not been reported as hantavirus carrier. Other studies identified *Eligmodontia* spp and *A. iniscatus* as the predominant rodent species in the north of the steppe region of Río Negro¹⁷. To the west of the region, one *A. olivaceus* specimen with antibodies against hantavirus was captured, being this a species predominant in the region (19.2%). Other studies will be required to define the possible role of *Abrothrix* spp. in hantavirus ecology in the Steppe region.

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Aside from driving editors crazy, does it really make any difference whether scientific writing is good, bad or ugly? We believe it does, and that it matters a great deal, for words are tools of science, no less than numbers are. Research is not complete until it is communicated, and publication in a primary journal is the fundamental unit of scientific communication. The decision not only to write but to make the effort to write well lies at the heart of scientific literacy. To most minds, sloppy scientific writing indicates sloppy thinking, and both are disastrous to research and research reporting.

Aparte de enloquecer a los redactores ¿hay realmente alguna diferencia si la redacción científica es buena, mala o fea? Nosotros creemos que sí, y que importa mucho, porque las palabras son herramientas de la ciencia, no menos que los números. La investigación no está completa hasta que se ha comunicado, y la publicación en una revista de publicación primaria es la unidad fundamental de la comunicación científica. La decisión no sólo de escribir sino de hacer el esfuerzo de escribir bien yace en el corazón de la alfabetización científica. Para la mayoría de las mentes, la redacción científica descuidada indica pensamiento descuidado y ambos son desastrosos para investigar y comunicar.

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Successful scientific writing. A step-by-step guide for biomedical scientists. Cambridge: Cambridge University Press, 1996, p 1