HANTAVIRUS IN THE AMERICAS

GUIDELINES FOR DIAGNOSIS, TREATMENT, PREVENTION, AND CONTROL

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The cover image of a hantavirus recently isolated from a rodent in Venezuela was provided by C. S. Goldsmith (U.S. Centers for Disease Control and Prevention) and C. F. Fulhorst (University of Texas).

PREFACE

Since the 1993 outbreak of hantavirus pulmonary syndrome in the United States of America's Southwest, human infections caused by the virus have been reported in Argentina, Canada, Paraguay, and Uruguay. Moreover, using specific diagnostic methods now available, several countries have been able to carry out retrospective diagnoses of hantavirus infection.

The gravity of the disease and its high lethality, as well as the scant knowledge of its epidemiology and of its clinical aspects, seriously worried the Member States of the Pan American Health Organization. In response, the Directing Council of the Organization at its 40th Meeting held in September 1997, adopted a resolution concerning hantavirus. Through it, the Directing Council requested the Director to bring together a working group to come up with recommendations for the surveillance, diagnosis, treatment, and prevention of hantavirus infection.

To fulfill this request, the Organization sponsored a meeting of international experts in March 1998, who elaborated the first manuscript for this publication. The text includes an overview of the ecology, zoology, and epidemiology of hantavirus pulmonary syndrome in the Americas. It also describes clinical, diagnostic, and treatment aspects of the syndrome, and sets forth recommendations for the prevention and control of the infection in the Region. This book provides the latest available data at the time of publication regarding the infection's epidemiological situation and its modes of transmission. In addition, it includes critical information on how to carry out epidemiological surveillance, research on outbreaks, and the clinical handling and treatment of patients.

These guidelines complement information in *Métodos para trampeo y muestreo de pequeños mamíferos para estudios virológicos* that the Organization published in February 1998 (original published in English by the U.S. Centers for Disease Control as *Methods for Trapping and Sampling Small Mammals for Virologic Testing*). Both publications are the successful result of the cooperation among countries.

The Organization hopes that this publication will fill the immediate need for information on hantavirus infections, thereby fulfilling our mandate of keeping health professionals and the community at large informed about current public health issues.

George A. O. Alleyne
Director

1. INTRODUCTION

Hantavirus is a genus of the family *Bunyaviridae* and takes its name from the Hantaan River in South Korea, near where the prototype member, Hantaan virus, was first isolated. Closely related viruses include Seoul virus, Dobrava virus, and Puumala virus, which are distributed throughout the Eurasian landmass and are responsible for the spectrum of illness collectively referred to as hemorrhagic fever with renal syndrome (HFRS). Outbreaks of what is believed to have been HFRS have been reported in Europe and Asia since at least the 1930s. Despite growing evidence in subsequent years pointing to a viral etiology, Hantaan virus was not isolated until 1978, when a rodent reservoir for HFRS-causing viruses was confirmed (*1*). With an annual incidence of 150,000 to 200,000 cases, HFRS occurs almost exclusively in regions outside the Americas and therefore will not be discussed extensively here.

Despite consistent serologic evidence supporting the presence of hantavirus-infected rodents in the Western Hemisphere, human illness due to hantavirus infection in the Americas was not recognized before the 1990s (*2, 3*). In 1993 an outbreak of severe respiratory illness in the southwestern United States of America led to the identification of a novel hantavirus (*15*) as the etiologic agent of a disease now known as hantavirus pulmonary syndrome (HPS) (*62*). The virus was called Sin Nombre virus (SNV) and the deer mouse, *Peromyscus maniculatus*, was found to be the primary rodent reservoir. Subsequent work has uncovered many additional hantaviruses in the Americas, several of which have been shown to cause HPS.

These guidelines review the epizoology and epidemiology of hantavirus pulmonary syndrome in the Americas; discuss clinical aspects, diagnosis, and treatment of hantavirus pulmonary syndrome; and provide recommendations for the prevention and control of hantavirus disease in the Americas.

1. INTRODUCTION

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These guidelines review the epizoology and epidemiology of hantavirus pulmonary syndrome in the Americas; discuss clinical aspects, diagnosis, and treatment of hantavirus pulmonary syndrome; and provide recommendations for the prevention and control of hantavirus disease in the Americas.

2. THE VIRUSES

Hantaviruses are lipid-enveloped, spherical viruses of 80 to 110 nm in diameter. The RNA genome is tri-segmented, with the large (L) segment approximately 6,500 nucleotides long, the middle (M) segment approximately 3,600–3,800 nucleotides long, and the small (S) segment approximately 1,700–2,100 nucleotides long (*4*). The L segment encodes a viral polymerase, the M segment encodes G1 and G2 envelope glycoproteins, and the S segment encodes the N nucleocapsid protein.

Phylogenetic analysis of rodent-borne hantavirus genes has revealed three main lineages. While HFRS-causing viruses are linked to an Old World lineage, all HPS-associated viruses have a common New World lineage and are associated with members of a single rodent subfamily (*Sigmodontinae*) of the family *Muridae* (*4, 5*). Some of the sigmodontine-derived viruses are clearly independent species based on genetic evidence, serology, and/or reservoir-host association (Table 1); others are in the process of evaluation (Table 2), as are our criteria for defining a hantavirus species. At least 13 hantavirus species have been identified exclusively in the Americas, and 6 have been shown to cause HPS (Table 1). The various HPS-causing hantaviruses generally differ by no more than 30% at the nucleotide level. Serum antibodies of HPS patients cross-react strongly with other New World viruses, but to varying degrees with Old World hantavirus antigens.

No evidence of genetic reassortment with previously recognized Old World hantaviruses was found in the initial characterization of Sin Nombre virus, and proven natural reassortment events have been restricted to different genotypes of SNV (*6, 7*). All known SNV strains share at least 90% nucleotide sequence homology and even higher amino acid sequence homologies. Natural reassortment may result in different nucleotide sequence homologies for one gene segment as compared to the other two, but this has not yet been related to differences in viral pathogenicity. Therefore, it is unlikely that genetic reassortment with other viruses accounts for the newly recognized pathogenicity of HPS-causing viruses. Rather, HPS and HPS-causing hantaviruses have likely existed in the Western Hemisphere for many years despite only recently having been detected.

TABLE 1. Viruses of the genus *Hantavirus*, family *Bunyaviridae.*

Virus	Abbr.	Original source	Location	Geographic distribution of rodent host[a]	Human disease	Isolated in cell culture
Murinae subfamily-associated viruses						
Hantaan	HTN	*Apodemus agrarius*	Korea	Asia, Europe	HFRS[b]	yes
Seoul	SEO	*Rattus norvegicus, R. rattus*	Korea	Asia, Europe, the Americas	HFRS	yes
Dobrava-Belgrade	DOB	*Apodemus flavicollis*	Slovenia	Europe, Middle East	HFRS	yes
Thai-749	THAI	*Bandicota indica*	Thailand	Asia	unknown	yes
Arvicolinae subfamily-associated viruses						
Puumala	PUU	*Clethrionomys glareolus*	Finland	Europe, Asia	HFRS	yes
Prospect Hill	PH	*Microtus pennsylvanicus*	Maryland	N. America	unknown	yes
Tula	TUL	*Microtus arvalis*	Russia	Europe	unknown	yes
Khabarovsk	KBR	*Microtus fortis*	Russia	Asia	unknown	yes
Topografov	TOP	*Lemmus sibiricus*	Siberia	Russia, Asia, N. America	unknown	yes
Isla Vista	ISLA	*Microtus californicus*	California	N. America	unknown	no
Sigmodontinae subfamily-associated viruses						
Sin Nombre	SN	*Peromyscus maniculatus*	New Mexico	N. America	HPS[c]	yes
New York	NY	*Peromyscus leucopus*	New York	N. America	HPS	yes
Black Creek Canal	BCC	*Sigmodon hispidus*	Florida	The Americas	HPS	yes
Bayou	BAY	*Oryzomys palustris*	Louisiana	Southeastern United States	HPS	yes
Caño Delgadito	CANO	*Sigmodon alstoni*	Venezuela	S. America	unknown	yes
Río Mamore	RM	*Oligoryzomys microtis*	Bolivia	S. America	unknown	yes
Laguna Negra	CHP	*Calomys laucha*	Paraguay	S. America	HPS	yes
Muleshoe	MULE	*Sigmodon hispidus*	Texas	The Americas	unknown	no
El Moro Canyon	ELMC	*Reithrodontomys megalotis*	California	N. America	unknown	no
Río Segundo	RIOS	*Reithrodontomys mexicanus*	Costa Rica	Mexico, Central America	unknown	no
Andes	AND	*Oligoryzomys longicaudatus*	Argentina	S. America	HPS	yes
Insectivore-associated virus						
Thottapalayam	TPM	*Suncus murinus*	India	Asia	unknown	yes

[a]Given as approximate distribution; many rodent species occur focally, many others have widespread distributions.
[b]HFRS = hemorrhagic fever with renal syndrome.
[c]HPS = hantavirus pulmonary syndrome.

TABLE 2. Genotypes of Sigmodontine-associated hantavirus under evaluation.

Virus	Original source	Location	Human disease
Monongahela	*Peromyscus maniculatus*	United States	HPS
Blue River	*Peromyscus leucopus*	United States	Unknown
Oran	*Oligoryzomys longicaudatus*	Argentina	HPS
Lechiguanas	*Oligoryzomys flavescens*	Argentina	HPS
Bermejo	*Oligoryzomys chacoensis*	Argentina	Unknown
Maciel	*Necromys benefactus*	Argentina	Unknown
Pergamino	*Akodon azarae*	Argentina	Unknown
Juquitiba	Unknown	Brazil	HPS
HU39694	Unknown	Argentina	HPS

3. RODENT ECOLOGY AND EPIZOOLOGY

Murid rodents (order *Rodentia,* family *Muridae*) are the natural hosts and reservoirs of hantaviruses. The fossil record provides evidence for the presence of murid rodents for at least the past 20 million years in North America and 3.5 million years in South America (*8*). Murids are currently found in a wide variety of habitats throughout the Americas. They shelter in burrows or crevices, under logs or other objects, in hollow trees or logs, or in nests built on the ground or in bushes or trees. Although principally nocturnal, they may be diurnal and are usually active throughout the year. Females often produce several litters annually, and breeding may occur throughout the year in warm regions. Most individuals probably live less than two years; however, the high reproductive potential of certain species sometimes results in a large increase in population. This is often followed by a sudden drop in numbers when food supplies in a given area are exhausted. These fluctuations may show a periodicity of around three or four years in some species and habitats (*8*).

Rodents of the murid subfamily *Sigmodontinae,* implicated as hosts of HPS-causing viruses, are primarily associated with rural environments, but some are considered habitat generalists. The propensity of rodents to enter human habitation and surrounding buildings is important. This characteristic of the deer mouse was an underlying factor in the 1993 epidemic in the southwestern United States. Fortunately, some common rodents closely associated with humans (e.g., the common house mouse, *M. musculus*) belong to other subfamilies and are not important reservoirs of hantaviruses.

Each hantavirus is generally associated with a single rodent host species. Thus, the range of its predominant rodent host species restricts the distribution of any particular virus. Viral distribution may occur throughout the host range or may be restricted to a smaller portion of the range. High levels of concordance exist between host and hantaviral phylogenies, supporting the long-term and likely coevolutionary relationship between virus and host. This observation adds further evidence to support the ancient presence of New World hantaviruses in the Western Hemisphere. Except for a single virus, which may be associated with an insectivore, each major branch of the viral phylogenetic tree is associated with a different subfamily of rodents (*4, 5*). All known HPS-related hantaviruses of the Western Hemisphere are associated with the *Sigmodontinae* subfamily of *Muridae* rodents. Several other viruses commonly found in North America are associated with the subfamily *Arvicolinae* but are not known to cause human disease. Old World hantaviruses responsible for HFRS are associated with the subfamily *Murinae* or some members of the subfamily *Arvicolinae.*

Hantavirus infection in the natural rodent host results in chronic, apparently asymptomatic infection. Despite the presence of serum neutralizing antibody, infectious virus may be persistently shed in rodent urine, feces, and saliva.

Horizontal transmission via infectious aerosols among rodents in the laboratory is well documented (*9, 10*). In the field, rodent seroprevalence generally increases with body weight, and therefore age, highlighting the predominant role of horizontal transmission in viral maintenance within reservoir populations (*14*). The frequency of wounds has also been shown to be correlated with antibody seroprevalence in rodents, suggesting a role for biting and aggressive encounters in viral transmission among rodents (*11*). Pups of infected dams demonstrate circulating maternal antibodies, but no definitive evidence of vertical viral transmission exists. Thus, the maintenance of hantaviruses in their rodent reservoirs is mainly through infections acquired during post-weaning intraspecific aggressive encounters.

The view of a single virus infecting a single rodent species may be somewhat oversimplified (*12*). Numerous studies have reported high rates of hantaviral infection among several members of a single genus (*13*). For example, while *P. maniculatus* is agreed to be the

primary reservoir for SNV, *P. boylii*, *P. truei*, and *P. leucopus* have also shown high rates of antibody reactive to SNV (*14*). This observation could represent circulation of a related virus and cross-reactivity to SNV-specific assays, or genuine infection with SNV among other *Peromyscus* species. One explanation for such observations is that in instances of high rodent density and increased probability of interspecific encounters, viral transmission to secondary host species (i.e., "spillover") may occur (*14*). Conversely, in instances of low rodent density and decreased probability of interspecific encounters, nonprimary rodent host species are less likely to show evidence of secondary infection. The taxonomy of New World rodents requires further work to separate and define individual species and their virus associations.

4. EPIDEMIOLOGY OF HUMAN DISEASE

These guidelines focus on the epidemiology of hantavirus pulmonary syndrome (HPS), a disease thus far reported only in the Western Hemisphere. No cases are known to have occurred in Mexico, Central America, or the Caribbean. HPS has been linked to at least six different viruses, with modest clinical differences noted between cases infected with differing viral species. This paper formulates the control and treatment of HPS as a single disease entity until sufficient evidence exists to discriminate it further.

4.1 NORTH AMERICA

As of 9 October 1998, 221 cases of HPS had been confirmed in 29 U.S. states and 3 Canadian provinces (Table 3). Cases have been predominantly from rural areas in the western half of the continent, on either side of the Rocky Mountains. While no cases have been confirmed in Mexico, the range of the primary North American rodent host, *P. maniculatus*, covers the northern half of that country. In addition, four HPS cases in the United States have occurred in areas near the border with Mexico.

In North America, at least four distinct hantaviruses have been associated with HPS. Although the majority of cases are thought to have been the result of Sin Nombre virus infection (*15*), New York (*16*), Bayou (*17*), and Black Creek Canal (*18*) viruses are known to have caused six cases of HPS in the eastern and southeastern United States. The deer mouse, *Peromyscus maniculatus*, is recognized as the primary rodent reservoir of SNV (*19*), while the white-footed mouse (*Peromyscus leucopus*) (*20*), the rice rat (*Oryzomys palustris*) (*21*), and the cotton rat (*Sigmodon hispidus*) (*22*) are believed to be the primary rodent reservoirs for New York, Bayou, and Black Creek Canal viruses, respectively.

4.1.1 United States of America

The initial recognition of HPS in the spring of 1993 stemmed from an epidemic of approximately 27 cases in the southwestern United States. Since then, retrospective analysis of HPS has uncovered cases occurring as far back as 1959. While smaller clusters of two or three cases occurring among co-workers or family members have been reported, the majority of cases since 1993 have occurred sporadically at a rate of 20 to 40 cases per year throughout the United States, suggesting an uncommon yet endemic pattern of occurrence. The common, widespread presence of hantavirus-infected rodents

TABLE 3. Number of hantavirus pulmonary syndrome cases reported in the Americas.

	Number of cases as of 31 December 1997	Most recent data—third quarter, 1998
North America	205	221
United States	181	196
Canada	24	25
South America	208	239
Argentina	133	142
Brazil	6	13
Chile	32	46
Paraguay (*52*)	35	35
Uruguay	2	3
Total	413	460

contrasts with the less-understood and rare circumstances of transmission to humans.

HPS cases have occurred in all months, but are less frequent during the winter months of December, January, and February. It is unclear if human behavioral or rodent ecological factors play a greater role in the observed seasonal pattern, but it is most likely a combination of both factors.

HPS patients range in age from 11 to 69 years (median = 37) and show a slight male predominance (61%). The disease has been notably rare in young children, with only nine cases (5.2%) in children under 18 years old (*23*). The racial and ethnic distribution of cases resembles that of the rural western United States. The possible role of genetic factors remains to be elucidated.

Twenty-four diagnosed HPS cases in the United States occurred prior to 1993, and the majority of these were confirmed through analysis of stored autopsy tissue. Of the first 23 cases of HPS occurring in 1993, 15 (65%) died as a result of their illness. The overall case fatality rate of HPS cases in the United States is 44%. However, this has steadily declined since the time of the initial outbreak in 1993; cases with onset of illness after 1 January 1994 had a case fatality rate of approximately 35%. Of those patients with onset of illness during 1997, 3 of 17 (18%) did not survive their illness. The apparent decreasing mortality of HPS can most likely be attributed to improved clinical management rather than changes in the virus or a specific pharmacological therapy. In addition, increased awareness among clinicians and improved diagnostic capabilities have undoubtedly led to the detection of more mild illnesses and improved characterization of the full spectrum of clinical disease.

HPS cases have been associated with activities such as inhabiting dwellings with indoor rodent populations, occupying previously vacant cabins or other dwellings, cleaning barns and other outbuildings, disturbing rodent-infested areas, residing in or visiting areas in which the rodent population has shown a marked increase in density, trapping rodents, and handling live or dead rodents or their excreta (*24–26*). Activities such as these may have occurred in the context of residential, recreational, or occupational exposures. However, the precise events resulting in human infection are unclear for most cases, since many potential exposures often occur in the weeks leading up to onset of illness.

Serologic testing of household case contacts and persons occupationally at risk for rodent exposure has generally shown less than 1% background seroprevalence of antibody reactive to SNV, supporting the conclusion that asymptomatic infection with HPS-causing hanta-viruses is rare. In addition, there is no evidence of person-to-person transmission of HPS-causing hantaviruses in North America. In one study of 266 health care workers with exposure to HPS patients or their body fluids, none tested positive for SNV antibodies (*27*). Similarly, all reported household or occupational clusters of two or more HPS cases in the United States showed ample evidence of rodent exposure for all cases involved, thus casting doubt on the likelihood that person-to-person transmission was responsible for the observed cluster (*28*).

4.1.2 Canada

For surveillance purposes, Canada has adopted the HPS case definition of the U.S. Centers for Disease Control and Prevention (CDC) (*29*). As of 31 December 1997, 24 laboratory-confirmed HPS cases had been reported and, as of 7 March 1998, one additional case had been reported. All 25 cases occurred in the three westernmost provinces—British Columbia, Alberta, and Saskatchewan—which represent approximately 25% of the Canadian population (*30*). The earliest known HPS case occurred in Alberta in 1989 and was identified retrospectively. Since 1994, when HPS was first recognized in Canada, five cases per year, on average, have occurred. More than 40% of cases have occurred during the months of April, May, and June. Alberta, representing approximately 9% of the Canadian population, has reported 64% (16 of 25) of the HPS cases. Overall, cases have ranged in age from 15 to 62 years (mean = 39.5 years); 68% (17 of 25) have been male and 32% (8 of 25) have died. Of those patients with onset of illness since 1 January 1997, one of eight (13%) did not survive the illness. The majority of cases were most likely exposed to SNV during farming and domestic activities in rural areas. Single cases have also been linked to occupational exposures during military exercises, cleanup of a lumber mill, and a wildlife survey. The characteristics of HPS in Canada appear to be similar to those of cases described in the U.S. (*30*).

Rodent surveys have shown the presence of Sin Nombre and Sin Nombre-like viruses in deer mice across Canada, with varying seroprevalence. Landscape composition in Canada was found to be a more important predictor of rodent seroprevalence than were such factors as season, viral strain, climate, buildings, or association with human disease (*31*).

4.2 CENTRAL AMERICA AND THE CARIBBEAN

No cases of HPS are known to have occurred in Central America or the Caribbean. However, the range of

Sigmodon hispidus, the probable host of Black Creek Canal virus, extends from the southeastern United States, through Central America, and into northern South America. In addition, Río Segundo virus has been identified with the harvest mouse, *Reithrodontomys mexicanus*, in Costa Rica but has not been linked to human disease (*32*). Species that inhabit portions of the Caribbean are more likely to be Old World members of the *Murinae* subfamily of rodents, such as the Norway rat. The absence of HPS in the Caribbean could be the result of the relative infrequency in the region of rodent host species of the *Sigmodontinae* subfamily.

4.3 SOUTH AMERICA

In South America, the presence of hantavirus-infected *Rattus norvegicus* has been known since the 1980s. Various studies conducted during that decade found up to 56% of captured rats seropositive for antibodies reactive to Hantaan virus antigen (*33, 34*). Other studies conducted near that time provided serologic evidence of past human infection in Brazil, Argentina, Bolivia, and Uruguay (*35, 36*).

In December 1993, following the outbreak in the United States, HPS was diagnosed in three people in Brazil (*37*). Active surveillance also led to the detection of several cases in Argentina. Currently, there are several genetically distinguishable viruses associated with HPS in South America and several others not known to cause disease (Tables 1 and 2). By the third quarter of 1998, 239 cases of HPS had been reported from five countries of South America. While cases have occurred throughout the year in an endemic fashion similar to that seen in North America, several clusters account for more than a quarter of all recognized cases on the continent. These clusters have generally occurred from September to January (spring and summer in the Southern Cone) in diverse habitat regions. A country-by-country synopsis of HPS activity will help illustrate the unique epidemiologic features of the disease in each country.

4.3.1 Argentina

As of 7 March 1998, 142 cases had been reported in Argentina. They were principally from Salta and Jujuy provinces in the northwest, Santa Fe and Buenos Aires provinces in the central part of the country, and Río Negro, Chubut, and Neuquen provinces in the south (*38, 39*). The mean age of HPS cases was 34.7 years, with a range of 4 to 71 years. Argentina has seen a larger proportion of pediatric cases than the United States (*40*). The overall case fatality rate of HPS in Argentina is approximately 44%.

Following the 1993 outbreak in North America, active, prospective, and retrospective surveillance was undertaken of patients presenting with fever and unexplained respiratory distress syndrome between 1987 and 1995. In central Argentina, HPS was found during surveillance conducted for suspected cases of leptospirosis and Argentine hemorrhagic fever for which laboratory tests were negative. In northern Argentina, local physicians in Orán, in Salta province, had been reporting case clusters of an acute respiratory distress syndrome of unknown etiology since the 1980s. In the early 1990s, *Leptospira interrogans* was identified as the causative agent of some of these illnesses. However, in 1995, serological studies of cases showed hantavirus as the etiologic agent of disease in some of the remaining undiagnosed cases.

In the south, a cluster of three family members with illness was identified in the province of Río Negro in March 1995. Investigation of this cluster led to the characterization of Andes virus as the etiologic agent in southern Argentina (*41*). Andes virus was shown to represent a distinct lineage from SNV (*41*) but to be most closely related to other sigmodontine hantaviruses. It differed from New World hantaviruses of the North American Sin Nombre complex by more than 20% at the amino acid level in the G2 protein region. At least seven viral genotypes associated with different rodent reservoirs have been found circulating in the country, four of which have been linked to HPS (*42*).

Between September and December 1996, an outbreak of HPS occurred in the same region of Río Negro, affecting at least 18 people. Four of the 18 cases were physicians who lived in the area. Epidemiological, molecular, and ecological data have established person-to-person transmission, particularly when a physician living in a nonendemic region became infected after coming in contact with HPS patients (*43, 44, 48*). The etiologic agent was again found to be Andes virus, and the putative rodent reservoir, the long-tailed pygmy rice rat, *Oligoryzomys longicaudatus* (*42*).

4.3.2 Bolivia

While no HPS cases have been reported, both humans and rodents have shown serologic evidence of infection with hantaviruses in Bolivia (*35, 45*).

4.3.3 Brazil

As of 7 March 1998, six HPS cases had been reported in Brazil, five of which resulted in death. In December 1993, three brothers from Juquitiba, in the São Paulo area, were diagnosed with HPS; two subsequently died of their illness. Lung tissue from one patient yielded evidence of a possibly distinct virus provisionally referred to as Juquitiba virus (*4*). The brothers lived together in a rural area that showed evidence of rodent infestation. Three of 49 case contacts (6.1%) were positive for antibodies reactive to hantavirus antigen, with no apparent disease (*37*). Field investigations failed to determine the probable reservoir. Since then, three additional HPS cases have been reported; one case occurred in the state of Mato Grosso in 1995, while the other two were reported from the state of São Paulo.

4.3.4 Chile

HPS was first recognized in Chile in 1995 in a patient from Cochamo, Los Lagos, Region X. As of 25 March 1998, a total of 46 HPS cases had been reported, mainly from Regions IX, X, and XI, in the south of the country. Of these, 28 cases occurred between October 1995 and December 1997, most as a result of an outbreak in Aysén, Region XI, that began in July 1997. The mean age of these 28 HPS patients was 29.7 years (range 2–60 years), and 75% were males; six (21.4%) of the cases were children under 17 years of age. A case fatality rate of 61% was observed. Three clinical outcomes of hantavirus infection were defined in the country: patients with HPS, patients with mild hantaviral disease, and asymptomatic infections. In addition to the 28 cases of HPS, 3 cases with mild febrile hantaviral disease and 1 case with asymptomatic acute infection were identified.

While the clinical description of cases is similar to that in North America, at least three children had petechiae, and all adult cases that had a urinalysis performed had microscopic hematuria and casts (*46*). Genetic sequencing of tissues from several patients implicated Andes virus as the causative agent (*47, 48*). Three family clusters occurred in the Aysén region. In one cluster, family members became ill within 1 to 5 days of each other. In another family cluster, illness occurred sequentially, with a period of 16 to 41 days between the index case and illness of the last family member. The third family cluster included a husband, who worked in a rural area, and his wife, who remained in the family home in urban Coyhaique. He developed symptoms suggestive of HPS 12 days after returning to his wife and home, was hospitalized, and died. His wife became ill 22 days after the initial onset of his symptoms. She had not traveled outside Coyhaique during the previous 12 months and reported no exposure to rodents. The only known exposures for the wife were washing her husband's clothing and caring for him while he was ill.

A serological study of health care workers from the Coyhaique Regional Hospital, where the majority of HPS patients were admitted during the 1997 outbreak, was performed (*49*). Out of 319 participants (87.9% of those eligible), 12 (3.6%) had IgG antibodies, consistent with the seroprevalence in the community in which the participants lived. Exposure to HPS patients was similar in both antibody-positive and antibody-negative individuals. A population-based, serological survey including individuals from four communities in the Aysén region, one urban and three rural, showed seroprevalence ranging from 2% in the urban area to 13.1% in one of the endemic localities (*50*).

Ecological studies were carried out in 1997 (*51*). Overall trap success ranged from 37% to 50%. The most frequently captured rodent was *Oligoryzomys longicaudatus*, with 13% antibody reactivity to Sin Nombre virus.

4.3.5 Paraguay

Thirty-five cases of HPS have been reported in western Paraguay (*52*). An outbreak of HPS occurred in an agricultural community in the western Chaco region, affecting at least 17 people in the spring and summer of 1995–1996 (*52*). Six additional cases, retrospectively identified in the region between 1987 and 1994, were serologically confirmed. The case fatality rate during the outbreak period was 12%, but this may have been underestimated due to the relative infrequency of autopsies performed in the region.

The background human seroprevalence was found to be between 7 and 21% among asymptomatic groups and community residents (*52*). This may indicate a milder illness and a much higher rate of subclinical infection than that observed elsewhere or infection with a less pathogenic, serologically cross-reactive hantavirus. The etiologic agent was named Laguna Negra virus and has been subsequently isolated in cell culture; the vesper mouse, *Calomys laucha*, was found to be the primary rodent reservoir (*53*).

4.3.6 Peru

There are currently no confirmed reports of hantavirus pulmonary syndrome cases in Peru. However, evidence of hantavirus infection has been found in a number of

rodent species within the country (R. Tesh and D. Watts, personal communication).

4.3.7 Uruguay

At least two cases of HPS have been reported in Uruguay, and previous serologic surveys had detected hantavirus antibodies in the general population (*35*). Little is known about the etiologic agent or the reservoir.

4.3.8 Venezuela

There are currently no confirmed reports of HPS cases in Venezuela. However, hantavirus antibodies have been detected in three rodents from the Venezuelan llanos, *Oryzomys bicolor, Sigmodon alstoni,* and *Zygodontomys brevicauda*. A genetically distinct hantavirus, Caño Delgadito virus, has been isolated from *Sigmodon alstoni*, but so far has not been linked to any human disease (*54*).

5. TRANSMISSION TO HUMANS

Although rodent infection is apparently asymptomatic, human infection is often associated with disease. The main route of transmission is likely respiratory via small-particle aerosols generated from rodent excreta, particularly freshly shed urine. However, it is also possible that infectious airborne particles may be generated during human activities that disturb contaminated soil, litter, or nesting materials. The chance of exposure to hantaviruses is greatest when individuals work, play, or live in closed spaces where there is an active rodent infestation. Human infection does not appear to be limited to a particular age, race, ethnic group, or gender.

It is unknown if direct transmission can occur when larger particles contact ocular, nasal, or oropharyngeal mucous membranes. However, small skin breaks and rodent bites are probably effective but uncommon routes of human infection. Ticks, fleas, mosquitoes, and other biting arthropods are not known to have a role in the transmission of hantaviruses. Although cats and dogs are not known to be a reservoir host of hantaviruses, these domestic animals may bring infected rodents into contact with humans.

Hantaviruses have lipid envelopes and are susceptible to 10% bleach, detergents, and common hospital disinfectants. How long these viruses survive in the environment after being shed is uncertain (*24*). In laboratory experiments simulating environmental conditions, Hantaan virus could still be recovered for several days after drying at room temperature. The virus was viable for short periods of time in temperature ranges of 4 °C to 42 °C and pH ranges of 6.6 to 8.8. These findings indicate that Hantaan virus and presumably all other hantaviruses may remain infectious for up to several days in natural conditions (*55*).

Hantaviruses have never been implicated in nosocomial transmission in European or Asian settings despite the large number of cases observed and hospitalized. During the 1993 SNV outbreak in the United States, neither clinical disease nor seropositivity was found among more than 266 health care workers, including persons who had performed mouth-to-mouth resuscitation or endotracheal intubation (*27*).

Person-to-person transmission was documented in a South American outbreak of Andes virus in 1996 (*43, 44, 48*). It is unknown if this represents a unique event or whether other such cases may occur. A retrospective analysis of the United States HPS Case Registry failed to find definitive evidence for interhuman or nosocomial spread; the few case clusters observed could well have originated from common exposure to rodent-infested living conditions. Further study of the epidemiology of naturally occurring infections is needed in order to understand the potential that the newly discovered American hantaviruses have for contagion.

6. HANTAVIRUS PULMONARY SYNDROME SURVEILLANCE AND CASE DEFINITION

In order to permit immediate epidemic control or to prevent the transmission of hantavirus infection, a surveillance system must be simple in its structure and operation. In the case of hantavirus infection, the surveillance system must address the disease from an integrated clinical, laboratory, and environmental perspective. The case definition provided below (Figure 1), initially developed by CDC, is also used in Canada and several South American countries for HPS surveillance. Serological tests on acute sera are needed to provide precise diagnosis, and molecular biological techniques are useful in establishing the type(s) of circulating virus. All clinical samples must be accompanied by a form identifying the patient, the individual's age and sex, the date of symptom onset, the date of sample collection, a short list of important manifestations, clinical laboratory data, the place of hospitalization, and the final outcome (see Annex 2).

6.1 OUTBREAK INVESTIGATION

6.1.1 When to Investigate

The occurrence of an unusual number of cases in an area of known hantavirus transmission requires an explanation and may also provide an opportunity to expand our knowledge of hantaviruses. This is particularly relevant with case clusters, since they provide an opportunity to address the problem of interhuman transmission.

A single case in an area where hantavirus infection has not previously been reported requires a full medical and epidemiological assessment, individual risk factor/exposure analysis, and an ecological/environmental evaluation as outlined in Section 6.1.2. Determinations of the virus type in circulation as well as potential reservoirs in these new areas are essential in designing future control and prevention strategies.

If a single new case occurs in an area with previous infection, current knowledge about the mode of transmission, clinical manifestations of disease, individual risk factors, circulating virus type, and potential reservoirs in the region should be taken into account and further investigations conducted if circumstances suggest.

In all cases, response procedures should include an evaluation of rodent infestation in domestic and peridomestic settings in order to propose appropriate rodent control measures.

6.1.2 Conducting the Investigation

In conducting the investigation, it is essential to establish a multidisciplinary investigative team involving epidemiologists, laboratorians, and ecologists. Each outbreak investigation should begin with a medical and epidemiologic assessment that includes the following steps:

- define the magnitude of the outbreak:
  - conduct active case finding through interviews and medical chart reviews
  - determine the relative frequency of infection versus disease (via serological survey)
  - map case locations with attention to results of the serological survey
- determine mode(s) of transmission
- characterize the clinical manifestation of disease within the outbreak
- ensure that in each activity above, clinical specimens are collected in a systematic manner with attention to use of specimens for serological diagnosis, PCR analysis, and possibly virus isolation.

The second major activity of the investigation involves individual risk factor/exposure assessment. A culturally appropriate individual risk factor/exposure questionnaire should be developed for use with case-patients, surrogates of case-patients, household or other close contacts, and/or control-patients if used.

The best methodological approach for the situation should be determined, including whether or not to use a case-control design.

FIGURE 1. Hantavirus pulmonary syndrome case definition.

Hantavirus Pulmonary Syndrome (HPS)

Rationale for Surveillance

HPS in the Americas is a rare, but usually severe, disease transmitted through close contact with the urine, feces, or saliva of infected rodents. Although HPS cases have been reported only from Argentina, Brazil, Canada, Chile, Paraguay, the United States of America, and Uruguay, the potential for disease exists throughout the Americas due to the widespread distribution of existing rodent reservoirs. Surveillance is therefore essential for all countries.

Recommended HPS Case Definition

Clinical Case Definition:

- A febrile illness (T >38.3 °C [101 °F] oral) requiring supplemental oxygen, *plus*
- Bilateral diffuse infiltrates (may resemble adult respiratory distress syndrome [ARDS]), *plus*
- Develops within 72 hours of hospitalization in a previously healthy person, **OR**
- Unexplained illness resulting in death *plus* an autopsy examination demonstrating noncardiogenic pulmonary edema without an identifiable specific cause of death

Laboratory Criteria for Diagnosis:

- Presence of hantavirus-specific IgM antibodies or a 4-fold or greater increase in IgG antibody titers **OR**
- Positive reverse transcriptase-polymerase chain reaction (RT-PCR) results for hantavirus RNA **OR**
- Positive immunohistochemical results for hantavirus antigens.

Case Classification:

Suspected: Presentation compatible with the clinical case definition
Confirmed: A suspected case that is laboratory confirmed

Recommendations for Surveillance

- Establish HPS as a reportable (compulsory reporting) disease in all PAHO Member Countries.
- Develop a case report form that identifies standard minimum data to be collected by all countries of the Americas (see Annex 2).
- If HPS is suspected, a blood count, chest X-ray, oxygen saturation, and hantavirus serology should be performed. Rodent exposure should be evaluated (see Annex 2).
- Postmortem blood, fresh frozen tissue, and formal fixed tissue should be collected from deceased HPS patients and properly transported to the nearest laboratory capable of HPS confirmation (see Section 6.1.4 and Annex 3).
- If hantavirus infection not meeting the case definition of HPS is suspected, specimens may also be submitted for testing along with a description of clinical manifestations.

The third main component of the investigation is an ecological/environmental assessment. This includes using standardized data collection forms and conducting systematic environmental assessments to evaluate indices of rodent presence/infestation at suspected sites of rodent exposure. Following the guidelines outlined in Section 6.1.5, the investigation team should initiate systematic assessments of potential rodent reservoirs in the outbreak region, including proper taxonomic evaluations.

6.1.3 Local Response to a Hantavirus Pulmonary Syndrome Case

Local officials should take action when a possible HPS case is laboratory confirmed, even though many cases meeting the screening case definition will not be HPS. Some actions may be taken if clinical evolution makes a positive laboratory diagnosis highly unlikely.

An essential step is to consult local and state public health authorities immediately. The management of zoonoses is specialized, and advice, explanations, and policy guidelines may be needed. Also, special samples from both humans and rodents may be required for investigation and analysis.

It should be suggested to family members that they reside elsewhere until domestic and peridomestic structures have been evaluated and rodents removed. This should be strongly recommended in cases where heavy rodent infestation is evident, especially in the home. The risk of removing clothing and possessions needed immediately is negligible. It may be necessary to obtain rodents from the house for study, depending on the situation and national policy. If rodents are not needed for study, it is sufficient to kill all those in the house, building, or peridomestic structure and properly dispose of them.

Household contacts should be placed under surveillance and any fever reported immediately. About 10% of hantavirus cases occur in clusters, and rare instances of person-to-person transmission occur with Andes virus. Early recognition can improve case management. In addition, contacts must be reassured.

A media strategy should be prepared. Intense interest often follows the first cases, and the media can be helpful in allaying anxiety and spreading public health messages. An effective media strategy can also counteract stigmatization of infected individuals or the community.

Finally, an educational campaign appropriate to the community situation should be developed. Its characteristics will depend on whether there is a single case or multiple cases and whether this is the first recognized case in the area or there is an established endemic. The campaign should target cases' family members as well as physicians.

6.1.4 Recommendations for Sample Storage and Preservation

Serum samples for serological tests can be stored at 4 °C for a few days but preferably should be frozen at –20 °C or at –60 °C. Acute serum for PCR tests should be kept frozen at –60 °C. Tissues from fatal cases should be frozen at –60 °C for PCR tests and fixed in 10% buffered formalin for histopathology and for immunohistochemical analysis. A formalin buffer (pH = 7.4) can be prepared as follows:

100 ml	pure formalin
900 ml	distilled water
4.0 g	monosodium phosphate
6.5 g	disodium phosphate

Lung is the most sensitive tissue for immunohistochemical diagnosis of HPS, but a complete autopsy should be performed and multiple tissues taken because of the limited information available on the pathology and pathogenesis of the different hantaviruses.

6.1.5 Reservoir Surveillance

The intensity and methodology of reservoir surveillance and case follow-up will depend on the resources available to public health authorities. As a minimum, the public health response to the first case(s) of HPS in a country or region where hantavirus infection was previously not identified should include small-mammal trapping in potential areas of human exposure. Trapping should be conducted in accordance with established safety and methodological guidelines (*56*). Primary objectives should include:

- identification of the principal reservoir species
- collection of samples to identify hantaviruses present and to provide a genetic link to human cases
- measurement of the relative density and prevalence of infection in potential reservoir populations
- determination of the most likely ecological zones, specific sites, and mechanisms of human infection

As resources permit, reservoir studies may be expanded to include specific trapping and sampling protocols designed to investigate:

- the potential (as indicated by reservoir presence and evidence of viral infection) for human cases of HPS in distinct geographic areas of the country
- the prevalence, incidence, and temporal patterns of infection in reservoir species
- the effect of climate, habitat quality, and host population dynamics on the viral transmission cycle
- potential mechanisms of transmission among reservoir populations, and from rodents to humans
- effects of infection on movement, longevity, and population dynamics of the host
- the identity of other hantaviruses that may cause human infection, including their hosts and geographic distribution
- potential methods for reservoir control and for decreasing the frequency of human contact with host species
- the relationship between reservoir population density, virus activity in reservoir populations, and the incidence of human disease

Discussions and examples of the application and utility of these kinds of studies are available (*14, 52, 56–59*). Investigators should be encouraged to establish a working relationship with museum taxonomists, universities, government agencies, and private consultants to ensure proper identification and permanent archiving of voucher specimens for all captured small mammals. Methodologies for voucher specimen preparation and preservation have been described (*56, 60*).

7. CLINICAL MANIFESTATIONS AND TREATMENT OF HANTAVIRUS PULMONARY SYNDROME (*61*)

7.1 INCUBATION PERIOD

Few cases have had clearly defined exposures in time and place. The incubation period of other hantavirus diseases is typically one to four weeks, although HFRS from Hantaan virus has apparently had an incubation period up to six weeks. In an effort to determine the incubation period of HPS-causing viruses in the United States, eight cases were identified with well-defined and isolated exposures. These findings suggested an incubation period ranging from 9 to 35 days from the time of probable infection to onset of symptoms (J. Young, personal communication). For seven of the eight cases reviewed, the incubation period was within 9 to 24 days.

7.2 CLINICAL MANIFESTATIONS

Following aerosol exposure and deposition of the virus deep in the lung, infection is initiated. A viremic period ensues, with extensive pulmonary endothelial infection. The onset of symptoms coincides with the onset of the immune response, which may reduce virus shedding, suggesting that the disease process itself is immunopathologic.

The disease is divided into four phases: febrile, cardiopulmonary, diuretic, and convalescent phases (*62*). The febrile, or prodromal, phase typically lasts 3 to 5 days (range 1–12 days) and is indistinguishable from other viral prodromes (*63*). This phase is characterized by fever, myalgias, chills, asthenia, dizziness, headache, anorexia, nausea with or without vomiting, abdominal pain, and diarrhea. The abdominal pain may be sufficiently severe to mimic appendicitis or pyelonephritis. While conjunctival suffusion is rarely seen in HPS in North America, facial flushing is commonly seen in HPS cases in the Patagonian region of South America. Indications of upper respiratory tract disease, including sore throat, rhinorrhea, sinusitis, and ear pain, are usually absent. Physical examination may or may not reveal rales or findings of pleural effusion. Cough, tachypnea, and exertional dyspnea are not reported at the onset of the prodrome, but appear later and herald the onset of pulmonary edema, the second phase.

The onset of hypotension and pulmonary edema may progress rapidly over the course of 4 to 24 hours. A respiratory rate of 24/min is a sensitive but not specific indicator of early pulmonary edema in HPS. Early pulmonary edema is imaged on the chest X-ray as Kerley B lines, peribronchial cuffing, and alveolar-interstitial fluid in the basal segments (*64*). At this point, hypoxemia becomes apparent, with an oxygen saturation of hemoglobin less than 95% at sea level and less than 90% at 2,000 m or more above sea level. Pulmonary edema is noncardiogenic in origin, as indicated by normal pulmonary capillary wedge pressures obtained through a Swan-Ganz catheter and normal heart size on the X-ray (*65, 66*). Markedly increased pulmonary capillary permeability results in high-protein pulmonary edema; severely ill patients may require up to 1 L/h of serum-resembling fluid to be removed from their airways by suction. Shock may be manifest as hypotension and is often accompanied by oliguria and delirium. Hypovolemia resulting from a shift in fluid from circulating blood to the lung interstitium and air spaces contributes to the fall in blood pressure. However, most patients also experience a serious depression of the myocardium (*65*). Seriously ill patients may have cardiac indices less than 2.2 L/min/m^2.

Spontaneous diuresis indicates the onset of the diuretic phase. This third phase of the disease is characterized by a rapid clearance of the pulmonary edema fluid, resolution of fever, and shock. Convalescence extends over the next two weeks to two months. Patients appear to recover fully, but formal studies of pulmonary function and other clinical parameters are needed.

In South America, some other clinical aspects have been described, including hemorrhagic complications (i.e., petechias, not observed in North America) and renal manifestations (*46*). As well, HPS has appeared in children, an uncommon finding in North America (*40*).

7.3 CLINICAL LABORATORY FINDINGS

Hematologic findings can be striking in HPS cases (*62, 67*). In SNV infection, the white blood cell count can be normal or elevated on admission (median 10,400 mm^3; range 3,100–65,300 mm^3) and usually increases, often to very high values (median of maximum values 26,000 mm^3 with range 5,600–65,300 mm^3). Similar values have been found with other viruses. There is an absolute neutrophilia and a relative lymphopenia. In addition to immature "band" forms, the blood almost always contains the more undifferentiated forms in the myeloid series, the myelocytes, and promyelocytes. Among the circulating lymphocytes are prominent mononuclear cells with deep blue cytoplasm by Giemsa stain and that measure greater than 18 μ in diameter. These immunoblasts are seen in few infections other than HPS and HFRS, and appear in the circulation coincident with the onset of pulmonary edema. Thrombocytopenia with a platelet count less than 150,000/mm^3 is seen in almost every case and, in rare cases, may fall to 20,000/mm^3. Thrombocytopenia is the first abnormality to appear in the peripheral blood, often two or three days before the onset of pulmonary edema, and may be used to screen undifferentiated fevers for HPS when the appropriate epidemiologic clues are elicited by history.

Elevated creatinine and blood urea nitrogen reflect the degree of shock and hypovolemia. Proteinuria may be seen and microscopic hematuria is found in most cases. Patients infected by Bayou, Black Creek Canal, and Andes viruses may have more prominent renal failure, even requiring hemodialysis (*17, 45, 68,* and Lázaro, personal communication). Elevated hepatic enzymes are seen in all cases, but rarely attain a level greater than five times the upper normal limit, and hyperbilirubinemia is not seen. The multiorgan failure common in sepsis or posttraumatic adult respiratory distress syndrome *(*ARDS) rarely occurs in HPS. Specific pathology of these organ systems has not yet been described with any of the HPS viruses, but experience and surveillance definitions are limited.

In contrast to HFRS, the coagulopathy of HPS is usually subclinical. Almost all patients have evidence of coagulopathy but with elevated partial thromboplastin times. Circulating D-dimers are not common, and fibrinogen levels falling below 200 mg/dl are rare.

7.4 EARLY CASE RECOGNITION

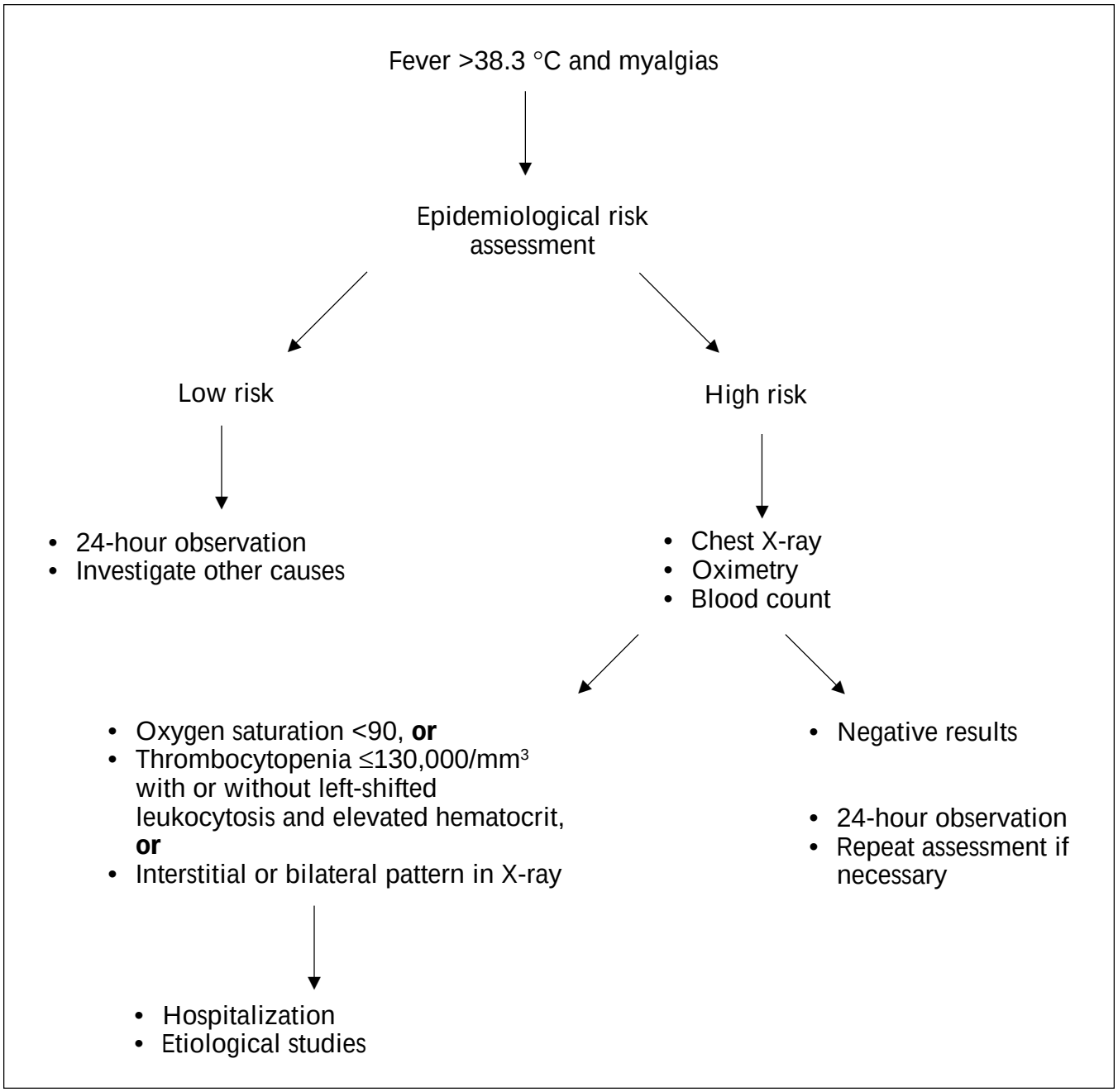
Clinicians should consider HPS in patients with fever and myalgias, particularly of the larger muscle groups, including shoulders, thighs, and lower back. The addition of such gastrointestinal complaints as nausea, vomiting, and abdominal pain should raise the index of suspicion and prompt the clinician to inquire about potential rodent exposures. Tachypnea is an important sign, and hypotension may be present. The absence of certain signs and symptoms can help to distinguish HPS from other acute viral syndromes: rash, conjunctivitis, sinusitis, otitis, rhinorrhea, exudative pharyngitis, and arthritis are notably rare in HPS (*63*). Initial laboratory workup in suspected cases should include pulse oximetry, chest radiograph, and a complete blood count. The likelihood of HPS is high in those with a compatible clinical history plus an oxygen saturation measurement of less than 90%, interstitial infiltrates or other indications of pulmonary edema on chest X-ray, and thrombocytopenia, particularly if the last is accompanied by left-shifted leukocytosis and an elevated hematocrit.

At the onset of pulmonary edema, almost every case displays thrombocytopenia, left-shifted myeloid series, and immunoblasts. This hematologic diagnostic triad is sufficiently sensitive and specific to use to initiate transfer to intensive care and treatment (see Section 7.6). Prior to the onset of the signs and symptoms of either shock or pulmonary edema, the diagnostic triad is not present on the peripheral blood smear. Therefore, to raise the suspicion of impending HPS, the clinician must use the combination of three factors: epidemiologic clues to potential exposure, the reported findings of fever and myalgias, and thrombocytopenia. Although fully developed HPS is a characteristic disease, no combination of symptoms is sufficiently sensitive or specific to distinguish its early stages from a host of other pulmonary infections (*63*); this requires the clinician to retain a level of suspicion until HPS is ruled out. When sufficient evidence for HPS has accumulated, the patient should be transported immediately to a unit skilled in intensive cardiopulmonary care, as rapid transport can be lifesaving. However, the decision to move the patient must be weighed against the rapid onset of hypoxemia and the local capabilities for medical evaluation. In all areas with previously known or suspected cases of HPS, active clinical investigation to definitively diagnose HPS should be performed in all persons with unexplained febrile syndrome and epidemiologic risk factors (see Figure 2).

7.5 DIFFERENTIAL DIAGNOSIS

The differential diagnosis is extensive prior to the serologic identification of hantavirus infection. Most commonly encountered are bilateral pneumonia with sepsis, adult respiratory distress syndrome complicating systemic infections, trauma and other life-threatening conditions, and sepsis syndrome complicated by either disseminated

FIGURE 2. Hantavirus pulmonary syndrome algorithm.



intravascular coagulation (DIC) or alcohol toxicity. A variety of enzootic infections encountered in rural areas of North America may be confused initially with HPS, particularly when thrombocytopenia is present. These include plague, tularemia, Rocky Mountain spotted fever or murine typhus, granulocytic or monocytic ehrlichiosis, leptospirosis, relapsing fever due to *Borrelia hermsii*, and acute parvovirus infection. In Latin America, other diagnostic possibilities would include dengue fever, dengue hemorrhagic fever, and arenavirus infections (Junin, Machupo, Sabia, and Guanarito viruses). When abdominal or back pain is severe, possible diagnoses of pyelonephritis, appendicitis, abdominal abscess, or gynecological infection should be considered.

7.6 LABORATORY DIAGNOSIS

The most practical approach for the laboratory diagnosis of hantavirus infection in humans is the detection

of IgM antibodies in acute serum samples using an ELISA IgM capture assay. Virtually all confirmed HPS patients have demonstrable IgM in the first or second serum sample taken after hospitalization. And while ELISA tests to detect IgG antibodies may also be used to confirm diagnosis, two serum samples taken two to three weeks apart are required to demonstrate rising titers of IgG antibodies. Results of testing can be obtained within a few hours after the specimen is received in the laboratory. Less commonly used serological tests, such as immunofluorescent assay and particle agglutination, can also be applied to hantaviral diagnosis (*69*).

Initial detection of HPS-related hantaviruses was accomplished using heterologous hantaviral antigen (*70*). A more sensitive Sin Nombre recombinant nucleocapsid antigen was developed in response to the outbreak in 1993 in the United States; it is now widely used throughout the Americas in ELISA tests for the detection of New World hantavirus infections. More recently, other recombinant antigens have been developed, such as Andes virus nucleocapsid. Due to the cross-reactive nature of these antigens, they cannot discriminate among closely related hantavirus species.

In fatal cases, fresh frozen tissue, fixed tissue, and blood can be used to confirm the diagnosis by RT-PCR, immunohistochemistry, or ELISA methods, respectively. Collection of blood clots from initial samples of all suspect cases is also recommended for subsequent RT-PCR on selected seropositive individuals. RT-PCR is a molecular diagnostic technique targeting specific regions of the virus genome and is available only at selected research laboratories. RT-PCR is not recommended for routine diagnosis, but is valuable in defining the virus genotype, searching for new viruses, and performing certain epidemiological studies. Immunohistochemistry is particularly well suited to retrospective diagnosis. Viral inclusions have rarely been observed in pulmonary capillary endothelial cells by electron microscopy.

Some Old World hantaviruses have occasionally been isolated from patient serum or whole blood drawn within three to nine days of onset of illness. However, propagation of hantaviruses is difficult and this is not a recommended diagnostic procedure (*71*).

7.7 PATHOGENESIS

The pathogenesis of HPS is related to a profound abnormality in vascular permeability. The capillary leak syndrome is virtually confined to the lungs, and chest radiograph series typically chronicle the rapid onset of diffuse, bilateral interstitial, and later alveolar, pulmonary edema (*64*). There is also evidence for myocardial failure as an important component of the shock syndrome observed (*65*).

At postmortem the lungs are massively edematous, but microscopic studies find little necrosis. There are scant to moderate hyaline membranes, intact pneumocytes, and scarce neutrophils (*67*). However, there is interstitial infiltration by T lymphocytes and activated macrophages (*72*). These findings differ from those of typical adult respiratory distress syndrome and many pneumonias. Hantaviral antigens are detected primarily in endothelial cells, and those in the lung are heavily involved. Lesser amounts of antigen are found in scattered endothelial cells throughout the body, as well as occasional involvement of macrophages, myocytes, and many other cell types.

In contrast to such diseases as South American hemorrhagic fevers, circulating antibodies appear early in the clinical course of HPS and often correspond to clinical decline rather than improvement (*73, 74*). Thus, the impaired vascular permeability is thought to be immunologically mediated, probably strongly influenced by the infiltrating T cells in the lungs.

7.8 TREATMENT

There is no known effective antiviral therapy for HPS, although the drug ribavirin has shown a treatment effect in reducing HFRS mortality (*75*). Open-label ribavirin treatment had no obvious effect in a limited number of HPS patients, and a placebo-controlled clinical trial is currently under way in the United States. In the absence of a proven pharmacological treatment and in light of the rapid progression of HPS, effective clinical management depends heavily on careful fluid management, hemodynamic monitoring, and ventilatory support. Therapeutic responses to shock in patients with HPS must be guided by an understanding of the underlying pathophysiology of this disorder, that is, profound pulmonary capillary leak in the presence of primary myocardial pump dysfunction.

Experimental therapies have been used to treat severely ill patients with HPS. These include extracorporeal membrane oxygenation (ECMO) and nitrous oxide inhalation. Experience is very limited in the use of these experimental measures to treat HPS patients, and they have generally been used only as a last resort form of therapy. There are no clinical data on the effectiveness of administering immune plasma to treat HPS patients. While this therapy has been effective for Argentine hemorrhagic fever (AHF), the differences in immune response and pathophysiology between AHF and HPS suggest it is unlikely to be effective in HPS.

Antiviral therapy with a drug such as ribavirin may be more effective if given to patients identified very early in the prodromal stage. Such patients might be close contacts of a confirmed HPS case (about 10% of hantavirus cases occur in clusters, regardless of the issue of possible

interhuman transmission of Andes virus) or persons with very high risk exposure. Protocols should be developed to permit controlled studies of early, expectant antiviral treatment initiated prior to laboratory testing. Argentina has such a protocol that may be requested as a template.[1] For every new procedure or therapeutic measure it is strongly recommended that controlled studies be performed.

7.8.1 Initial Treatment of Hantavirus Pulmonary Syndrome in the Emergency Room and During Transport

Initial treatment during the observation period should be directed to symptomatic and supportive measures, such as the control of fever and pain with paracetamol (avoiding the use of aspirin), antiemetics, and bed rest. The observation period could be managed at a primary care center. However, if there is a high suspicion of HPS according to the proposed HPS algorithm (Figure 2), patients should be immediately transferred to an emergency room (ER).

Treatment in the ER should focus on maintenance of blood pressure and oxygenation while transfer to an intensive care unit (ICU) is organized. When patients present with shock to the ER, the case fatality rate exceeds 80%. In contrast, the case fatality rate is 10% in the absence of shock at this time, indicating the importance of cardiogenic shock as a cause of death. While some patients may have fluid requirements of 1 to 2 L due to vomiting and diarrhea, it must be kept in mind that excessive fluid resuscitation will exacerbate the pulmonary edema without commensurate improvement in cardiac output. Early use of inotropic agents (see Section 7.8.2) may be necessary, depending on the ability to monitor response to therapy. Due to the rapid onset of pulmonary edema, hypoxemia may deteriorate rapidly over several hours, and continuous monitoring of oxygenation by pulse oximetry is preferred.

7.8.2 Treatment in the Intensive Care Unit

Close monitoring of oxygenation is extremely important so that timely intubation and mechanical ventilation can be provided when required (when PAO_2/FIO_2 falls below 150). Oxygen delivery is usually maintained until the cardiac index falls below 2.2 L/min/m^2. Mechanical ventilation is required for about two-thirds of patients and typically lasts for five to seven days. Because patients with this viral infection can deteriorate so rapidly, a Swan-Ganz catheter should be inserted as soon as is clinically warranted. Intravenous crystalloid fluid is used to maintain as low a wedge pressure (8–12 mmHg) as is compatible with satisfactory cardiac indices (cardiac index >2.2 L/min/m^2). Inotropic agents, such as dobutamine, dopamine, and norepinephrine, are begun earlier in the resuscitation of these patients than in the usual patient, rather than continued fluid boluses. The use of loop diuretics such as furosemide is discouraged, since salt and water will be removed from circulating blood before being removed from the alveolar and interstitial compartments in the lung, thus exacerbating hypotension. Red blood cells are usually not required to maintain oxygen delivery unless hemoglobin concentration falls below 8.5–10 g/dl. Thrombocytopenia has not required support with platelet transfusion. So far there is no evidence that pharmacological doses of corticosteroid offer any benefit in the treatment of HPS. Cardiac arrhythmias, particularly any episodes of electromechanical dissociation, portend a poor outcome and should be aggressively treated. Renal failure and need for hemodialysis is rare among Sin Nombre virus infections but was reported for two HPS cases due to Andes virus in southern Argentina and Chile. Extracorporeal membrane oxygenation (an experimental procedure) should be considered when available if the serum lactate level exceeds 4 mmol/l and cardiac index <2.2 L/min/m^2.

Due to the extensive differential diagnosis, all patients should be treated for more common events, such as sepsis. A broad-spectrum antibiotic such as intravenous ceftriaxone or ampicillin-sulbactam, as well as doxycycline used to treat rickettsioses, ehrlichioses, plague, and tularemia, should be administered until either HPS is confirmed or another diagnosis is made.

7.8.3 Case Management in a Rural Setting

In rural settings without access to intensive care facilities, treatment of cases should focus on maintenance of blood pressure and oxygenation. In addition, broad-spectrum antibiotics such as suggested in Section 7.8.2 should be administered until either HPS is confirmed or another diagnosis is made. Intravenous crystalloid fluid should be used carefully so as not to exacerbate pulmonary edema. It is recommended that fluid balance be maintained, with replacement fluid administered according to the amount lost. In case of shock, it would be necessary to use such inotropic agents as dobutamine or dopamine, even in the absence of cardiac monitoring. Oxygen delivery should also be initiated early on, and a nonrebreathing mask could be used to ensure 100% oxygen concentration.

[1]For further information contact Dr. Delia Enría, Instituto Nacional de Enfermedades Virales Humanas, Monteagudo 2510, 2700 Pergamino, Argentina; Telephone: (54-477) 29712/14; Fax: (54-477) 33045; E-mail: enria@inevh.sld.arg.

8. PREVENTION AND CONTROL

The prevention guidelines offered here borrow heavily from experience in North America and the interim guidelines established by CDC following the initial outbreak of HPS in 1993 (*24*). Recommendations for personal risk reduction are given in Section 8.1. (For easy reproduction and distribution, a number of these risk reduction guidelines are presented in Annex 9.) Also below are prevention guidelines for health professionals caring for patients infected with hantavirus (Section 8.2), people working with body fluids or tissue potentially infected with hantaviruses in the laboratory (Section 8.3), and researchers involved in handling and processing rodents (Section 8.4). Ultimately, each country of the Americas should establish prevention guidelines appropriate to its own circumstances.

There is no effective vaccine for the hantaviruses in the Americas. Viruses causing HFRS are antigenically distant, and their vaccines should not be used until future research proves otherwise.

Preventing contact with rodents and their excreta is the cornerstone to primary prevention of hantaviral illness in the Americas and throughout the world. Rodents of the subfamily *Sigmodontinae* are the reservoirs of hantaviruses that cause HPS. Most of the subfamily are field rodents that occupy areas away from urban population centers. However, they may enter areas of human habitation, particularly under circumstances of high rodent density and competition for shelter and food resources. Eradication of rodent hantavirus host species is neither desirable nor feasible due to the large number of species implicated and their wide distribution and abundance. Further, in regions where plague is endemic, control of rodents without concurrent control of fleas may increase the risk of human plague as the rodent fleas seek an alternative food source. The best currently available approach for hantavirus disease control and prevention is risk reduction through the use of precautions against infection by rodent excreta, combined with environmental hygiene practices that deter rodents from colonizing the home, recreational, and work environments.

8.1 PERSONAL RISK REDUCTION

Personal risk reduction is based on principles of rodent and infection control. Below are specific recommendations for reducing rodent shelter and food sources in and around the home, recommendations for eliminating rodents inside the home and preventing them from entering the home, precautions for preventing hantavirus infection while rodent-contaminated areas are being cleaned up, prevention measures for persons who have occupational exposure to wild rodents, and precautions for campers and hikers.

These guidelines can be readily followed with minimal investment in expensive or hard-to-use equipment or materials. They also can be applied generally to help reduce encounters with rodents and their excreta, and they do not require specialized skills in rodent species identification.

8.1.1 General Household Precautions in Affected Areas

Although epidemiologic studies are being conducted to identify specific behaviors that may increase the risk for hantavirus infection in humans, rodent control in and around the home will continue to be the primary prevention strategy (see Box 1). CDC has issued recommendations for rodent-proofing urban and suburban dwellings and reducing rodent populations around homes through habitat modification and sanitation.

8.1.2 Prevent Rodents from Entering the Home

A number of steps can be taken to prevent rodents from entering the home. A set of general guidelines is given in Box 2. These practices should be adapted to local circumstances.

In addition, if rodent nests are encountered while these prevention measures are being carried out, follow the

BOX 1. General precautions for residents of affected areas.

- Reduce the availability of food sources and nesting sites used by rodents inside the home.
- Eliminate rodents inside the home (see Box 3).
- Discourage children from playing with rodents or their nests, and advise them to tell their parents if they see rodents or their nests.
- Keep food (including pet food) and water covered and stored in rodent-proof metal or thick plastic containers with tight-fitting lids.
- Store garbage inside homes in rodent-proof metal or thick plastic containers with tight-fitting lids.
- Wash dishes and cooking utensils immediately after use and remove all spilled food.
- Dispose of trash and clutter.
- Use spring-loaded rodent traps in the home continuously.
- As an adjunct to traps, use rodenticide with bait under a plywood or plastic shelter (a covered bait station) on an ongoing basis inside the house.

BOX 2. General practices for the prevention of rodent infestation of homes.

- Use steel wool or cement to seal, screen, or otherwise cover all openings into the home that have a diameter of 0.5 cm or more.
- Place metal roof flashing as a rodent barrier around the base of wooden, earthen, or adobe dwellings up to a height of 30 cm and buried in the soil to a depth of 15 cm.
- Place 10 cm of gravel under the base of homes or under mobile homes to discourage rodent burrowing.
- Reduce rodent shelter and food sources within 30 m of the home.
- Cut grass, brush, and dense shrubbery within 30 m of the home.
- Use raised cement foundations in new construction of sheds, barns, outbuildings, or woodpiles.
- When possible, place woodpiles 30 m or more from the house and elevate wood at least 30 cm off the ground.
- Store grains and animal feed in rodent-proof containers.
- Near buildings, remove food sources that might attract rodents, or store food and water in rodent-proof containers.
- Store hay on pallets, and use traps or rodenticide continuously to keep hay free of rodents.
- Do not leave pet food in feeding dishes.
- Dispose of garbage and trash in rodent-proof containers that are elevated at least 30 cm off the ground.
- Haul away trash, abandoned vehicles, discarded tires, and other items that may serve as rodent nesting sites.
- Place spring-loaded rodent traps at likely spots for rodent shelter within 30 m around the home, and use continuously.
- Use a nationally approved rodenticide certified for outside use in covered bait stations at places likely to shelter rodents within 30 m of the home.

recommendations in Section 8.1.4. on the cleanup of rodent-contaminated areas.

8.1.3 Eliminating Rodents Inside the Home and Reducing Rodent Access to the Home

Rodent infestation can be determined by direct observation of the animals or inferred from the presence of feces in closets or cabinets or on floors or from evidence that rodents have been gnawing at food. If rodent infestation is detected inside the home or outbuildings, rodent abatement measures should be carried out (Box 3). The directions in Section 8.1.5 on special precautions should be followed if evidence of heavy rodent infestation is present (e.g., piles of feces or numerous dead animals) or if a structure is associated with a confirmed case of hantavirus disease.

Many rodenticides can be used; instructions on product use should always be followed. Products that are used outdoors should be specifically approved for exterior use. Any interior use of a rodenticide should be preceded by use of an insecticide to reduce the risk of plague transmission; fleas that may transmit plague may leave the body of trapped or poisoned animals. Insecticide sprays or powders can be used in place of aerosols if they are appropriately labeled for flea control. When rodent densities are high, rodenticides may be used to control populations before clearing or cutting tall grass or brush. If rodenticides are used in or around homes, precautions must be used to prevent accidental poisoning of children and domestic animals.

Trapping in the home should be done with snap traps that result in immediate death of the animal. Live traps or adhesive papers should not be used because virus excretion may continue. The dead animal should be disposed of as indicated in Box 3.

There is no reason to routinely test trapped animals for hantaviruses. Routine testing can potentially increase the public biohazard since more people would catch and handle rodents if they expected them to be tested. Also, a large sample size is required in order to get an accurate picture. Usually, only a small number of rodents are infected in a given locality, so routine testing of a few trapped animals is likely to give a false negative.

Predators are important in reducing the number of rodents, but increasing the number of household cats is

BOX 3. Eliminating rodent infestation: guidance for residents of affected areas.

- Before rodent elimination work is begun, ventilate closed buildings or areas inside buildings by opening doors and windows for at least 30 minutes. Use an exhaust fan or cross ventilation if possible. Leave the area until the airing-out period is finished. This airing may help remove any aerosolized virus inside the closed-in structure.
- Seal, screen, or otherwise cover all openings into the home that have a diameter of 0.5 cm or more. Then set rodent traps inside the house, using peanut butter, fruit, sugarcane, or other substitutes as bait. Use only spring-loaded traps that kill rodents.
- Next, treat the interior of the structure with an insecticide labeled for flea control, following label instructions. Insecticide sprays or powders can be used in place of aerosols if they are appropriately labeled for flea control.
- Rodenticides may also be used while the interior is being treated, as outlined below:
  - Remove dead rodents from the traps. Wear rubber or plastic gloves while handling rodents. Place the carcasses in a plastic bag containing a sufficient amount of a general-purpose household disinfectant to thoroughly wet the carcasses. Seal and double-bag the carcasses, then dispose of them by burying them in a hole 0.5–1 m deep or by burning. If burying or burning is not feasible, contact your local or state health department about other appropriate disposal methods. Rebait and reset all sprung traps.
  - Before removing the gloves, wash gloved hands in a general household disinfectant and then in soap and water. A hypochlorite solution prepared by mixing 3 tbsp of household bleach in 4.5 L of water may be used in place of a commercial disinfectant. When using the solution, avoid spilling the mixture on clothing or other items that could be damaged.
  - Thoroughly wash hands with soap and water after removing the gloves.
  - Leave several baited spring-loaded traps inside the house at all times as a further precaution against rodent reinfestation. Examine the traps regularly.
  - Disinfect traps no longer in use by washing in a general household disinfectant or the hypochlorite solution and ***rinsing*** clean. Disinfect and wash gloves as described above, and wash hands thoroughly with soap and water before beginning other activities.

not encouraged. Although they do not become infected and excrete virus, cats may bring rodents into the home and may contaminate the home after killing or eating rodents. Asian studies have suggested that cats may actually be a risk factor for human infection, although this was not found in the United States (*25*).

To date no hantavirus disease risk has been associated with rodents of the *Sciuridae* family (squirrels and chipmunks) or the groups of rodents used as food sources (guinea pigs, capybara, agouti, nutria, and tepisquintle).

8.1.4 Cleanup of Rodent-contaminated Areas

Areas with such evidence of rodent activity as dead rodents and rodent excreta should be thoroughly cleaned to reduce the likelihood of exposure to hantavirus-infected materials. Cleanup procedures must be performed in a manner that limits the potential for aerosolization of dirt or dust from all potentially contaminated surfaces and household goods (see Box 4).

Because hantaviruses are susceptible to standard disinfectants, these should be used extensively in cleaning. Household bleach diluted 1:10 in water is excellent for heavily contaminated areas but may damage many materials and dyes. Even common detergents will decrease viral infectivity, and the wetting action will diminish aerosol formation. The local health department should be consulted for advice on appropriate local brands and disinfectant concentrations.

Opening and cleaning buildings that have not been used for a period of time pose special problems. Rural schools, cabins, and storage sheds should be opened and allowed to ventilate for at least 30 minutes before entering to clean them (see Box 3). The delay will allow time for aerosols to decay and be diluted by outside air. Otherwise, infectious aerosols may be generated when rodents are disturbed and be retained within the room, protected from sunshine and the deleterious effect of ultraviolet light. Cleanup of the cabin should be accomplished as in Box 4*;* ***under no circumstance should a vacuum cleaner or a broom be used.***

Persons may elect to use surgical or painter's masks to protect the nose and mouth against larger particles, but they must be aware that no protection is afforded against small particle aerosols.

8.1.5 Special Precautions for Homes of Persons with Confirmed Hantavirus Infection or Buildings with Heavy Rodent Infestation

Special precautions are indicated for cleaning homes or buildings with heavy rodent infestation or that have been occupied by persons with confirmed hantavirus infection (see Box 5). Persons conducting these activities should contact the responsible local, state, or federal public health agency for guidance. These precautions may also apply to vacant dwellings that have attracted large numbers of rodents. Workers who are ei-

BOX 4. Cleanup of rodent-contaminated areas: guidance for residents of affected areas.

- Persons involved in the cleanup should wear rubber or plastic gloves.
- Spray dead rodents, rodent nests, droppings, and foods or other items that have been tainted by rodents with a general-purpose household disinfectant.
- Soak the material thoroughly and place in a plastic bag.
- When cleanup is complete (or when the bag is full), seal the bag, then place it into a second plastic bag and seal.
- Dispose of the bagged material by burying in a hole 0.5–1 m deep or by burning. If these alternatives are not feasible, contact the local or state health department concerning other appropriate disposal methods.
- After the above items have been removed, ***mop*** floors with a solution of water, detergent, and disinfectant. To avoid generating potentially infectious aerosols, do not vacuum or sweep dry surfaces before mopping.
- Spray dirt floors with a disinfectant solution. A second mopping or spraying of floors with a general-purpose household disinfectant is optional.
- Carpets can be effectively disinfected with household disinfectants or by commercial-grade steam cleaning or shampooing.
- Disinfect countertops, cabinets, drawers, and other durable surfaces by washing them with a solution of detergent, water, and disinfectant, followed by an optional wiping-down with a general-purpose household disinfectant.
- Rugs and upholstered furniture should be steam cleaned or shampooed. If rodents have nested inside furniture and the nests are not accessible for decontamination, the furniture should be removed and burned.
- Launder potentially contaminated bedding and clothing with hot water and detergent. (Use rubber or plastic gloves when handling the dirty laundry, then wash and disinfect gloves as described in Box 3.) Machine-dry laundry on a high setting or hang it to air-dry in the sun.

ther hired specifically to perform the cleanup or asked to do so as part of their work activities should receive a thorough orientation from the responsible health agency about hantavirus transmission, and should be trained to perform the required activities safely.

8.1.6 Precautions for Workers in Affected Areas Who Are Regularly Exposed to Rodents

Mammalogists, pest-control workers, and other persons who frequently handle or are exposed to rodents in the affected area are probably at higher risk for hantavirus infection than is the general public. The enhanced precautions warranted to protect those persons against hantavirus infection are shown in Box 6.

BOX 5. Special precautions for cleanup in homes of persons with hantavirus infection or buildings with heavy rodent infestation.

- A baseline serum sample, preferably drawn at the time these activities are initiated, should be available for all persons conducting the cleanup of homes or buildings with heavy rodent infestation. The serum sample should be stored at –20 °C.
- Persons involved in the cleanup should wear coveralls (disposable, if possible), rubber boots or disposable shoe covers, rubber or plastic gloves, protective goggles, and an appropriate respiratory protection device, such as a half-mask air-purifying (or negative-pressure) respirator with a high-efficiency particulate air (HEPA) filter or a powered air-purifying respirator (PAPR) with HEPA filters. Respirators (including positive-pressure types) are not considered protective if facial hair interferes with the face seal, since proper fit cannot be assured. Respirator practices should follow a comprehensive user program and be supervised by a knowledgeable person. Personal protective gear should be decontaminated upon removal at the end of the day. If the coveralls are not disposable, they should be laundered on site. If no laundry facilities are available, the coveralls should be immersed in liquid disinfectant until they can be washed.
- All potentially infective waste material (including respirator filters) from cleanup operations that cannot be burned or deep-buried on site should be double-bagged in appropriate plastic bags. The bagged material should then be labeled as infectious (if it is to be transported) and disposed of in accordance with local requirements for infectious waste.
- Workers who develop symptoms suggestive of HPS within 45 days of the last potential exposure should immediately seek medical attention. The physician should contact local health authorities promptly if hantavirus-associated illness is suspected. A blood sample should be obtained and forwarded with the baseline serum through the state health department to the appropriate reference laboratory for hantavirus antibody testing.

8.1.7 Precautions for Other Occupational Groups Who Have Potential Rodent Contact

Insufficient information is available at this time to allow general recommendations regarding risks or precautions for persons in the affected areas who work in occupations with unpredictable or incidental contact with rodents or their habitations. Examples of such occupations include telephone installers, maintenance workers, plumbers, electricians, and certain construction workers. Workers in these jobs may have to enter various buildings, crawl spaces, or other sites that may be rodent infested. Occasional cases have occurred among

such persons, but overall risk is very low (*76*). Recommendations for such circumstances must be made on a case-by-case basis after the specific working environment has been assessed and state or local health departments have been consulted.

8.1.8 Precautions for Campers and Hikers in the Affected Areas

There is no evidence to suggest that travel into the affected areas should be restricted. Most usual tourist activities pose little or no risk that travelers will be exposed to rodents or their excreta. However, persons engaged in such outdoor activities as camping or hiking should take precautions to reduce the likelihood of their exposure to potentially infectious materials (see Box 7).

BOX 6. Precautions for workers in affected areas who are exposed to rodents.

- A baseline serum sample, preferably drawn at the time of employment, should be available for all persons whose occupation involves frequent rodent contact. The serum sample should be stored at –20 °C.
- Workers in potentially high-risk settings should be informed about the symptoms of HPS and be given detailed guidance on prevention measures.
- Workers who develop a febrile or respiratory illness within 45 days of the last potential exposure should immediately seek medical attention and inform the attending physician of the potential occupational risk of hantavirus infection. The physician should contact local health authorities promptly if hantavirus-associated illness is suspected. A blood sample should be obtained and forwarded with the baseline serum to the appropriate reference laboratory for hantavirus antibody testing.
- Workers should wear a half-face air-purifying (or negative-pressure) respirator with eye protection or a PAPR equipped with HEPA filters when removing rodents from traps or handling rodents in the affected area. Respirators (including positive-pressure types) are not considered protective if facial hair interferes with the face seal, since proper fit cannot be assured. Respirator use practices should be in accord with a comprehensive user program and should be supervised by a knowledgeable person. Workers should wear rubber or plastic gloves when handling rodents or handling traps containing rodents. Gloves should be washed and disinfected before removal, as described earlier.
- Traps contaminated by rodent urine or feces or in which a rodent was captured should be disinfected with a commercial disinfectant or bleach solution. Dispose of dead rodents as described in Section 8.1.3.
- Persons removing organs or obtaining blood from rodents in affected areas should follow published safety guidelines (*56*).

8.2 RECOMMENDATIONS ON HOSPITAL ISOLATION PROCEDURES FOR PATIENTS WITH HANTAVIRUS PULMONARY SYNDROME

In North America, there is no evidence for person-to-person hantavirus transmission, and no health care workers involved in the care of HPS patients are known to have become infected with the virus (*27, 28*). In South America, however, there has been an outbreak of person-to-person transmission of Andes virus involving several health care workers (*43, 44, 48*).

Universal precautions with such barrier methods as gowns and gloves should be followed when caring for all hospitalized patients with HPS. In North America, there is insufficient evidence of interhuman transmission to warrant respiratory isolation procedures. Such procedures are practiced, however, in some hospitals until infection with SNV is confirmed, particularly in those regions where pneumonic plague and other respiratory transmitted infections are known to occur. Patients with respiratory disease should be managed with precautions appropriate to prevalent regional diseases.

In South America, if HPS is a consideration, universal precautions should be applied, surgical masks should be used, and the patient should be placed in a private room. These added safety measures are recommended, but each country should administer them based on its own epidemiological situation and local acute care facilities. Surgical masks are recommended because of the question of interhuman transmission with Andes virus

BOX 7. Reducing risk of hantavirus infection: guidance for hikers and campers.

- Avoid coming into contact with rodents and rodent burrows or disturbing dens, such as pack rat nests.
- Do not use cabins or other enclosed shelters that are rodent infested until they have been appropriately cleaned and disinfected.
- Do not pitch tents or place sleeping bags in areas in proximity to rodent feces or burrows or near possible rodent shelters (e.g., garbage dumps or woodpiles).
- If possible, do not sleep on the bare ground. Use a cot with the sleeping surface at least 30 cm above the ground. Use tents with floors.
- Keep food in rodent-proof containers.
- Promptly bury (or—preferably—burn, followed by burying, when in accordance with local requirements) all garbage and trash, or discard in covered trash containers.
- Use only bottled water or water that has been disinfected by filtration, boiling, chlorination, or iodination for drinking, cooking, washing dishes, and brushing teeth.

and other American viruses with which we have little practical experience. A surgical mask covering the mouth and nose will protect mucous membranes against droplets but will not protect against the inhalation of small-particle aerosols. In the previously mentioned Andes virus outbreak, the exact route of transmission was not defined, but small-particle aerosols were not implicated (*43, 44, 77*). If procedures which may be associated with generating high concentrations of droplets and small-particle aerosols, such as tracheostomy or intubation, are undertaken, additional protection is desirable, including goggles and a HEPA mask.

Intensive care unit staff should carefully adhere to the use of universal precautions, including surgical mask, gown, and gloves. If available, a private room should be used. If not, the risk for others in the ICU is very low. Even in the outbreak with person-to-person transmission, there were no cases among ICU staff and the effective contacts between cases were thought to occur before or shortly after hospital admission.

Studies to evaluate the potential for interhuman transmission of HPS-causing viruses are ongoing in South America, and recommendations for isolation procedures will evolve accordingly.

8.3 RECOMMENDED LABORATORY PRECAUTIONS WHEN WORKING WITH HANTAVIRUSES

Extensive experience with the hantaviruses that cause HFRS and a lesser experience with HPS indicate that infection has not been transmitted from clinical laboratory specimens. Viral antigens have been detected in necropsy specimens, and RT-PCR readily detects viral genetic material. Viral RNA has been found in tracheal aspirates and bronchial washings and has been detected by RT-PCR in blood and plasma obtained early in the course of disease. The implications of these findings for the infectivity of blood or tissues are unknown, but the potential for transmission may be present.

On the basis of available evidence regarding risk for laboratory-acquired hantavirus infection, at least Biosafety Level 2 (BSL-2) facilities and practices are recommended for laboratory handling of sera from persons potentially infected with the agents of HPS (see Annex 4). It is recommended that universal precautions be followed whenever human blood is handled. The use of a certified biological safety cabinet is recommended for all handling of human body fluids when potential exists for splatter or aerosolization.

Manipulation of disease-causing hantaviruses in cell culture and rodent tissues should be performed at Biosafety Level 3 (BSL-3) (Annex 4). Four laboratory workers were infected while working with cell culture-adapted Hantaan virus. Although the procedures associated with infection are unclear, all four persons worked repeatedly with hantavirus cultures and performed centrifugation of concentrated virus (*54*). This has led to recommendations for special precautions when working with virus concentrates (*78*).

Laboratory transmission of Old World hantaviruses from rodents to humans via the aerosol route is well documented (*78*). Exposures to rodent excreta, fresh rodent necropsy material, and animal bedding are associated with risk. In animal holding areas, the period of exposure to infectious animal excreta required for transmission may be short. For this reason, experimental rodent inoculations should be performed at BSL-3 with respiratory protection, or at BSL-4 (*78*). For more information, see Annex 4.

8.4 GUIDELINES FOR HANDLING AND PROCESSING RODENTS

Although inhalation of aerosolized virus is thought to be the most common route of infection, it is also possible that human infection occurs when virus or virus-contaminated materials are introduced into broken skin, conjunctivae, or mucous membranes, or when accidentally ingested with food or water (*56*). Infection has been transmitted by bite. Personnel collecting blood or tissue samples from live or freshly killed rodents are at risk for exposure to virus in the blood and organs of hantavirus-infected animals. The most important prophylactic measure for personnel who are trapping, handling, bleeding, or dissecting rodents is to be aware of potential routes of infection and carefully avoid conditions that may lead to infection. Fundamental precautions include minimizing exposure to rodent excreta, avoiding the creation of aerosols, always wearing proper personal protective equipment, properly anesthetizing animals before handling them, and carefully disinfecting contaminated working spaces, equipment, and clothing. Precautions should also be used when handling frozen tissues or blood taken from potentially infected animals (*56*).

More detailed information on precise rodent trapping and processing procedures and recommended precautions can be found in a report entitled "Methods for Trapping and Sampling Small Mammals for Virologic Testing," published by CDC (*56*). A Spanish version of this document is also available through the Pan American Health Organization (PAHO).

The control and prevention recommendations in this report represent general measures to minimize the like-

lihood of human exposure to hantavirus-infected rodents in areas affected by the outbreak of hantavirus-associated respiratory illness. Many of the recommendations may not be applicable or necessary in unaffected locales. The impact and utility of the recommendations will be assessed as they are implemented and will be continually reviewed by PAHO/WHO, CDC, and national, state, and local health agencies as additional epidemiologic and laboratory data related to HPS become available.

8.5 HEALTH EDUCATION

Health education efforts for HPS are intended to enhance recognition and management of disease and to prevent cases by reducing human contact with rodents. Amelioration of the impact of clinical disease depends on health care providers having adequate knowledge and skills. Prevention relies on the knowledge and ability of the general public to reduce their contact with rodents. Multiple communication channels and messages should be used to reach these two target populations.

This section outlines the numerous communication channels, messages, and issues surrounding HPS health education for health professionals (Section 8.5.1) and for the general public (Section 8.5.2). Suggested materials and services for HPS prevention are also provided (Section 8.5.3). Specific HPS educational materials available for use in educating health professionals and the general public are listed in Annex 5. Examples are also provided of health education methods in Argentina (Annex 6), Chile (Annex 7), and the United States of America (Annex 8).

8.5.1 Education for Health Professionals

Since early recognition of a case may improve the patient's chance of survival (through the application of appropriate supportive measures), physicians and other medical personnel play an important role in early case identification. Therefore, educational programs should be targeted to all medical personnel and should focus on the clinical features of the disease, diagnosis, patient management and treatment, and prevention recommendations. It is also necessary for other health professionals, such as public health officials, epidemiologists, laboratorians, and public health educators, to be knowledgeable of the latest research, including those results particularly pertinent to their region, in order to maintain an active surveillance system and to develop effective community-based programs. Additionally, materials targeting the general public should be made available to physicians to distribute to their patients.

8.5.2 Education for the General Public

Health education programs for the general public can be divided into two types of interventions: preventive measures during nonoutbreak situations and rapid response when there is a suspected case. Prevention is the best strategy and can be approached by following simple precautions to reduce human contact with rodents. The information provided in Sections 8.1 through 8.4 lists numerous step-by-step recommendations to reduce contact between humans and rodents. Promoting these recommendations in areas with large rodent populations should reduce the risk of infection. However, cases may still occur, and an effective health education response must be implemented quickly to ensure that patients seek medical attention at an early and appropriate time, to prevent additional cases, and to relieve the public's concerns.

Preventive Measures During Nonoutbreak Situations

Health education programs targeting the general public during nonoutbreak situations should accomplish three goals: inform about the disease, help to identify personal risk, and provide prevention recommendations. The messages should be tailored to the cultural and socioeconomic status of the at-risk populations, their level of disease risk, and the rodent habits, population density, and infection prevalence. It is particularly important to emphasize the following common areas of confusion:

- Not all species of rodents are reservoirs for HPS-associated hantaviruses. In order to develop appropriate messages for the public, health professionals need to be informed about the differences among rodent species, such as geographic distribution and behavior of rodent reservoirs, and which of the local species are particularly dangerous. For example, *Rattus norvegicus* is a common rodent found in urban areas. The number of *R. norvegicus* found near and in the home or the workplace should be reduced for sanitary reasons, but not for controlling HPS since this species is not a carrier of HPS-associated hantaviruses.
- Among those rodent species that are reservoirs for HPS-associated hantaviruses, infection is common and every rodent is potentially dangerous, but the risk of human disease is very low.
- While direct contact with rodents or their excreta is potentially dangerous and should be avoided, the main route of human infection is aerosols that may be generated by the rodents or from the rodent excreta.

In most communities, it will be impossible to completely eliminate rodents around the home or worksite. Therefore, messages should be based on managing human contact with the rodent population using the recommendations presented in this section.

Because supportive care is important to survival and patients may deteriorate rapidly, those who have symptoms suggesting HPS must be educated to seek medical attention. The wording of the message will vary depending on the cultural context, proximity of hospitals, diagnostic capability available, and other diseases endemic to the area.

Messages and materials should be directed at the many diverse groups within the general public. Multiple cultural perspectives, such as needs, values, and beliefs for each group, should be considered and addressed. Human contact with the rodent reservoirs tends to be higher in rural areas. Therefore, obstacles commonly encountered in these areas, such as lower economic status, lower reading levels, use of a local language, and accessibility difficulties, should be considered when developing the educational program.

Schools, parks, tourist areas, grocery stores, doctors' offices, health centers, campgrounds, and other areas frequently visited by the target population are possible sites to promote prevention messages. Parks, tourist areas, and campgrounds are particularly important to target because of the increased number of rodents in these settings.

Rapid Response When There Is a Suspected Case

Health education works in conjunction with clinical, laboratory, and epidemiology disciplines when responding to a suspected case. Once the risk factors associated with disease transmission have been identified and prevention measures have been developed, the population at risk can be targeted with education materials and campaigns. Additionally, intensive efforts should be made in the local communities and with the family members of any cases to provide information on the warning signs and symptoms of hantavirus infection, as well as prevention and control measures.

8.5.3 Materials and Services

Many materials and services can be used to educate health professionals and the general public. These include videotapes, slide sets, print materials, the Internet, mass media news coverage, public service announcements, national campaigns, audio conferences, seminars, and telephone hot lines. Annex 5 lists brochures, posters, pamphlets, and other educational materials provided by CDC. The information provided in the materials can be easily adapted to meet local needs.

Videotapes

A videotape can provide numerous messages within a short amount of time. Primarily used as a teaching tool, videotapes can reach a large audience and provide for repetitious viewing to clarify points and recommendations. For example, videotapes may be used to improve viewer comprehension of prevention recommendations by demonstrating specific cleanup procedures of rodent-contaminated areas. Videotapes do not provide any interaction between health educators and the general public, so they should be used as part of a comprehensive prevention program that employs other information dissemination methods and materials.

CDC has developed two videotapes on HPS. *Preventing Hantavirus Disease* targets the general public, and *A New Hantavirus* targets health professionals. Both videos are available in English and Spanish, in both VHS and PAL formats, and are free of charge. The two videos are described in Annex 5, and CDC's overall health education program is profiled in Annex 8.

Slide Sets

Slide sets are relatively inexpensive tools for teaching health professionals about HPS. As new information is discovered, slide sets can be updated and adapted easily. For example, slide sets may be used to show chest X-rays from patients with HPS to give a better picture of findings upon clinical presentation. CDC has developed a slide set with accompanying text which is available for public health workers, epidemiologists, medical professors, or infectious disease physicians for their use in giving presentations to their own audiences. The slides can be downloaded from the CDC Internet site in PowerPoint™ format in either English or Spanish. The slides provided may be combined with other slides addressing the local situation.

Print Materials

Brochures, posters, and pamphlets can be used to educate both health professionals and the general public. Different types of print materials are more effective de-

pending upon the amount of information presented. If numerous facts must be presented, brochures and pamphlets are beneficial. These materials are effective when introducing new information, presenting guidelines, or serving as a reference for suggested recommendations, such as the recommendations for keeping homes rodent-proof. In comparison, posters should be used to present small amounts of information. They can be placed on the walls of health centers, grocery stores, doctors' offices, and other common places, serving as a quick reference or constant reminder. For example, posters can be placed in rural grocery stores serving as a reminder to place food in sealed containers. As with any print material, consideration must be made for those who are unable to read or who read at a lower level or use another language. Pictures or drawings can help communicate messages to these audiences.

Educational efforts in Argentina included door-to-door distribution of brochures by health workers. This method ensured that families received information about HPS and also provided a mechanism to answer individual questions. Argentina's health education program is described in Annex 6.

The Internet

The Internet is an easy and quick delivery channel to educate health professionals and the general public about HPS. The information presented on an Internet Web site can be easily categorized and users can select what is useful to them, thereby satisfying the needs of various audiences. Additionally, the Internet is inexpensive, can be easily updated, and can be accessed worldwide. Although probably directly accessible to only a small fraction of the target audience, the Internet still has the capability to reach large audiences through downloaded information. CDC has an extensive Internet site on HPS. Information can be downloaded freely, reproduced, and used in educational publications or as a teaching supplement. The CDC HPS Web page (http://www.cdc.gov/ncidod/diseases/hanta/hantvrus.htm) can also be linked to a local Internet page.

Mass Media and Public Service Announcements

The use of the mass media can be quite successful in reaching target audiences quickly. This is especially important during an outbreak. Television, radio, and newspapers can be helpful in disseminating information to large audiences, but it is important that the disseminated messages be correct. A public health liaison can be identified to work specifically with the media to help ensure accuracy in news coverage.

Public service announcements (PSAs) are another way to reach large audiences. While the content of PSAs can be controlled, the times they are broadcast on either radio or television are chosen by the stations, which may not be the most popular listening or viewing times. The Ministry of Health in Chile has developed numerous PSAs for television, with topics ranging from rodent-proofing homes to cleaning cabins before summer vacation. Chile's PSA campaign is described in Annex 7.

National Campaigns

National campaigns can serve as an effective medium to bring information about HPS to large audiences at one time. Since many differing audiences within the general public need to be reached simultaneously, numerous messages and communication channels must be used. Successful campaigns utilize many of the other materials and education tools described in this section. Even if the epidemic is at the local level, national campaigns provide the opportunity to educate the general public about HPS and allay fears, abolish rumors and exaggerations, minimize stigmatization of individuals from affected areas, and prevent economic losses from a consumer boycott of products manufactured in affected areas. Since the media are usually involved in national campaigns, they must be educated about HPS to ensure information is reported accurately and responsibly. The recent appearance of HPS, with its dramatic clinical picture, has generated an inordinate amount of media interest in the United States and other countries. Education of the media will also improve the quality of their reporting. The description in Annex 7 of the national campaign in Chile includes much information on that country's use of the mass media.

Audio Conferences

Numerous health care professionals, public health workers, and medical and nursing students from several regions in a country can all participate simultaneously in listening to presentations via a speaker telephone. Prior to the audio conference, participants are provided with a copy of slides and a syllabus for each topic discussed. This is a simple and fairly inexpensive way (depending on long distance telephone services and rates) to provide health care professionals with up-to-date informa-

tion in a timely manner. It also provides a mechanism for the listener to interact with hantavirus experts, better addressing specific needs and questions. Additionally, the materials provided can be used to teach others. HPS topics that might be addressed in audio conferences include epidemiology, ecology, clinical features, patient management, diagnostics, pathology, and health education and prevention.

Seminars

Regional or national hantavirus experts can conduct seminars on all aspects of the disease for physicians and health care providers in their communities or through professional associations. They also allow for interaction among participants and immediate feedback on content and future needs.

Telephone Hot Lines

A telephone hot line is an inexpensive mechanism for health educators to answer questions from both the general public and health professionals. Additionally, callers can be asked to help identify topics that are important to them, as well as to identify topics not addressed in the educational programs. A telephone hot line may also serve as a mechanism for the public to request print materials to be sent by mail or fax.

2. THE VIRUSES

Hantaviruses are lipid-enveloped, spherical viruses of 80 to 110 nm in diameter. The RNA genome is tri-segmented, with the large (L) segment approximately 6,500 nucleotides long, the middle (M) segment approximately 3,600–3,800 nucleotides long, and the small (S) segment approximately 1,700–2,100 nucleotides long (*4*). The L segment encodes a viral polymerase, the M segment encodes G1 and G2 envelope glycoproteins, and the S segment encodes the N nucleocapsid protein.

Phylogenetic analysis of rodent-borne hantavirus genes has revealed three main lineages. While HFRS-causing viruses are linked to an Old World lineage, all HPS-associated viruses have a common New World lineage and are associated with members of a single rodent subfamily (*Sigmodontinae*) of the family *Muridae* (*4, 5*). Some of the sigmodontine-derived viruses are clearly independent species based on genetic evidence, serology, and/or reservoir-host association (Table 1); others are in the process of evaluation (Table 2), as are our criteria for defining a hantavirus species. At least 13 hantavirus species have been identified exclusively in the Americas, and 6 have been shown to cause HPS (Table 1). The various HPS-causing hantaviruses generally differ by no more than 30% at the nucleotide level. Serum antibodies of HPS patients cross-react strongly with other New World viruses, but to varying degrees with Old World hantavirus antigens.

No evidence of genetic reassortment with previously recognized Old World hantaviruses was found in the initial characterization of Sin Nombre virus, and proven natural reassortment events have been restricted to different genotypes of SNV (*6, 7*). All known SNV strains share at least 90% nucleotide sequence homology and even higher amino acid sequence homologies. Natural reassortment may result in different nucleotide sequence homologies for one gene segment as compared to the other two, but this has not yet been related to differences in viral pathogenicity. Therefore, it is unlikely that genetic reassortment with other viruses accounts for the newly recognized pathogenicity of HPS-causing viruses. Rather, HPS and HPS-causing hantaviruses have likely existed in the Western Hemisphere for many years despite only recently having been detected.

TABLE 1. Viruses of the genus *Hantavirus*, family *Bunyaviridae.*

Virus	Abbr.	Original source	Location	Geographic distribution of rodent host[a]	Human disease	Isolated in cell culture
Murinae subfamily-associated viruses						
Hantaan	HTN	*Apodemus agrarius*	Korea	Asia, Europe	HFRS[b]	yes
Seoul	SEO	*Rattus norvegicus, R. rattus*	Korea	Asia, Europe, the Americas	HFRS	yes
Dobrava-Belgrade	DOB	*Apodemus flavicollis*	Slovenia	Europe, Middle East	HFRS	yes
Thai-749	THAI	*Bandicota indica*	Thailand	Asia	unknown	yes
Arvicolinae subfamily-associated viruses						
Puumala	PUU	*Clethrionomys glareolus*	Finland	Europe, Asia	HFRS	yes
Prospect Hill	PH	*Microtus pennsylvanicus*	Maryland	N. America	unknown	yes
Tula	TUL	*Microtus arvalis*	Russia	Europe	unknown	yes
Khabarovsk	KBR	*Microtus fortis*	Russia	Asia	unknown	yes
Topografov	TOP	*Lemmus sibiricus*	Siberia	Russia, Asia, N. America	unknown	yes
Isla Vista	ISLA	*Microtus californicus*	California	N. America	unknown	no
Sigmodontinae subfamily-associated viruses						
Sin Nombre	SN	*Peromyscus maniculatus*	New Mexico	N. America	HPS[c]	yes
New York	NY	*Peromyscus leucopus*	New York	N. America	HPS	yes
Black Creek Canal	BCC	*Sigmodon hispidus*	Florida	The Americas	HPS	yes
Bayou	BAY	*Oryzomys palustris*	Louisiana	Southeastern United States	HPS	yes
Caño Delgadito	CANO	*Sigmodon alstoni*	Venezuela	S. America	unknown	yes
Río Mamore	RM	*Oligoryzomys microtis*	Bolivia	S. America	unknown	yes
Laguna Negra	CHP	*Calomys laucha*	Paraguay	S. America	HPS	yes
Muleshoe	MULE	*Sigmodon hispidus*	Texas	The Americas	unknown	no
El Moro Canyon	ELMC	*Reithrodontomys megalotis*	California	N. America	unknown	no
Río Segundo	RIOS	*Reithrodontomys mexicanus*	Costa Rica	Mexico, Central America	unknown	no
Andes	AND	*Oligoryzomys longicaudatus*	Argentina	S. America	HPS	yes
Insectivore-associated virus						
Thottapalayam	TPM	*Suncus murinus*	India	Asia	unknown	yes

[a]Given as approximate distribution; many rodent species occur focally, many others have widespread distributions.
[b]HFRS = hemorrhagic fever with renal syndrome.
[c]HPS = hantavirus pulmonary syndrome.

TABLE 2. Genotypes of Sigmodontine-associated hantavirus under evaluation.

Virus	Original source	Location	Human disease
Monongahela	*Peromyscus maniculatus*	United States	HPS
Blue River	*Peromyscus leucopus*	United States	Unknown
Oran	*Oligoryzomys longicaudatus*	Argentina	HPS
Lechiguanas	*Oligoryzomys flavescens*	Argentina	HPS
Bermejo	*Oligoryzomys chacoensis*	Argentina	Unknown
Maciel	*Necromys benefactus*	Argentina	Unknown
Pergamino	*Akodon azarae*	Argentina	Unknown
Juquitiba	Unknown	Brazil	HPS
HU39694	Unknown	Argentina	HPS

3. RODENT ECOLOGY AND EPIZOOLOGY

Murid rodents (order *Rodentia,* family *Muridae*) are the natural hosts and reservoirs of hantaviruses. The fossil record provides evidence for the presence of murid rodents for at least the past 20 million years in North America and 3.5 million years in South America (*8*). Murids are currently found in a wide variety of habitats throughout the Americas. They shelter in burrows or crevices, under logs or other objects, in hollow trees or logs, or in nests built on the ground or in bushes or trees. Although principally nocturnal, they may be diurnal and are usually active throughout the year. Females often produce several litters annually, and breeding may occur throughout the year in warm regions. Most individuals probably live less than two years; however, the high reproductive potential of certain species sometimes results in a large increase in population. This is often followed by a sudden drop in numbers when food supplies in a given area are exhausted. These fluctuations may show a periodicity of around three or four years in some species and habitats (*8*).

Rodents of the murid subfamily *Sigmodontinae,* implicated as hosts of HPS-causing viruses, are primarily associated with rural environments, but some are considered habitat generalists. The propensity of rodents to enter human habitation and surrounding buildings is important. This characteristic of the deer mouse was an underlying factor in the 1993 epidemic in the southwestern United States. Fortunately, some common rodents closely associated with humans (e.g., the common house mouse, *M. musculus*) belong to other subfamilies and are not important reservoirs of hantaviruses.

Each hantavirus is generally associated with a single rodent host species. Thus, the range of its predominant rodent host species restricts the distribution of any particular virus. Viral distribution may occur throughout the host range or may be restricted to a smaller portion of the range. High levels of concordance exist between host and hantaviral phylogenies, supporting the long-term and likely coevolutionary relationship between virus and host. This observation adds further evidence to support the ancient presence of New World hantaviruses in the Western Hemisphere. Except for a single virus, which may be associated with an insectivore, each major branch of the viral phylogenetic tree is associated with a different subfamily of rodents (*4, 5*). All known HPS-related hantaviruses of the Western Hemisphere are associated with the *Sigmodontinae* subfamily of *Muridae* rodents. Several other viruses commonly found in North America are associated with the subfamily *Arvicolinae* but are not known to cause human disease. Old World hantaviruses responsible for HFRS are associated with the subfamily *Murinae* or some members of the subfamily *Arvicolinae.*

Hantavirus infection in the natural rodent host results in chronic, apparently asymptomatic infection. Despite the presence of serum neutralizing antibody, infectious virus may be persistently shed in rodent urine, feces, and saliva.

Horizontal transmission via infectious aerosols among rodents in the laboratory is well documented (*9, 10*). In the field, rodent seroprevalence generally increases with body weight, and therefore age, highlighting the predominant role of horizontal transmission in viral maintenance within reservoir populations (*14*). The frequency of wounds has also been shown to be correlated with antibody seroprevalence in rodents, suggesting a role for biting and aggressive encounters in viral transmission among rodents (*11*). Pups of infected dams demonstrate circulating maternal antibodies, but no definitive evidence of vertical viral transmission exists. Thus, the maintenance of hantaviruses in their rodent reservoirs is mainly through infections acquired during post-weaning intraspecific aggressive encounters.

The view of a single virus infecting a single rodent species may be somewhat oversimplified (*12*). Numerous studies have reported high rates of hantaviral infection among several members of a single genus (*13*). For example, while *P. maniculatus* is agreed to be the

primary reservoir for SNV, *P. boylii*, *P. truei*, and *P. leucopus* have also shown high rates of antibody reactive to SNV (*14*). This observation could represent circulation of a related virus and cross-reactivity to SNV-specific assays, or genuine infection with SNV among other *Peromyscus* species. One explanation for such observations is that in instances of high rodent density and increased probability of interspecific encounters, viral transmission to secondary host species (i.e., "spillover") may occur (*14*). Conversely, in instances of low rodent density and decreased probability of interspecific encounters, nonprimary rodent host species are less likely to show evidence of secondary infection. The taxonomy of New World rodents requires further work to separate and define individual species and their virus associations.

4. EPIDEMIOLOGY OF HUMAN DISEASE

These guidelines focus on the epidemiology of hantavirus pulmonary syndrome (HPS), a disease thus far reported only in the Western Hemisphere. No cases are known to have occurred in Mexico, Central America, or the Caribbean. HPS has been linked to at least six different viruses, with modest clinical differences noted between cases infected with differing viral species. This paper formulates the control and treatment of HPS as a single disease entity until sufficient evidence exists to discriminate it further.

4.1 NORTH AMERICA

As of 9 October 1998, 221 cases of HPS had been confirmed in 29 U.S. states and 3 Canadian provinces (Table 3). Cases have been predominantly from rural areas in the western half of the continent, on either side of the Rocky Mountains. While no cases have been confirmed in Mexico, the range of the primary North American rodent host, *P. maniculatus*, covers the northern half of that country. In addition, four HPS cases in the United States have occurred in areas near the border with Mexico.

In North America, at least four distinct hantaviruses have been associated with HPS. Although the majority of cases are thought to have been the result of Sin Nombre virus infection (*15*), New York (*16*), Bayou (*17*), and Black Creek Canal (*18*) viruses are known to have caused six cases of HPS in the eastern and southeastern United States. The deer mouse, *Peromyscus maniculatus*, is recognized as the primary rodent reservoir of SNV (*19*), while the white-footed mouse (*Peromyscus leucopus*) (*20*), the rice rat (*Oryzomys palustris*) (*21*), and the cotton rat (*Sigmodon hispidus*) (*22*) are believed to be the primary rodent reservoirs for New York, Bayou, and Black Creek Canal viruses, respectively.

4.1.1 United States of America

The initial recognition of HPS in the spring of 1993 stemmed from an epidemic of approximately 27 cases in the southwestern United States. Since then, retrospective analysis of HPS has uncovered cases occurring as far back as 1959. While smaller clusters of two or three cases occurring among co-workers or family members have been reported, the majority of cases since 1993 have occurred sporadically at a rate of 20 to 40 cases per year throughout the United States, suggesting an uncommon yet endemic pattern of occurrence. The common, widespread presence of hantavirus-infected rodents

TABLE 3. Number of hantavirus pulmonary syndrome cases reported in the Americas.

	Number of cases as of 31 December 1997	Most recent data—third quarter, 1998
North America	205	221
United States	181	196
Canada	24	25
South America	208	239
Argentina	133	142
Brazil	6	13
Chile	32	46
Paraguay (*52*)	35	35
Uruguay	2	3
Total	413	460

contrasts with the less-understood and rare circumstances of transmission to humans.

HPS cases have occurred in all months, but are less frequent during the winter months of December, January, and February. It is unclear if human behavioral or rodent ecological factors play a greater role in the observed seasonal pattern, but it is most likely a combination of both factors.

HPS patients range in age from 11 to 69 years (median = 37) and show a slight male predominance (61%). The disease has been notably rare in young children, with only nine cases (5.2%) in children under 18 years old (*23*). The racial and ethnic distribution of cases resembles that of the rural western United States. The possible role of genetic factors remains to be elucidated.

Twenty-four diagnosed HPS cases in the United States occurred prior to 1993, and the majority of these were confirmed through analysis of stored autopsy tissue. Of the first 23 cases of HPS occurring in 1993, 15 (65%) died as a result of their illness. The overall case fatality rate of HPS cases in the United States is 44%. However, this has steadily declined since the time of the initial outbreak in 1993; cases with onset of illness after 1 January 1994 had a case fatality rate of approximately 35%. Of those patients with onset of illness during 1997, 3 of 17 (18%) did not survive their illness. The apparent decreasing mortality of HPS can most likely be attributed to improved clinical management rather than changes in the virus or a specific pharmacological therapy. In addition, increased awareness among clinicians and improved diagnostic capabilities have undoubtedly led to the detection of more mild illnesses and improved characterization of the full spectrum of clinical disease.

HPS cases have been associated with activities such as inhabiting dwellings with indoor rodent populations, occupying previously vacant cabins or other dwellings, cleaning barns and other outbuildings, disturbing rodent-infested areas, residing in or visiting areas in which the rodent population has shown a marked increase in density, trapping rodents, and handling live or dead rodents or their excreta (*24–26*). Activities such as these may have occurred in the context of residential, recreational, or occupational exposures. However, the precise events resulting in human infection are unclear for most cases, since many potential exposures often occur in the weeks leading up to onset of illness.

Serologic testing of household case contacts and persons occupationally at risk for rodent exposure has generally shown less than 1% background seroprevalence of antibody reactive to SNV, supporting the conclusion that asymptomatic infection with HPS-causing hanta-viruses is rare. In addition, there is no evidence of person-to-person transmission of HPS-causing hantaviruses in North America. In one study of 266 health care workers with exposure to HPS patients or their body fluids, none tested positive for SNV antibodies (*27*). Similarly, all reported household or occupational clusters of two or more HPS cases in the United States showed ample evidence of rodent exposure for all cases involved, thus casting doubt on the likelihood that person-to-person transmission was responsible for the observed cluster (*28*).

4.1.2 Canada

For surveillance purposes, Canada has adopted the HPS case definition of the U.S. Centers for Disease Control and Prevention (CDC) (*29*). As of 31 December 1997, 24 laboratory-confirmed HPS cases had been reported and, as of 7 March 1998, one additional case had been reported. All 25 cases occurred in the three westernmost provinces—British Columbia, Alberta, and Saskatchewan—which represent approximately 25% of the Canadian population (*30*). The earliest known HPS case occurred in Alberta in 1989 and was identified retrospectively. Since 1994, when HPS was first recognized in Canada, five cases per year, on average, have occurred. More than 40% of cases have occurred during the months of April, May, and June. Alberta, representing approximately 9% of the Canadian population, has reported 64% (16 of 25) of the HPS cases. Overall, cases have ranged in age from 15 to 62 years (mean = 39.5 years); 68% (17 of 25) have been male and 32% (8 of 25) have died. Of those patients with onset of illness since 1 January 1997, one of eight (13%) did not survive the illness. The majority of cases were most likely exposed to SNV during farming and domestic activities in rural areas. Single cases have also been linked to occupational exposures during military exercises, cleanup of a lumber mill, and a wildlife survey. The characteristics of HPS in Canada appear to be similar to those of cases described in the U.S. (*30*).

Rodent surveys have shown the presence of Sin Nombre and Sin Nombre-like viruses in deer mice across Canada, with varying seroprevalence. Landscape composition in Canada was found to be a more important predictor of rodent seroprevalence than were such factors as season, viral strain, climate, buildings, or association with human disease (*31*).

4.2 CENTRAL AMERICA AND THE CARIBBEAN

No cases of HPS are known to have occurred in Central America or the Caribbean. However, the range of

Sigmodon hispidus, the probable host of Black Creek Canal virus, extends from the southeastern United States, through Central America, and into northern South America. In addition, Río Segundo virus has been identified with the harvest mouse, *Reithrodontomys mexicanus*, in Costa Rica but has not been linked to human disease (*32*). Species that inhabit portions of the Caribbean are more likely to be Old World members of the *Murinae* subfamily of rodents, such as the Norway rat. The absence of HPS in the Caribbean could be the result of the relative infrequency in the region of rodent host species of the *Sigmodontinae* subfamily.

4.3 SOUTH AMERICA

In South America, the presence of hantavirus-infected *Rattus norvegicus* has been known since the 1980s. Various studies conducted during that decade found up to 56% of captured rats seropositive for antibodies reactive to Hantaan virus antigen (*33, 34*). Other studies conducted near that time provided serologic evidence of past human infection in Brazil, Argentina, Bolivia, and Uruguay (*35, 36*).

In December 1993, following the outbreak in the United States, HPS was diagnosed in three people in Brazil (*37*). Active surveillance also led to the detection of several cases in Argentina. Currently, there are several genetically distinguishable viruses associated with HPS in South America and several others not known to cause disease (Tables 1 and 2). By the third quarter of 1998, 239 cases of HPS had been reported from five countries of South America. While cases have occurred throughout the year in an endemic fashion similar to that seen in North America, several clusters account for more than a quarter of all recognized cases on the continent. These clusters have generally occurred from September to January (spring and summer in the Southern Cone) in diverse habitat regions. A country-by-country synopsis of HPS activity will help illustrate the unique epidemiologic features of the disease in each country.

4.3.1 Argentina

As of 7 March 1998, 142 cases had been reported in Argentina. They were principally from Salta and Jujuy provinces in the northwest, Santa Fe and Buenos Aires provinces in the central part of the country, and Río Negro, Chubut, and Neuquen provinces in the south (*38, 39*). The mean age of HPS cases was 34.7 years, with a range of 4 to 71 years. Argentina has seen a larger proportion of pediatric cases than the United States (*40*). The overall case fatality rate of HPS in Argentina is approximately 44%.

Following the 1993 outbreak in North America, active, prospective, and retrospective surveillance was undertaken of patients presenting with fever and unexplained respiratory distress syndrome between 1987 and 1995. In central Argentina, HPS was found during surveillance conducted for suspected cases of leptospirosis and Argentine hemorrhagic fever for which laboratory tests were negative. In northern Argentina, local physicians in Orán, in Salta province, had been reporting case clusters of an acute respiratory distress syndrome of unknown etiology since the 1980s. In the early 1990s, *Leptospira interrogans* was identified as the causative agent of some of these illnesses. However, in 1995, serological studies of cases showed hantavirus as the etiologic agent of disease in some of the remaining undiagnosed cases.

In the south, a cluster of three family members with illness was identified in the province of Río Negro in March 1995. Investigation of this cluster led to the characterization of Andes virus as the etiologic agent in southern Argentina (*41*). Andes virus was shown to represent a distinct lineage from SNV (*41*) but to be most closely related to other sigmodontine hantaviruses. It differed from New World hantaviruses of the North American Sin Nombre complex by more than 20% at the amino acid level in the G2 protein region. At least seven viral genotypes associated with different rodent reservoirs have been found circulating in the country, four of which have been linked to HPS (*42*).

Between September and December 1996, an outbreak of HPS occurred in the same region of Río Negro, affecting at least 18 people. Four of the 18 cases were physicians who lived in the area. Epidemiological, molecular, and ecological data have established person-to-person transmission, particularly when a physician living in a nonendemic region became infected after coming in contact with HPS patients (*43, 44, 48*). The etiologic agent was again found to be Andes virus, and the putative rodent reservoir, the long-tailed pygmy rice rat, *Oligoryzomys longicaudatus* (*42*).

4.3.2 Bolivia

While no HPS cases have been reported, both humans and rodents have shown serologic evidence of infection with hantaviruses in Bolivia (*35, 45*).

4.3.3 Brazil

As of 7 March 1998, six HPS cases had been reported in Brazil, five of which resulted in death. In December 1993, three brothers from Juquitiba, in the São Paulo area, were diagnosed with HPS; two subsequently died of their illness. Lung tissue from one patient yielded evidence of a possibly distinct virus provisionally referred to as Juquitiba virus (*4*). The brothers lived together in a rural area that showed evidence of rodent infestation. Three of 49 case contacts (6.1%) were positive for antibodies reactive to hantavirus antigen, with no apparent disease (*37*). Field investigations failed to determine the probable reservoir. Since then, three additional HPS cases have been reported; one case occurred in the state of Mato Grosso in 1995, while the other two were reported from the state of São Paulo.

4.3.4 Chile

HPS was first recognized in Chile in 1995 in a patient from Cochamo, Los Lagos, Region X. As of 25 March 1998, a total of 46 HPS cases had been reported, mainly from Regions IX, X, and XI, in the south of the country. Of these, 28 cases occurred between October 1995 and December 1997, most as a result of an outbreak in Aysén, Region XI, that began in July 1997. The mean age of these 28 HPS patients was 29.7 years (range 2–60 years), and 75% were males; six (21.4%) of the cases were children under 17 years of age. A case fatality rate of 61% was observed. Three clinical outcomes of hantavirus infection were defined in the country: patients with HPS, patients with mild hantaviral disease, and asymptomatic infections. In addition to the 28 cases of HPS, 3 cases with mild febrile hantaviral disease and 1 case with asymptomatic acute infection were identified.

While the clinical description of cases is similar to that in North America, at least three children had petechiae, and all adult cases that had a urinalysis performed had microscopic hematuria and casts (*46*). Genetic sequencing of tissues from several patients implicated Andes virus as the causative agent (*47, 48*). Three family clusters occurred in the Aysén region. In one cluster, family members became ill within 1 to 5 days of each other. In another family cluster, illness occurred sequentially, with a period of 16 to 41 days between the index case and illness of the last family member. The third family cluster included a husband, who worked in a rural area, and his wife, who remained in the family home in urban Coyhaique. He developed symptoms suggestive of HPS 12 days after returning to his wife and home, was hospitalized, and died. His wife became ill 22 days after the initial onset of his symptoms. She had not traveled outside Coyhaique during the previous 12 months and reported no exposure to rodents. The only known exposures for the wife were washing her husband's clothing and caring for him while he was ill.

A serological study of health care workers from the Coyhaique Regional Hospital, where the majority of HPS patients were admitted during the 1997 outbreak, was performed (*49*). Out of 319 participants (87.9% of those eligible), 12 (3.6%) had IgG antibodies, consistent with the seroprevalence in the community in which the participants lived. Exposure to HPS patients was similar in both antibody-positive and antibody-negative individuals. A population-based, serological survey including individuals from four communities in the Aysén region, one urban and three rural, showed seroprevalence ranging from 2% in the urban area to 13.1% in one of the endemic localities (*50*).

Ecological studies were carried out in 1997 (*51*). Overall trap success ranged from 37% to 50%. The most frequently captured rodent was *Oligoryzomys longicaudatus*, with 13% antibody reactivity to Sin Nombre virus.

4.3.5 Paraguay

Thirty-five cases of HPS have been reported in western Paraguay (*52*). An outbreak of HPS occurred in an agricultural community in the western Chaco region, affecting at least 17 people in the spring and summer of 1995–1996 (*52*). Six additional cases, retrospectively identified in the region between 1987 and 1994, were serologically confirmed. The case fatality rate during the outbreak period was 12%, but this may have been underestimated due to the relative infrequency of autopsies performed in the region.

The background human seroprevalence was found to be between 7 and 21% among asymptomatic groups and community residents (*52*). This may indicate a milder illness and a much higher rate of subclinical infection than that observed elsewhere or infection with a less pathogenic, serologically cross-reactive hantavirus. The etiologic agent was named Laguna Negra virus and has been subsequently isolated in cell culture; the vesper mouse, *Calomys laucha*, was found to be the primary rodent reservoir (*53*).

4.3.6 Peru

There are currently no confirmed reports of hantavirus pulmonary syndrome cases in Peru. However, evidence of hantavirus infection has been found in a number of

rodent species within the country (R. Tesh and D. Watts, personal communication).

4.3.7 Uruguay

At least two cases of HPS have been reported in Uruguay, and previous serologic surveys had detected hantavirus antibodies in the general population (*35*). Little is known about the etiologic agent or the reservoir.

4.3.8 Venezuela

There are currently no confirmed reports of HPS cases in Venezuela. However, hantavirus antibodies have been detected in three rodents from the Venezuelan llanos, *Oryzomys bicolor, Sigmodon alstoni,* and *Zygodontomys brevicauda*. A genetically distinct hantavirus, Caño Delgadito virus, has been isolated from *Sigmodon alstoni*, but so far has not been linked to any human disease (*54*).

5. TRANSMISSION TO HUMANS

Although rodent infection is apparently asymptomatic, human infection is often associated with disease. The main route of transmission is likely respiratory via small-particle aerosols generated from rodent excreta, particularly freshly shed urine. However, it is also possible that infectious airborne particles may be generated during human activities that disturb contaminated soil, litter, or nesting materials. The chance of exposure to hantaviruses is greatest when individuals work, play, or live in closed spaces where there is an active rodent infestation. Human infection does not appear to be limited to a particular age, race, ethnic group, or gender.

It is unknown if direct transmission can occur when larger particles contact ocular, nasal, or oropharyngeal mucous membranes. However, small skin breaks and rodent bites are probably effective but uncommon routes of human infection. Ticks, fleas, mosquitoes, and other biting arthropods are not known to have a role in the transmission of hantaviruses. Although cats and dogs are not known to be a reservoir host of hantaviruses, these domestic animals may bring infected rodents into contact with humans.

Hantaviruses have lipid envelopes and are susceptible to 10% bleach, detergents, and common hospital disinfectants. How long these viruses survive in the environment after being shed is uncertain (*24*). In laboratory experiments simulating environmental conditions, Hantaan virus could still be recovered for several days after drying at room temperature. The virus was viable for short periods of time in temperature ranges of 4 °C to 42 °C and pH ranges of 6.6 to 8.8. These findings indicate that Hantaan virus and presumably all other hantaviruses may remain infectious for up to several days in natural conditions (*55*).

Hantaviruses have never been implicated in nosocomial transmission in European or Asian settings despite the large number of cases observed and hospitalized. During the 1993 SNV outbreak in the United States, neither clinical disease nor seropositivity was found among more than 266 health care workers, including persons who had performed mouth-to-mouth resuscitation or endotracheal intubation (*27*).

Person-to-person transmission was documented in a South American outbreak of Andes virus in 1996 (*43, 44, 48*). It is unknown if this represents a unique event or whether other such cases may occur. A retrospective analysis of the United States HPS Case Registry failed to find definitive evidence for interhuman or nosocomial spread; the few case clusters observed could well have originated from common exposure to rodent-infested living conditions. Further study of the epidemiology of naturally occurring infections is needed in order to understand the potential that the newly discovered American hantaviruses have for contagion.

6. HANTAVIRUS PULMONARY SYNDROME SURVEILLANCE AND CASE DEFINITION

In order to permit immediate epidemic control or to prevent the transmission of hantavirus infection, a surveillance system must be simple in its structure and operation. In the case of hantavirus infection, the surveillance system must address the disease from an integrated clinical, laboratory, and environmental perspective. The case definition provided below (Figure 1), initially developed by CDC, is also used in Canada and several South American countries for HPS surveillance. Serological tests on acute sera are needed to provide precise diagnosis, and molecular biological techniques are useful in establishing the type(s) of circulating virus. All clinical samples must be accompanied by a form identifying the patient, the individual's age and sex, the date of symptom onset, the date of sample collection, a short list of important manifestations, clinical laboratory data, the place of hospitalization, and the final outcome (see Annex 2).

6.1 OUTBREAK INVESTIGATION

6.1.1 When to Investigate

The occurrence of an unusual number of cases in an area of known hantavirus transmission requires an explanation and may also provide an opportunity to expand our knowledge of hantaviruses. This is particularly relevant with case clusters, since they provide an opportunity to address the problem of interhuman transmission.

A single case in an area where hantavirus infection has not previously been reported requires a full medical and epidemiological assessment, individual risk factor/exposure analysis, and an ecological/environmental evaluation as outlined in Section 6.1.2. Determinations of the virus type in circulation as well as potential reservoirs in these new areas are essential in designing future control and prevention strategies.

If a single new case occurs in an area with previous infection, current knowledge about the mode of transmission, clinical manifestations of disease, individual risk factors, circulating virus type, and potential reservoirs in the region should be taken into account and further investigations conducted if circumstances suggest.

In all cases, response procedures should include an evaluation of rodent infestation in domestic and peridomestic settings in order to propose appropriate rodent control measures.

6.1.2 Conducting the Investigation

In conducting the investigation, it is essential to establish a multidisciplinary investigative team involving epidemiologists, laboratorians, and ecologists. Each outbreak investigation should begin with a medical and epidemiologic assessment that includes the following steps:

- define the magnitude of the outbreak:
  - conduct active case finding through interviews and medical chart reviews
  - determine the relative frequency of infection versus disease (via serological survey)
  - map case locations with attention to results of the serological survey
- determine mode(s) of transmission
- characterize the clinical manifestation of disease within the outbreak
- ensure that in each activity above, clinical specimens are collected in a systematic manner with attention to use of specimens for serological diagnosis, PCR analysis, and possibly virus isolation.

The second major activity of the investigation involves individual risk factor/exposure assessment. A culturally appropriate individual risk factor/exposure questionnaire should be developed for use with case-patients, surrogates of case-patients, household or other close contacts, and/or control-patients if used.

The best methodological approach for the situation should be determined, including whether or not to use a case-control design.

FIGURE 1. Hantavirus pulmonary syndrome case definition.

Hantavirus Pulmonary Syndrome (HPS)

Rationale for Surveillance

HPS in the Americas is a rare, but usually severe, disease transmitted through close contact with the urine, feces, or saliva of infected rodents. Although HPS cases have been reported only from Argentina, Brazil, Canada, Chile, Paraguay, the United States of America, and Uruguay, the potential for disease exists throughout the Americas due to the widespread distribution of existing rodent reservoirs. Surveillance is therefore essential for all countries.

Recommended HPS Case Definition

Clinical Case Definition:

- A febrile illness (T >38.3 °C [101 °F] oral) requiring supplemental oxygen, *plus*
- Bilateral diffuse infiltrates (may resemble adult respiratory distress syndrome [ARDS]), *plus*
- Develops within 72 hours of hospitalization in a previously healthy person, **OR**
- Unexplained illness resulting in death *plus* an autopsy examination demonstrating noncardiogenic pulmonary edema without an identifiable specific cause of death

Laboratory Criteria for Diagnosis:

- Presence of hantavirus-specific IgM antibodies or a 4-fold or greater increase in IgG antibody titers **OR**
- Positive reverse transcriptase-polymerase chain reaction (RT-PCR) results for hantavirus RNA **OR**
- Positive immunohistochemical results for hantavirus antigens.

Case Classification:

Suspected: Presentation compatible with the clinical case definition
Confirmed: A suspected case that is laboratory confirmed

Recommendations for Surveillance

- Establish HPS as a reportable (compulsory reporting) disease in all PAHO Member Countries.
- Develop a case report form that identifies standard minimum data to be collected by all countries of the Americas (see Annex 2).
- If HPS is suspected, a blood count, chest X-ray, oxygen saturation, and hantavirus serology should be performed. Rodent exposure should be evaluated (see Annex 2).
- Postmortem blood, fresh frozen tissue, and formal fixed tissue should be collected from deceased HPS patients and properly transported to the nearest laboratory capable of HPS confirmation (see Section 6.1.4 and Annex 3).
- If hantavirus infection not meeting the case definition of HPS is suspected, specimens may also be submitted for testing along with a description of clinical manifestations.

The third main component of the investigation is an ecological/environmental assessment. This includes using standardized data collection forms and conducting systematic environmental assessments to evaluate indices of rodent presence/infestation at suspected sites of rodent exposure. Following the guidelines outlined in Section 6.1.5, the investigation team should initiate systematic assessments of potential rodent reservoirs in the outbreak region, including proper taxonomic evaluations.

6.1.3 Local Response to a Hantavirus Pulmonary Syndrome Case

Local officials should take action when a possible HPS case is laboratory confirmed, even though many cases meeting the screening case definition will not be HPS. Some actions may be taken if clinical evolution makes a positive laboratory diagnosis highly unlikely.

An essential step is to consult local and state public health authorities immediately. The management of zoonoses is specialized, and advice, explanations, and policy guidelines may be needed. Also, special samples from both humans and rodents may be required for investigation and analysis.

It should be suggested to family members that they reside elsewhere until domestic and peridomestic structures have been evaluated and rodents removed. This should be strongly recommended in cases where heavy rodent infestation is evident, especially in the home. The risk of removing clothing and possessions needed immediately is negligible. It may be necessary to obtain rodents from the house for study, depending on the situation and national policy. If rodents are not needed for study, it is sufficient to kill all those in the house, building, or peridomestic structure and properly dispose of them.

Household contacts should be placed under surveillance and any fever reported immediately. About 10% of hantavirus cases occur in clusters, and rare instances of person-to-person transmission occur with Andes virus. Early recognition can improve case management. In addition, contacts must be reassured.

A media strategy should be prepared. Intense interest often follows the first cases, and the media can be helpful in allaying anxiety and spreading public health messages. An effective media strategy can also counteract stigmatization of infected individuals or the community.

Finally, an educational campaign appropriate to the community situation should be developed. Its characteristics will depend on whether there is a single case or multiple cases and whether this is the first recognized case in the area or there is an established endemic. The campaign should target cases' family members as well as physicians.

6.1.4 Recommendations for Sample Storage and Preservation

Serum samples for serological tests can be stored at 4 °C for a few days but preferably should be frozen at –20 °C or at –60 °C. Acute serum for PCR tests should be kept frozen at –60 °C. Tissues from fatal cases should be frozen at –60 °C for PCR tests and fixed in 10% buffered formalin for histopathology and for immunohistochemical analysis. A formalin buffer (pH = 7.4) can be prepared as follows:

100 ml	pure formalin
900 ml	distilled water
4.0 g	monosodium phosphate
6.5 g	disodium phosphate

Lung is the most sensitive tissue for immunohistochemical diagnosis of HPS, but a complete autopsy should be performed and multiple tissues taken because of the limited information available on the pathology and pathogenesis of the different hantaviruses.

6.1.5 Reservoir Surveillance

The intensity and methodology of reservoir surveillance and case follow-up will depend on the resources available to public health authorities. As a minimum, the public health response to the first case(s) of HPS in a country or region where hantavirus infection was previously not identified should include small-mammal trapping in potential areas of human exposure. Trapping should be conducted in accordance with established safety and methodological guidelines (*56*). Primary objectives should include:

- identification of the principal reservoir species
- collection of samples to identify hantaviruses present and to provide a genetic link to human cases
- measurement of the relative density and prevalence of infection in potential reservoir populations
- determination of the most likely ecological zones, specific sites, and mechanisms of human infection

As resources permit, reservoir studies may be expanded to include specific trapping and sampling protocols designed to investigate:

- the potential (as indicated by reservoir presence and evidence of viral infection) for human cases of HPS in distinct geographic areas of the country
- the prevalence, incidence, and temporal patterns of infection in reservoir species
- the effect of climate, habitat quality, and host population dynamics on the viral transmission cycle
- potential mechanisms of transmission among reservoir populations, and from rodents to humans
- effects of infection on movement, longevity, and population dynamics of the host
- the identity of other hantaviruses that may cause human infection, including their hosts and geographic distribution
- potential methods for reservoir control and for decreasing the frequency of human contact with host species
- the relationship between reservoir population density, virus activity in reservoir populations, and the incidence of human disease

Discussions and examples of the application and utility of these kinds of studies are available (*14, 52, 56–59*). Investigators should be encouraged to establish a working relationship with museum taxonomists, universities, government agencies, and private consultants to ensure proper identification and permanent archiving of voucher specimens for all captured small mammals. Methodologies for voucher specimen preparation and preservation have been described (*56, 60*).

7. CLINICAL MANIFESTATIONS AND TREATMENT OF HANTAVIRUS PULMONARY SYNDROME (*61*)

7.1 INCUBATION PERIOD

Few cases have had clearly defined exposures in time and place. The incubation period of other hantavirus diseases is typically one to four weeks, although HFRS from Hantaan virus has apparently had an incubation period up to six weeks. In an effort to determine the incubation period of HPS-causing viruses in the United States, eight cases were identified with well-defined and isolated exposures. These findings suggested an incubation period ranging from 9 to 35 days from the time of probable infection to onset of symptoms (J. Young, personal communication). For seven of the eight cases reviewed, the incubation period was within 9 to 24 days.

7.2 CLINICAL MANIFESTATIONS

Following aerosol exposure and deposition of the virus deep in the lung, infection is initiated. A viremic period ensues, with extensive pulmonary endothelial infection. The onset of symptoms coincides with the onset of the immune response, which may reduce virus shedding, suggesting that the disease process itself is immunopathologic.

The disease is divided into four phases: febrile, cardiopulmonary, diuretic, and convalescent phases (*62*). The febrile, or prodromal, phase typically lasts 3 to 5 days (range 1–12 days) and is indistinguishable from other viral prodromes (*63*). This phase is characterized by fever, myalgias, chills, asthenia, dizziness, headache, anorexia, nausea with or without vomiting, abdominal pain, and diarrhea. The abdominal pain may be sufficiently severe to mimic appendicitis or pyelonephritis. While conjunctival suffusion is rarely seen in HPS in North America, facial flushing is commonly seen in HPS cases in the Patagonian region of South America. Indications of upper respiratory tract disease, including sore throat, rhinorrhea, sinusitis, and ear pain, are usually absent. Physical examination may or may not reveal rales or findings of pleural effusion. Cough, tachypnea, and exertional dyspnea are not reported at the onset of the prodrome, but appear later and herald the onset of pulmonary edema, the second phase.

The onset of hypotension and pulmonary edema may progress rapidly over the course of 4 to 24 hours. A respiratory rate of 24/min is a sensitive but not specific indicator of early pulmonary edema in HPS. Early pulmonary edema is imaged on the chest X-ray as Kerley B lines, peribronchial cuffing, and alveolar-interstitial fluid in the basal segments (*64*). At this point, hypoxemia becomes apparent, with an oxygen saturation of hemoglobin less than 95% at sea level and less than 90% at 2,000 m or more above sea level. Pulmonary edema is noncardiogenic in origin, as indicated by normal pulmonary capillary wedge pressures obtained through a Swan-Ganz catheter and normal heart size on the X-ray (*65, 66*). Markedly increased pulmonary capillary permeability results in high-protein pulmonary edema; severely ill patients may require up to 1 L/h of serum-resembling fluid to be removed from their airways by suction. Shock may be manifest as hypotension and is often accompanied by oliguria and delirium. Hypovolemia resulting from a shift in fluid from circulating blood to the lung interstitium and air spaces contributes to the fall in blood pressure. However, most patients also experience a serious depression of the myocardium (*65*). Seriously ill patients may have cardiac indices less than 2.2 L/min/m^2.

Spontaneous diuresis indicates the onset of the diuretic phase. This third phase of the disease is characterized by a rapid clearance of the pulmonary edema fluid, resolution of fever, and shock. Convalescence extends over the next two weeks to two months. Patients appear to recover fully, but formal studies of pulmonary function and other clinical parameters are needed.

In South America, some other clinical aspects have been described, including hemorrhagic complications (i.e., petechias, not observed in North America) and renal manifestations (*46*). As well, HPS has appeared in children, an uncommon finding in North America (*40*).

7.3 CLINICAL LABORATORY FINDINGS

Hematologic findings can be striking in HPS cases (*62, 67*). In SNV infection, the white blood cell count can be normal or elevated on admission (median 10,400 mm^3; range 3,100–65,300 mm^3) and usually increases, often to very high values (median of maximum values 26,000 mm^3 with range 5,600–65,300 mm^3). Similar values have been found with other viruses. There is an absolute neutrophilia and a relative lymphopenia. In addition to immature "band" forms, the blood almost always contains the more undifferentiated forms in the myeloid series, the myelocytes, and promyelocytes. Among the circulating lymphocytes are prominent mononuclear cells with deep blue cytoplasm by Giemsa stain and that measure greater than 18 μ in diameter. These immunoblasts are seen in few infections other than HPS and HFRS, and appear in the circulation coincident with the onset of pulmonary edema. Thrombocytopenia with a platelet count less than 150,000/mm^3 is seen in almost every case and, in rare cases, may fall to 20,000/mm^3. Thrombocytopenia is the first abnormality to appear in the peripheral blood, often two or three days before the onset of pulmonary edema, and may be used to screen undifferentiated fevers for HPS when the appropriate epidemiologic clues are elicited by history.

Elevated creatinine and blood urea nitrogen reflect the degree of shock and hypovolemia. Proteinuria may be seen and microscopic hematuria is found in most cases. Patients infected by Bayou, Black Creek Canal, and Andes viruses may have more prominent renal failure, even requiring hemodialysis (*17, 45, 68,* and Lázaro, personal communication). Elevated hepatic enzymes are seen in all cases, but rarely attain a level greater than five times the upper normal limit, and hyperbilirubinemia is not seen. The multiorgan failure common in sepsis or posttraumatic adult respiratory distress syndrome *(*ARDS) rarely occurs in HPS. Specific pathology of these organ systems has not yet been described with any of the HPS viruses, but experience and surveillance definitions are limited.

In contrast to HFRS, the coagulopathy of HPS is usually subclinical. Almost all patients have evidence of coagulopathy but with elevated partial thromboplastin times. Circulating D-dimers are not common, and fibrinogen levels falling below 200 mg/dl are rare.

7.4 EARLY CASE RECOGNITION

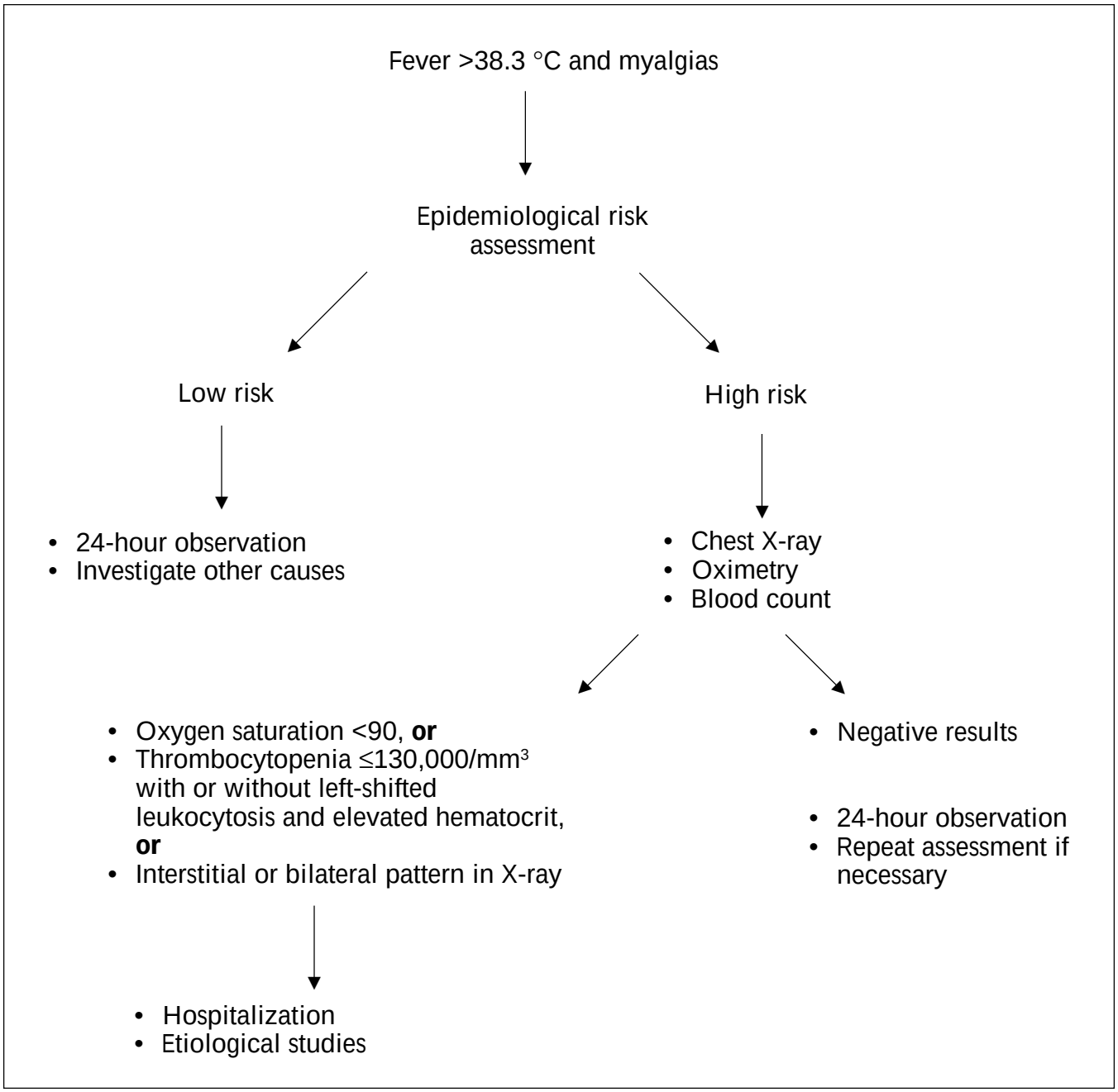
Clinicians should consider HPS in patients with fever and myalgias, particularly of the larger muscle groups, including shoulders, thighs, and lower back. The addition of such gastrointestinal complaints as nausea, vomiting, and abdominal pain should raise the index of suspicion and prompt the clinician to inquire about potential rodent exposures. Tachypnea is an important sign, and hypotension may be present. The absence of certain signs and symptoms can help to distinguish HPS from other acute viral syndromes: rash, conjunctivitis, sinusitis, otitis, rhinorrhea, exudative pharyngitis, and arthritis are notably rare in HPS (*63*). Initial laboratory workup in suspected cases should include pulse oximetry, chest radiograph, and a complete blood count. The likelihood of HPS is high in those with a compatible clinical history plus an oxygen saturation measurement of less than 90%, interstitial infiltrates or other indications of pulmonary edema on chest X-ray, and thrombocytopenia, particularly if the last is accompanied by left-shifted leukocytosis and an elevated hematocrit.

At the onset of pulmonary edema, almost every case displays thrombocytopenia, left-shifted myeloid series, and immunoblasts. This hematologic diagnostic triad is sufficiently sensitive and specific to use to initiate transfer to intensive care and treatment (see Section 7.6). Prior to the onset of the signs and symptoms of either shock or pulmonary edema, the diagnostic triad is not present on the peripheral blood smear. Therefore, to raise the suspicion of impending HPS, the clinician must use the combination of three factors: epidemiologic clues to potential exposure, the reported findings of fever and myalgias, and thrombocytopenia. Although fully developed HPS is a characteristic disease, no combination of symptoms is sufficiently sensitive or specific to distinguish its early stages from a host of other pulmonary infections (*63*); this requires the clinician to retain a level of suspicion until HPS is ruled out. When sufficient evidence for HPS has accumulated, the patient should be transported immediately to a unit skilled in intensive cardiopulmonary care, as rapid transport can be lifesaving. However, the decision to move the patient must be weighed against the rapid onset of hypoxemia and the local capabilities for medical evaluation. In all areas with previously known or suspected cases of HPS, active clinical investigation to definitively diagnose HPS should be performed in all persons with unexplained febrile syndrome and epidemiologic risk factors (see Figure 2).

7.5 DIFFERENTIAL DIAGNOSIS

The differential diagnosis is extensive prior to the serologic identification of hantavirus infection. Most commonly encountered are bilateral pneumonia with sepsis, adult respiratory distress syndrome complicating systemic infections, trauma and other life-threatening conditions, and sepsis syndrome complicated by either disseminated

FIGURE 2. Hantavirus pulmonary syndrome algorithm.



intravascular coagulation (DIC) or alcohol toxicity. A variety of enzootic infections encountered in rural areas of North America may be confused initially with HPS, particularly when thrombocytopenia is present. These include plague, tularemia, Rocky Mountain spotted fever or murine typhus, granulocytic or monocytic ehrlichiosis, leptospirosis, relapsing fever due to *Borrelia hermsii*, and acute parvovirus infection. In Latin America, other diagnostic possibilities would include dengue fever, dengue hemorrhagic fever, and arenavirus infections (Junin, Machupo, Sabia, and Guanarito viruses). When abdominal or back pain is severe, possible diagnoses of pyelonephritis, appendicitis, abdominal abscess, or gynecological infection should be considered.

7.6 LABORATORY DIAGNOSIS

The most practical approach for the laboratory diagnosis of hantavirus infection in humans is the detection

of IgM antibodies in acute serum samples using an ELISA IgM capture assay. Virtually all confirmed HPS patients have demonstrable IgM in the first or second serum sample taken after hospitalization. And while ELISA tests to detect IgG antibodies may also be used to confirm diagnosis, two serum samples taken two to three weeks apart are required to demonstrate rising titers of IgG antibodies. Results of testing can be obtained within a few hours after the specimen is received in the laboratory. Less commonly used serological tests, such as immunofluorescent assay and particle agglutination, can also be applied to hantaviral diagnosis (*69*).

Initial detection of HPS-related hantaviruses was accomplished using heterologous hantaviral antigen (*70*). A more sensitive Sin Nombre recombinant nucleocapsid antigen was developed in response to the outbreak in 1993 in the United States; it is now widely used throughout the Americas in ELISA tests for the detection of New World hantavirus infections. More recently, other recombinant antigens have been developed, such as Andes virus nucleocapsid. Due to the cross-reactive nature of these antigens, they cannot discriminate among closely related hantavirus species.

In fatal cases, fresh frozen tissue, fixed tissue, and blood can be used to confirm the diagnosis by RT-PCR, immunohistochemistry, or ELISA methods, respectively. Collection of blood clots from initial samples of all suspect cases is also recommended for subsequent RT-PCR on selected seropositive individuals. RT-PCR is a molecular diagnostic technique targeting specific regions of the virus genome and is available only at selected research laboratories. RT-PCR is not recommended for routine diagnosis, but is valuable in defining the virus genotype, searching for new viruses, and performing certain epidemiological studies. Immunohistochemistry is particularly well suited to retrospective diagnosis. Viral inclusions have rarely been observed in pulmonary capillary endothelial cells by electron microscopy.

Some Old World hantaviruses have occasionally been isolated from patient serum or whole blood drawn within three to nine days of onset of illness. However, propagation of hantaviruses is difficult and this is not a recommended diagnostic procedure (*71*).

7.7 PATHOGENESIS

The pathogenesis of HPS is related to a profound abnormality in vascular permeability. The capillary leak syndrome is virtually confined to the lungs, and chest radiograph series typically chronicle the rapid onset of diffuse, bilateral interstitial, and later alveolar, pulmonary edema (*64*). There is also evidence for myocardial failure as an important component of the shock syndrome observed (*65*).

At postmortem the lungs are massively edematous, but microscopic studies find little necrosis. There are scant to moderate hyaline membranes, intact pneumocytes, and scarce neutrophils (*67*). However, there is interstitial infiltration by T lymphocytes and activated macrophages (*72*). These findings differ from those of typical adult respiratory distress syndrome and many pneumonias. Hantaviral antigens are detected primarily in endothelial cells, and those in the lung are heavily involved. Lesser amounts of antigen are found in scattered endothelial cells throughout the body, as well as occasional involvement of macrophages, myocytes, and many other cell types.

In contrast to such diseases as South American hemorrhagic fevers, circulating antibodies appear early in the clinical course of HPS and often correspond to clinical decline rather than improvement (*73, 74*). Thus, the impaired vascular permeability is thought to be immunologically mediated, probably strongly influenced by the infiltrating T cells in the lungs.

7.8 TREATMENT

There is no known effective antiviral therapy for HPS, although the drug ribavirin has shown a treatment effect in reducing HFRS mortality (*75*). Open-label ribavirin treatment had no obvious effect in a limited number of HPS patients, and a placebo-controlled clinical trial is currently under way in the United States. In the absence of a proven pharmacological treatment and in light of the rapid progression of HPS, effective clinical management depends heavily on careful fluid management, hemodynamic monitoring, and ventilatory support. Therapeutic responses to shock in patients with HPS must be guided by an understanding of the underlying pathophysiology of this disorder, that is, profound pulmonary capillary leak in the presence of primary myocardial pump dysfunction.

Experimental therapies have been used to treat severely ill patients with HPS. These include extracorporeal membrane oxygenation (ECMO) and nitrous oxide inhalation. Experience is very limited in the use of these experimental measures to treat HPS patients, and they have generally been used only as a last resort form of therapy. There are no clinical data on the effectiveness of administering immune plasma to treat HPS patients. While this therapy has been effective for Argentine hemorrhagic fever (AHF), the differences in immune response and pathophysiology between AHF and HPS suggest it is unlikely to be effective in HPS.

Antiviral therapy with a drug such as ribavirin may be more effective if given to patients identified very early in the prodromal stage. Such patients might be close contacts of a confirmed HPS case (about 10% of hantavirus cases occur in clusters, regardless of the issue of possible

interhuman transmission of Andes virus) or persons with very high risk exposure. Protocols should be developed to permit controlled studies of early, expectant antiviral treatment initiated prior to laboratory testing. Argentina has such a protocol that may be requested as a template.[1] For every new procedure or therapeutic measure it is strongly recommended that controlled studies be performed.

7.8.1 Initial Treatment of Hantavirus Pulmonary Syndrome in the Emergency Room and During Transport

Initial treatment during the observation period should be directed to symptomatic and supportive measures, such as the control of fever and pain with paracetamol (avoiding the use of aspirin), antiemetics, and bed rest. The observation period could be managed at a primary care center. However, if there is a high suspicion of HPS according to the proposed HPS algorithm (Figure 2), patients should be immediately transferred to an emergency room (ER).

Treatment in the ER should focus on maintenance of blood pressure and oxygenation while transfer to an intensive care unit (ICU) is organized. When patients present with shock to the ER, the case fatality rate exceeds 80%. In contrast, the case fatality rate is 10% in the absence of shock at this time, indicating the importance of cardiogenic shock as a cause of death. While some patients may have fluid requirements of 1 to 2 L due to vomiting and diarrhea, it must be kept in mind that excessive fluid resuscitation will exacerbate the pulmonary edema without commensurate improvement in cardiac output. Early use of inotropic agents (see Section 7.8.2) may be necessary, depending on the ability to monitor response to therapy. Due to the rapid onset of pulmonary edema, hypoxemia may deteriorate rapidly over several hours, and continuous monitoring of oxygenation by pulse oximetry is preferred.

7.8.2 Treatment in the Intensive Care Unit

Close monitoring of oxygenation is extremely important so that timely intubation and mechanical ventilation can be provided when required (when PAO_2/FIO_2 falls below 150). Oxygen delivery is usually maintained until the cardiac index falls below 2.2 L/min/m^2. Mechanical ventilation is required for about two-thirds of patients and typically lasts for five to seven days. Because patients with this viral infection can deteriorate so rapidly, a Swan-Ganz catheter should be inserted as soon as is clinically warranted. Intravenous crystalloid fluid is used to maintain as low a wedge pressure (8–12 mmHg) as is compatible with satisfactory cardiac indices (cardiac index >2.2 L/min/m^2). Inotropic agents, such as dobutamine, dopamine, and norepinephrine, are begun earlier in the resuscitation of these patients than in the usual patient, rather than continued fluid boluses. The use of loop diuretics such as furosemide is discouraged, since salt and water will be removed from circulating blood before being removed from the alveolar and interstitial compartments in the lung, thus exacerbating hypotension. Red blood cells are usually not required to maintain oxygen delivery unless hemoglobin concentration falls below 8.5–10 g/dl. Thrombocytopenia has not required support with platelet transfusion. So far there is no evidence that pharmacological doses of corticosteroid offer any benefit in the treatment of HPS. Cardiac arrhythmias, particularly any episodes of electromechanical dissociation, portend a poor outcome and should be aggressively treated. Renal failure and need for hemodialysis is rare among Sin Nombre virus infections but was reported for two HPS cases due to Andes virus in southern Argentina and Chile. Extracorporeal membrane oxygenation (an experimental procedure) should be considered when available if the serum lactate level exceeds 4 mmol/l and cardiac index <2.2 L/min/m^2.

Due to the extensive differential diagnosis, all patients should be treated for more common events, such as sepsis. A broad-spectrum antibiotic such as intravenous ceftriaxone or ampicillin-sulbactam, as well as doxycycline used to treat rickettsioses, ehrlichioses, plague, and tularemia, should be administered until either HPS is confirmed or another diagnosis is made.

7.8.3 Case Management in a Rural Setting

In rural settings without access to intensive care facilities, treatment of cases should focus on maintenance of blood pressure and oxygenation. In addition, broad-spectrum antibiotics such as suggested in Section 7.8.2 should be administered until either HPS is confirmed or another diagnosis is made. Intravenous crystalloid fluid should be used carefully so as not to exacerbate pulmonary edema. It is recommended that fluid balance be maintained, with replacement fluid administered according to the amount lost. In case of shock, it would be necessary to use such inotropic agents as dobutamine or dopamine, even in the absence of cardiac monitoring. Oxygen delivery should also be initiated early on, and a nonrebreathing mask could be used to ensure 100% oxygen concentration.

[1]For further information contact Dr. Delia Enría, Instituto Nacional de Enfermedades Virales Humanas, Monteagudo 2510, 2700 Pergamino, Argentina; Telephone: (54-477) 29712/14; Fax: (54-477) 33045; E-mail: enria@inevh.sld.arg.

8. PREVENTION AND CONTROL

The prevention guidelines offered here borrow heavily from experience in North America and the interim guidelines established by CDC following the initial outbreak of HPS in 1993 (*24*). Recommendations for personal risk reduction are given in Section 8.1. (For easy reproduction and distribution, a number of these risk reduction guidelines are presented in Annex 9.) Also below are prevention guidelines for health professionals caring for patients infected with hantavirus (Section 8.2), people working with body fluids or tissue potentially infected with hantaviruses in the laboratory (Section 8.3), and researchers involved in handling and processing rodents (Section 8.4). Ultimately, each country of the Americas should establish prevention guidelines appropriate to its own circumstances.

There is no effective vaccine for the hantaviruses in the Americas. Viruses causing HFRS are antigenically distant, and their vaccines should not be used until future research proves otherwise.

Preventing contact with rodents and their excreta is the cornerstone to primary prevention of hantaviral illness in the Americas and throughout the world. Rodents of the subfamily *Sigmodontinae* are the reservoirs of hantaviruses that cause HPS. Most of the subfamily are field rodents that occupy areas away from urban population centers. However, they may enter areas of human habitation, particularly under circumstances of high rodent density and competition for shelter and food resources. Eradication of rodent hantavirus host species is neither desirable nor feasible due to the large number of species implicated and their wide distribution and abundance. Further, in regions where plague is endemic, control of rodents without concurrent control of fleas may increase the risk of human plague as the rodent fleas seek an alternative food source. The best currently available approach for hantavirus disease control and prevention is risk reduction through the use of precautions against infection by rodent excreta, combined with environmental hygiene practices that deter rodents from colonizing the home, recreational, and work environments.

8.1 PERSONAL RISK REDUCTION

Personal risk reduction is based on principles of rodent and infection control. Below are specific recommendations for reducing rodent shelter and food sources in and around the home, recommendations for eliminating rodents inside the home and preventing them from entering the home, precautions for preventing hantavirus infection while rodent-contaminated areas are being cleaned up, prevention measures for persons who have occupational exposure to wild rodents, and precautions for campers and hikers.

These guidelines can be readily followed with minimal investment in expensive or hard-to-use equipment or materials. They also can be applied generally to help reduce encounters with rodents and their excreta, and they do not require specialized skills in rodent species identification.

8.1.1 General Household Precautions in Affected Areas

Although epidemiologic studies are being conducted to identify specific behaviors that may increase the risk for hantavirus infection in humans, rodent control in and around the home will continue to be the primary prevention strategy (see Box 1). CDC has issued recommendations for rodent-proofing urban and suburban dwellings and reducing rodent populations around homes through habitat modification and sanitation.

8.1.2 Prevent Rodents from Entering the Home

A number of steps can be taken to prevent rodents from entering the home. A set of general guidelines is given in Box 2. These practices should be adapted to local circumstances.

In addition, if rodent nests are encountered while these prevention measures are being carried out, follow the

BOX 1. General precautions for residents of affected areas.

- Reduce the availability of food sources and nesting sites used by rodents inside the home.
- Eliminate rodents inside the home (see Box 3).
- Discourage children from playing with rodents or their nests, and advise them to tell their parents if they see rodents or their nests.
- Keep food (including pet food) and water covered and stored in rodent-proof metal or thick plastic containers with tight-fitting lids.
- Store garbage inside homes in rodent-proof metal or thick plastic containers with tight-fitting lids.
- Wash dishes and cooking utensils immediately after use and remove all spilled food.
- Dispose of trash and clutter.
- Use spring-loaded rodent traps in the home continuously.
- As an adjunct to traps, use rodenticide with bait under a plywood or plastic shelter (a covered bait station) on an ongoing basis inside the house.

BOX 2. General practices for the prevention of rodent infestation of homes.

- Use steel wool or cement to seal, screen, or otherwise cover all openings into the home that have a diameter of 0.5 cm or more.
- Place metal roof flashing as a rodent barrier around the base of wooden, earthen, or adobe dwellings up to a height of 30 cm and buried in the soil to a depth of 15 cm.
- Place 10 cm of gravel under the base of homes or under mobile homes to discourage rodent burrowing.
- Reduce rodent shelter and food sources within 30 m of the home.
- Cut grass, brush, and dense shrubbery within 30 m of the home.
- Use raised cement foundations in new construction of sheds, barns, outbuildings, or woodpiles.
- When possible, place woodpiles 30 m or more from the house and elevate wood at least 30 cm off the ground.
- Store grains and animal feed in rodent-proof containers.
- Near buildings, remove food sources that might attract rodents, or store food and water in rodent-proof containers.
- Store hay on pallets, and use traps or rodenticide continuously to keep hay free of rodents.
- Do not leave pet food in feeding dishes.
- Dispose of garbage and trash in rodent-proof containers that are elevated at least 30 cm off the ground.
- Haul away trash, abandoned vehicles, discarded tires, and other items that may serve as rodent nesting sites.
- Place spring-loaded rodent traps at likely spots for rodent shelter within 30 m around the home, and use continuously.
- Use a nationally approved rodenticide certified for outside use in covered bait stations at places likely to shelter rodents within 30 m of the home.

recommendations in Section 8.1.4. on the cleanup of rodent-contaminated areas.

8.1.3 Eliminating Rodents Inside the Home and Reducing Rodent Access to the Home

Rodent infestation can be determined by direct observation of the animals or inferred from the presence of feces in closets or cabinets or on floors or from evidence that rodents have been gnawing at food. If rodent infestation is detected inside the home or outbuildings, rodent abatement measures should be carried out (Box 3). The directions in Section 8.1.5 on special precautions should be followed if evidence of heavy rodent infestation is present (e.g., piles of feces or numerous dead animals) or if a structure is associated with a confirmed case of hantavirus disease.

Many rodenticides can be used; instructions on product use should always be followed. Products that are used outdoors should be specifically approved for exterior use. Any interior use of a rodenticide should be preceded by use of an insecticide to reduce the risk of plague transmission; fleas that may transmit plague may leave the body of trapped or poisoned animals. Insecticide sprays or powders can be used in place of aerosols if they are appropriately labeled for flea control. When rodent densities are high, rodenticides may be used to control populations before clearing or cutting tall grass or brush. If rodenticides are used in or around homes, precautions must be used to prevent accidental poisoning of children and domestic animals.

Trapping in the home should be done with snap traps that result in immediate death of the animal. Live traps or adhesive papers should not be used because virus excretion may continue. The dead animal should be disposed of as indicated in Box 3.

There is no reason to routinely test trapped animals for hantaviruses. Routine testing can potentially increase the public biohazard since more people would catch and handle rodents if they expected them to be tested. Also, a large sample size is required in order to get an accurate picture. Usually, only a small number of rodents are infected in a given locality, so routine testing of a few trapped animals is likely to give a false negative.

Predators are important in reducing the number of rodents, but increasing the number of household cats is

BOX 3. Eliminating rodent infestation: guidance for residents of affected areas.

- Before rodent elimination work is begun, ventilate closed buildings or areas inside buildings by opening doors and windows for at least 30 minutes. Use an exhaust fan or cross ventilation if possible. Leave the area until the airing-out period is finished. This airing may help remove any aerosolized virus inside the closed-in structure.
- Seal, screen, or otherwise cover all openings into the home that have a diameter of 0.5 cm or more. Then set rodent traps inside the house, using peanut butter, fruit, sugarcane, or other substitutes as bait. Use only spring-loaded traps that kill rodents.
- Next, treat the interior of the structure with an insecticide labeled for flea control, following label instructions. Insecticide sprays or powders can be used in place of aerosols if they are appropriately labeled for flea control.
- Rodenticides may also be used while the interior is being treated, as outlined below:
  - Remove dead rodents from the traps. Wear rubber or plastic gloves while handling rodents. Place the carcasses in a plastic bag containing a sufficient amount of a general-purpose household disinfectant to thoroughly wet the carcasses. Seal and double-bag the carcasses, then dispose of them by burying them in a hole 0.5–1 m deep or by burning. If burying or burning is not feasible, contact your local or state health department about other appropriate disposal methods. Rebait and reset all sprung traps.
  - Before removing the gloves, wash gloved hands in a general household disinfectant and then in soap and water. A hypochlorite solution prepared by mixing 3 tbsp of household bleach in 4.5 L of water may be used in place of a commercial disinfectant. When using the solution, avoid spilling the mixture on clothing or other items that could be damaged.
  - Thoroughly wash hands with soap and water after removing the gloves.
  - Leave several baited spring-loaded traps inside the house at all times as a further precaution against rodent reinfestation. Examine the traps regularly.
  - Disinfect traps no longer in use by washing in a general household disinfectant or the hypochlorite solution and ***rinsing*** clean. Disinfect and wash gloves as described above, and wash hands thoroughly with soap and water before beginning other activities.

not encouraged. Although they do not become infected and excrete virus, cats may bring rodents into the home and may contaminate the home after killing or eating rodents. Asian studies have suggested that cats may actually be a risk factor for human infection, although this was not found in the United States (*25*).

To date no hantavirus disease risk has been associated with rodents of the *Sciuridae* family (squirrels and chipmunks) or the groups of rodents used as food sources (guinea pigs, capybara, agouti, nutria, and tepisquintle).

8.1.4 Cleanup of Rodent-contaminated Areas

Areas with such evidence of rodent activity as dead rodents and rodent excreta should be thoroughly cleaned to reduce the likelihood of exposure to hantavirus-infected materials. Cleanup procedures must be performed in a manner that limits the potential for aerosolization of dirt or dust from all potentially contaminated surfaces and household goods (see Box 4).

Because hantaviruses are susceptible to standard disinfectants, these should be used extensively in cleaning. Household bleach diluted 1:10 in water is excellent for heavily contaminated areas but may damage many materials and dyes. Even common detergents will decrease viral infectivity, and the wetting action will diminish aerosol formation. The local health department should be consulted for advice on appropriate local brands and disinfectant concentrations.

Opening and cleaning buildings that have not been used for a period of time pose special problems. Rural schools, cabins, and storage sheds should be opened and allowed to ventilate for at least 30 minutes before entering to clean them (see Box 3). The delay will allow time for aerosols to decay and be diluted by outside air. Otherwise, infectious aerosols may be generated when rodents are disturbed and be retained within the room, protected from sunshine and the deleterious effect of ultraviolet light. Cleanup of the cabin should be accomplished as in Box 4*;* ***under no circumstance should a vacuum cleaner or a broom be used.***

Persons may elect to use surgical or painter's masks to protect the nose and mouth against larger particles, but they must be aware that no protection is afforded against small particle aerosols.

8.1.5 Special Precautions for Homes of Persons with Confirmed Hantavirus Infection or Buildings with Heavy Rodent Infestation

Special precautions are indicated for cleaning homes or buildings with heavy rodent infestation or that have been occupied by persons with confirmed hantavirus infection (see Box 5). Persons conducting these activities should contact the responsible local, state, or federal public health agency for guidance. These precautions may also apply to vacant dwellings that have attracted large numbers of rodents. Workers who are ei-

BOX 4. Cleanup of rodent-contaminated areas: guidance for residents of affected areas.

- Persons involved in the cleanup should wear rubber or plastic gloves.
- Spray dead rodents, rodent nests, droppings, and foods or other items that have been tainted by rodents with a general-purpose household disinfectant.
- Soak the material thoroughly and place in a plastic bag.
- When cleanup is complete (or when the bag is full), seal the bag, then place it into a second plastic bag and seal.
- Dispose of the bagged material by burying in a hole 0.5–1 m deep or by burning. If these alternatives are not feasible, contact the local or state health department concerning other appropriate disposal methods.
- After the above items have been removed, ***mop*** floors with a solution of water, detergent, and disinfectant. To avoid generating potentially infectious aerosols, do not vacuum or sweep dry surfaces before mopping.
- Spray dirt floors with a disinfectant solution. A second mopping or spraying of floors with a general-purpose household disinfectant is optional.
- Carpets can be effectively disinfected with household disinfectants or by commercial-grade steam cleaning or shampooing.
- Disinfect countertops, cabinets, drawers, and other durable surfaces by washing them with a solution of detergent, water, and disinfectant, followed by an optional wiping-down with a general-purpose household disinfectant.
- Rugs and upholstered furniture should be steam cleaned or shampooed. If rodents have nested inside furniture and the nests are not accessible for decontamination, the furniture should be removed and burned.
- Launder potentially contaminated bedding and clothing with hot water and detergent. (Use rubber or plastic gloves when handling the dirty laundry, then wash and disinfect gloves as described in Box 3.) Machine-dry laundry on a high setting or hang it to air-dry in the sun.

ther hired specifically to perform the cleanup or asked to do so as part of their work activities should receive a thorough orientation from the responsible health agency about hantavirus transmission, and should be trained to perform the required activities safely.

8.1.6 Precautions for Workers in Affected Areas Who Are Regularly Exposed to Rodents

Mammalogists, pest-control workers, and other persons who frequently handle or are exposed to rodents in the affected area are probably at higher risk for hantavirus infection than is the general public. The enhanced precautions warranted to protect those persons against hantavirus infection are shown in Box 6.

BOX 5. Special precautions for cleanup in homes of persons with hantavirus infection or buildings with heavy rodent infestation.

- A baseline serum sample, preferably drawn at the time these activities are initiated, should be available for all persons conducting the cleanup of homes or buildings with heavy rodent infestation. The serum sample should be stored at –20 °C.
- Persons involved in the cleanup should wear coveralls (disposable, if possible), rubber boots or disposable shoe covers, rubber or plastic gloves, protective goggles, and an appropriate respiratory protection device, such as a half-mask air-purifying (or negative-pressure) respirator with a high-efficiency particulate air (HEPA) filter or a powered air-purifying respirator (PAPR) with HEPA filters. Respirators (including positive-pressure types) are not considered protective if facial hair interferes with the face seal, since proper fit cannot be assured. Respirator practices should follow a comprehensive user program and be supervised by a knowledgeable person. Personal protective gear should be decontaminated upon removal at the end of the day. If the coveralls are not disposable, they should be laundered on site. If no laundry facilities are available, the coveralls should be immersed in liquid disinfectant until they can be washed.
- All potentially infective waste material (including respirator filters) from cleanup operations that cannot be burned or deep-buried on site should be double-bagged in appropriate plastic bags. The bagged material should then be labeled as infectious (if it is to be transported) and disposed of in accordance with local requirements for infectious waste.
- Workers who develop symptoms suggestive of HPS within 45 days of the last potential exposure should immediately seek medical attention. The physician should contact local health authorities promptly if hantavirus-associated illness is suspected. A blood sample should be obtained and forwarded with the baseline serum through the state health department to the appropriate reference laboratory for hantavirus antibody testing.

8.1.7 Precautions for Other Occupational Groups Who Have Potential Rodent Contact

Insufficient information is available at this time to allow general recommendations regarding risks or precautions for persons in the affected areas who work in occupations with unpredictable or incidental contact with rodents or their habitations. Examples of such occupations include telephone installers, maintenance workers, plumbers, electricians, and certain construction workers. Workers in these jobs may have to enter various buildings, crawl spaces, or other sites that may be rodent infested. Occasional cases have occurred among

such persons, but overall risk is very low (*76*). Recommendations for such circumstances must be made on a case-by-case basis after the specific working environment has been assessed and state or local health departments have been consulted.

8.1.8 Precautions for Campers and Hikers in the Affected Areas

There is no evidence to suggest that travel into the affected areas should be restricted. Most usual tourist activities pose little or no risk that travelers will be exposed to rodents or their excreta. However, persons engaged in such outdoor activities as camping or hiking should take precautions to reduce the likelihood of their exposure to potentially infectious materials (see Box 7).

BOX 6. Precautions for workers in affected areas who are exposed to rodents.

- A baseline serum sample, preferably drawn at the time of employment, should be available for all persons whose occupation involves frequent rodent contact. The serum sample should be stored at –20 °C.
- Workers in potentially high-risk settings should be informed about the symptoms of HPS and be given detailed guidance on prevention measures.
- Workers who develop a febrile or respiratory illness within 45 days of the last potential exposure should immediately seek medical attention and inform the attending physician of the potential occupational risk of hantavirus infection. The physician should contact local health authorities promptly if hantavirus-associated illness is suspected. A blood sample should be obtained and forwarded with the baseline serum to the appropriate reference laboratory for hantavirus antibody testing.
- Workers should wear a half-face air-purifying (or negative-pressure) respirator with eye protection or a PAPR equipped with HEPA filters when removing rodents from traps or handling rodents in the affected area. Respirators (including positive-pressure types) are not considered protective if facial hair interferes with the face seal, since proper fit cannot be assured. Respirator use practices should be in accord with a comprehensive user program and should be supervised by a knowledgeable person. Workers should wear rubber or plastic gloves when handling rodents or handling traps containing rodents. Gloves should be washed and disinfected before removal, as described earlier.
- Traps contaminated by rodent urine or feces or in which a rodent was captured should be disinfected with a commercial disinfectant or bleach solution. Dispose of dead rodents as described in Section 8.1.3.
- Persons removing organs or obtaining blood from rodents in affected areas should follow published safety guidelines (*56*).

8.2 RECOMMENDATIONS ON HOSPITAL ISOLATION PROCEDURES FOR PATIENTS WITH HANTAVIRUS PULMONARY SYNDROME

In North America, there is no evidence for person-to-person hantavirus transmission, and no health care workers involved in the care of HPS patients are known to have become infected with the virus (*27, 28*). In South America, however, there has been an outbreak of person-to-person transmission of Andes virus involving several health care workers (*43, 44, 48*).

Universal precautions with such barrier methods as gowns and gloves should be followed when caring for all hospitalized patients with HPS. In North America, there is insufficient evidence of interhuman transmission to warrant respiratory isolation procedures. Such procedures are practiced, however, in some hospitals until infection with SNV is confirmed, particularly in those regions where pneumonic plague and other respiratory transmitted infections are known to occur. Patients with respiratory disease should be managed with precautions appropriate to prevalent regional diseases.

In South America, if HPS is a consideration, universal precautions should be applied, surgical masks should be used, and the patient should be placed in a private room. These added safety measures are recommended, but each country should administer them based on its own epidemiological situation and local acute care facilities. Surgical masks are recommended because of the question of interhuman transmission with Andes virus

BOX 7. Reducing risk of hantavirus infection: guidance for hikers and campers.

- Avoid coming into contact with rodents and rodent burrows or disturbing dens, such as pack rat nests.
- Do not use cabins or other enclosed shelters that are rodent infested until they have been appropriately cleaned and disinfected.
- Do not pitch tents or place sleeping bags in areas in proximity to rodent feces or burrows or near possible rodent shelters (e.g., garbage dumps or woodpiles).
- If possible, do not sleep on the bare ground. Use a cot with the sleeping surface at least 30 cm above the ground. Use tents with floors.
- Keep food in rodent-proof containers.
- Promptly bury (or—preferably—burn, followed by burying, when in accordance with local requirements) all garbage and trash, or discard in covered trash containers.
- Use only bottled water or water that has been disinfected by filtration, boiling, chlorination, or iodination for drinking, cooking, washing dishes, and brushing teeth.

and other American viruses with which we have little practical experience. A surgical mask covering the mouth and nose will protect mucous membranes against droplets but will not protect against the inhalation of small-particle aerosols. In the previously mentioned Andes virus outbreak, the exact route of transmission was not defined, but small-particle aerosols were not implicated (*43, 44, 77*). If procedures which may be associated with generating high concentrations of droplets and small-particle aerosols, such as tracheostomy or intubation, are undertaken, additional protection is desirable, including goggles and a HEPA mask.

Intensive care unit staff should carefully adhere to the use of universal precautions, including surgical mask, gown, and gloves. If available, a private room should be used. If not, the risk for others in the ICU is very low. Even in the outbreak with person-to-person transmission, there were no cases among ICU staff and the effective contacts between cases were thought to occur before or shortly after hospital admission.

Studies to evaluate the potential for interhuman transmission of HPS-causing viruses are ongoing in South America, and recommendations for isolation procedures will evolve accordingly.

8.3 RECOMMENDED LABORATORY PRECAUTIONS WHEN WORKING WITH HANTAVIRUSES

Extensive experience with the hantaviruses that cause HFRS and a lesser experience with HPS indicate that infection has not been transmitted from clinical laboratory specimens. Viral antigens have been detected in necropsy specimens, and RT-PCR readily detects viral genetic material. Viral RNA has been found in tracheal aspirates and bronchial washings and has been detected by RT-PCR in blood and plasma obtained early in the course of disease. The implications of these findings for the infectivity of blood or tissues are unknown, but the potential for transmission may be present.

On the basis of available evidence regarding risk for laboratory-acquired hantavirus infection, at least Biosafety Level 2 (BSL-2) facilities and practices are recommended for laboratory handling of sera from persons potentially infected with the agents of HPS (see Annex 4). It is recommended that universal precautions be followed whenever human blood is handled. The use of a certified biological safety cabinet is recommended for all handling of human body fluids when potential exists for splatter or aerosolization.

Manipulation of disease-causing hantaviruses in cell culture and rodent tissues should be performed at Biosafety Level 3 (BSL-3) (Annex 4). Four laboratory workers were infected while working with cell culture-adapted Hantaan virus. Although the procedures associated with infection are unclear, all four persons worked repeatedly with hantavirus cultures and performed centrifugation of concentrated virus (*54*). This has led to recommendations for special precautions when working with virus concentrates (*78*).

Laboratory transmission of Old World hantaviruses from rodents to humans via the aerosol route is well documented (*78*). Exposures to rodent excreta, fresh rodent necropsy material, and animal bedding are associated with risk. In animal holding areas, the period of exposure to infectious animal excreta required for transmission may be short. For this reason, experimental rodent inoculations should be performed at BSL-3 with respiratory protection, or at BSL-4 (*78*). For more information, see Annex 4.

8.4 GUIDELINES FOR HANDLING AND PROCESSING RODENTS

Although inhalation of aerosolized virus is thought to be the most common route of infection, it is also possible that human infection occurs when virus or virus-contaminated materials are introduced into broken skin, conjunctivae, or mucous membranes, or when accidentally ingested with food or water (*56*). Infection has been transmitted by bite. Personnel collecting blood or tissue samples from live or freshly killed rodents are at risk for exposure to virus in the blood and organs of hantavirus-infected animals. The most important prophylactic measure for personnel who are trapping, handling, bleeding, or dissecting rodents is to be aware of potential routes of infection and carefully avoid conditions that may lead to infection. Fundamental precautions include minimizing exposure to rodent excreta, avoiding the creation of aerosols, always wearing proper personal protective equipment, properly anesthetizing animals before handling them, and carefully disinfecting contaminated working spaces, equipment, and clothing. Precautions should also be used when handling frozen tissues or blood taken from potentially infected animals (*56*).

More detailed information on precise rodent trapping and processing procedures and recommended precautions can be found in a report entitled "Methods for Trapping and Sampling Small Mammals for Virologic Testing," published by CDC (*56*). A Spanish version of this document is also available through the Pan American Health Organization (PAHO).

The control and prevention recommendations in this report represent general measures to minimize the like-

lihood of human exposure to hantavirus-infected rodents in areas affected by the outbreak of hantavirus-associated respiratory illness. Many of the recommendations may not be applicable or necessary in unaffected locales. The impact and utility of the recommendations will be assessed as they are implemented and will be continually reviewed by PAHO/WHO, CDC, and national, state, and local health agencies as additional epidemiologic and laboratory data related to HPS become available.

8.5 HEALTH EDUCATION

Health education efforts for HPS are intended to enhance recognition and management of disease and to prevent cases by reducing human contact with rodents. Amelioration of the impact of clinical disease depends on health care providers having adequate knowledge and skills. Prevention relies on the knowledge and ability of the general public to reduce their contact with rodents. Multiple communication channels and messages should be used to reach these two target populations.

This section outlines the numerous communication channels, messages, and issues surrounding HPS health education for health professionals (Section 8.5.1) and for the general public (Section 8.5.2). Suggested materials and services for HPS prevention are also provided (Section 8.5.3). Specific HPS educational materials available for use in educating health professionals and the general public are listed in Annex 5. Examples are also provided of health education methods in Argentina (Annex 6), Chile (Annex 7), and the United States of America (Annex 8).

8.5.1 Education for Health Professionals

Since early recognition of a case may improve the patient's chance of survival (through the application of appropriate supportive measures), physicians and other medical personnel play an important role in early case identification. Therefore, educational programs should be targeted to all medical personnel and should focus on the clinical features of the disease, diagnosis, patient management and treatment, and prevention recommendations. It is also necessary for other health professionals, such as public health officials, epidemiologists, laboratorians, and public health educators, to be knowledgeable of the latest research, including those results particularly pertinent to their region, in order to maintain an active surveillance system and to develop effective community-based programs. Additionally, materials targeting the general public should be made available to physicians to distribute to their patients.

8.5.2 Education for the General Public

Health education programs for the general public can be divided into two types of interventions: preventive measures during nonoutbreak situations and rapid response when there is a suspected case. Prevention is the best strategy and can be approached by following simple precautions to reduce human contact with rodents. The information provided in Sections 8.1 through 8.4 lists numerous step-by-step recommendations to reduce contact between humans and rodents. Promoting these recommendations in areas with large rodent populations should reduce the risk of infection. However, cases may still occur, and an effective health education response must be implemented quickly to ensure that patients seek medical attention at an early and appropriate time, to prevent additional cases, and to relieve the public's concerns.

Preventive Measures During Nonoutbreak Situations

Health education programs targeting the general public during nonoutbreak situations should accomplish three goals: inform about the disease, help to identify personal risk, and provide prevention recommendations. The messages should be tailored to the cultural and socioeconomic status of the at-risk populations, their level of disease risk, and the rodent habits, population density, and infection prevalence. It is particularly important to emphasize the following common areas of confusion:

- Not all species of rodents are reservoirs for HPS-associated hantaviruses. In order to develop appropriate messages for the public, health professionals need to be informed about the differences among rodent species, such as geographic distribution and behavior of rodent reservoirs, and which of the local species are particularly dangerous. For example, *Rattus norvegicus* is a common rodent found in urban areas. The number of *R. norvegicus* found near and in the home or the workplace should be reduced for sanitary reasons, but not for controlling HPS since this species is not a carrier of HPS-associated hantaviruses.
- Among those rodent species that are reservoirs for HPS-associated hantaviruses, infection is common and every rodent is potentially dangerous, but the risk of human disease is very low.
- While direct contact with rodents or their excreta is potentially dangerous and should be avoided, the main route of human infection is aerosols that may be generated by the rodents or from the rodent excreta.

In most communities, it will be impossible to completely eliminate rodents around the home or worksite. Therefore, messages should be based on managing human contact with the rodent population using the recommendations presented in this section.

Because supportive care is important to survival and patients may deteriorate rapidly, those who have symptoms suggesting HPS must be educated to seek medical attention. The wording of the message will vary depending on the cultural context, proximity of hospitals, diagnostic capability available, and other diseases endemic to the area.

Messages and materials should be directed at the many diverse groups within the general public. Multiple cultural perspectives, such as needs, values, and beliefs for each group, should be considered and addressed. Human contact with the rodent reservoirs tends to be higher in rural areas. Therefore, obstacles commonly encountered in these areas, such as lower economic status, lower reading levels, use of a local language, and accessibility difficulties, should be considered when developing the educational program.

Schools, parks, tourist areas, grocery stores, doctors' offices, health centers, campgrounds, and other areas frequently visited by the target population are possible sites to promote prevention messages. Parks, tourist areas, and campgrounds are particularly important to target because of the increased number of rodents in these settings.

Rapid Response When There Is a Suspected Case

Health education works in conjunction with clinical, laboratory, and epidemiology disciplines when responding to a suspected case. Once the risk factors associated with disease transmission have been identified and prevention measures have been developed, the population at risk can be targeted with education materials and campaigns. Additionally, intensive efforts should be made in the local communities and with the family members of any cases to provide information on the warning signs and symptoms of hantavirus infection, as well as prevention and control measures.

8.5.3 Materials and Services

Many materials and services can be used to educate health professionals and the general public. These include videotapes, slide sets, print materials, the Internet, mass media news coverage, public service announcements, national campaigns, audio conferences, seminars, and telephone hot lines. Annex 5 lists brochures, posters, pamphlets, and other educational materials provided by CDC. The information provided in the materials can be easily adapted to meet local needs.

Videotapes

A videotape can provide numerous messages within a short amount of time. Primarily used as a teaching tool, videotapes can reach a large audience and provide for repetitious viewing to clarify points and recommendations. For example, videotapes may be used to improve viewer comprehension of prevention recommendations by demonstrating specific cleanup procedures of rodent-contaminated areas. Videotapes do not provide any interaction between health educators and the general public, so they should be used as part of a comprehensive prevention program that employs other information dissemination methods and materials.

CDC has developed two videotapes on HPS. *Preventing Hantavirus Disease* targets the general public, and *A New Hantavirus* targets health professionals. Both videos are available in English and Spanish, in both VHS and PAL formats, and are free of charge. The two videos are described in Annex 5, and CDC's overall health education program is profiled in Annex 8.

Slide Sets

Slide sets are relatively inexpensive tools for teaching health professionals about HPS. As new information is discovered, slide sets can be updated and adapted easily. For example, slide sets may be used to show chest X-rays from patients with HPS to give a better picture of findings upon clinical presentation. CDC has developed a slide set with accompanying text which is available for public health workers, epidemiologists, medical professors, or infectious disease physicians for their use in giving presentations to their own audiences. The slides can be downloaded from the CDC Internet site in PowerPoint™ format in either English or Spanish. The slides provided may be combined with other slides addressing the local situation.

Print Materials

Brochures, posters, and pamphlets can be used to educate both health professionals and the general public. Different types of print materials are more effective de-

pending upon the amount of information presented. If numerous facts must be presented, brochures and pamphlets are beneficial. These materials are effective when introducing new information, presenting guidelines, or serving as a reference for suggested recommendations, such as the recommendations for keeping homes rodent-proof. In comparison, posters should be used to present small amounts of information. They can be placed on the walls of health centers, grocery stores, doctors' offices, and other common places, serving as a quick reference or constant reminder. For example, posters can be placed in rural grocery stores serving as a reminder to place food in sealed containers. As with any print material, consideration must be made for those who are unable to read or who read at a lower level or use another language. Pictures or drawings can help communicate messages to these audiences.

Educational efforts in Argentina included door-to-door distribution of brochures by health workers. This method ensured that families received information about HPS and also provided a mechanism to answer individual questions. Argentina's health education program is described in Annex 6.

The Internet

The Internet is an easy and quick delivery channel to educate health professionals and the general public about HPS. The information presented on an Internet Web site can be easily categorized and users can select what is useful to them, thereby satisfying the needs of various audiences. Additionally, the Internet is inexpensive, can be easily updated, and can be accessed worldwide. Although probably directly accessible to only a small fraction of the target audience, the Internet still has the capability to reach large audiences through downloaded information. CDC has an extensive Internet site on HPS. Information can be downloaded freely, reproduced, and used in educational publications or as a teaching supplement. The CDC HPS Web page (http://www.cdc.gov/ncidod/diseases/hanta/hantvrus.htm) can also be linked to a local Internet page.

Mass Media and Public Service Announcements

The use of the mass media can be quite successful in reaching target audiences quickly. This is especially important during an outbreak. Television, radio, and newspapers can be helpful in disseminating information to large audiences, but it is important that the disseminated messages be correct. A public health liaison can be identified to work specifically with the media to help ensure accuracy in news coverage.

Public service announcements (PSAs) are another way to reach large audiences. While the content of PSAs can be controlled, the times they are broadcast on either radio or television are chosen by the stations, which may not be the most popular listening or viewing times. The Ministry of Health in Chile has developed numerous PSAs for television, with topics ranging from rodent-proofing homes to cleaning cabins before summer vacation. Chile's PSA campaign is described in Annex 7.

National Campaigns

National campaigns can serve as an effective medium to bring information about HPS to large audiences at one time. Since many differing audiences within the general public need to be reached simultaneously, numerous messages and communication channels must be used. Successful campaigns utilize many of the other materials and education tools described in this section. Even if the epidemic is at the local level, national campaigns provide the opportunity to educate the general public about HPS and allay fears, abolish rumors and exaggerations, minimize stigmatization of individuals from affected areas, and prevent economic losses from a consumer boycott of products manufactured in affected areas. Since the media are usually involved in national campaigns, they must be educated about HPS to ensure information is reported accurately and responsibly. The recent appearance of HPS, with its dramatic clinical picture, has generated an inordinate amount of media interest in the United States and other countries. Education of the media will also improve the quality of their reporting. The description in Annex 7 of the national campaign in Chile includes much information on that country's use of the mass media.

Audio Conferences

Numerous health care professionals, public health workers, and medical and nursing students from several regions in a country can all participate simultaneously in listening to presentations via a speaker telephone. Prior to the audio conference, participants are provided with a copy of slides and a syllabus for each topic discussed. This is a simple and fairly inexpensive way (depending on long distance telephone services and rates) to provide health care professionals with up-to-date informa-

tion in a timely manner. It also provides a mechanism for the listener to interact with hantavirus experts, better addressing specific needs and questions. Additionally, the materials provided can be used to teach others. HPS topics that might be addressed in audio conferences include epidemiology, ecology, clinical features, patient management, diagnostics, pathology, and health education and prevention.

Seminars

Regional or national hantavirus experts can conduct seminars on all aspects of the disease for physicians and health care providers in their communities or through professional associations. They also allow for interaction among participants and immediate feedback on content and future needs.

Telephone Hot Lines

A telephone hot line is an inexpensive mechanism for health educators to answer questions from both the general public and health professionals. Additionally, callers can be asked to help identify topics that are important to them, as well as to identify topics not addressed in the educational programs. A telephone hot line may also serve as a mechanism for the public to request print materials to be sent by mail or fax.

ANNEX 1. LIST OF PARTICIPANTS AT THE HANTAVIRUS GUIDELINES MEETING

MEETING OF THE HANTAVIRUS TASK FORCE

7–8 March 1998

Holiday Inn, Decatur, Georgia, United States of America

Argentina

Delia A. Enría, *Instituto Nacional de Enfermedades Virales Humanas Dr. Julio I. Maiztegui*

Elsa Segura, *Administración Nacional de Laboratorios e Institutos de Salud Dr. Carlos G. Malbrán*

Paula Padula, *Administración Nacional de Laboratorios e Institutos de Salud Dr. Carlos G. Malbrán*

Zaida Yadón, *Administración Nacional de Laboratorios e Institutos de Salud Dr. Carlos G. Malbrán*

Brazil

Luiza T. Souza, *Instituto Adolfo Lutz*

Canada

Harvey Artsob, *Zoonotic Diseases, Laboratory Center for Disease Control, Health Canada*

Denise Werker, *Field Epidemiology Training Program, Laboratory Center for Disease Control, Health Canada*

Chile

Roberto Belmar, *División de Salud Ambiental, Ministerio de Salud*

Jorge Montecinos, *Servicio de Salud Aysén*

Paraguay

Eugenio Báez, *Departamento de Enfermedades Infecciosas, Sistema de Seguro Social del Paraguay*

United States of America

Ralph Bryan, *Border Health of American Indian Collaborators, National Center for Infectious Diseases, Centers for Disease Control and Prevention*

Fred Koster, *University of New Mexico, School of Medicine*

Amy Corneli, *Health Education and Prevention Unit, Centers for Disease Control and Prevention*

James N. Mills, *Special Pathogens Branch, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention*

Stuart Nichol, *Special Pathogens Branch, Centers for Disease Control and Prevention*

C. J. Peters, *Chairman, Special Pathogens Branch, National Center for Infectious Diseases, Centers for Disease Control and Prevention*

Connie Schmaljohn, *U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick*

William Terry, *Special Pathogens Branch, National Center for Infectious Diseases, Centers for Disease Control and Prevention*

Pan American Health Organization

Roberto Chuit, *former Regional Adviser on Communicable Diseases, Communicable Diseases Program, Division of Disease Prevention and Control*

Stephen Corber, *Director, Division of Disease Prevention and Control*

Laura MacDougall, *Short-term Consultant, Communicable Diseases Program, Division of Disease Prevention and Control*

Raúl José Penna Melo, *former PAHO/WHO Representative in Chile*

Francisco Pinheiro, *Short-term Consultant, Communicable Diseases Program, Division of Disease Prevention and Control*

Marisa Shepherd, *Secretary, Communicable Diseases Program, Division of Disease Prevention and Control*

Jeannette Vega, *National Professional, PAHO/WHO Representation in Chile*

ANNEX 2. CASE REPORT FORMS

RECOMMENDED MINIMUM DATA ELEMENTS FOR INCLUSION IN A SURVEILLANCE FORM

- Case identification number
- Name, address, telephone, fax, e-mail of person completing the surveillance form
- Name, address, telephone, fax, e-mail of hospital or clinic
- Patient name, age/gender, race/ethnicity, residence, occupation, and place of work
- Checklist of surveillance case definition clinical criteria that were evaluated at time of first hospital admission
- Important dates:
  a) Date of symptom onset
  b) Date of first medical contact
  c) Date of first hospitalization
  d) Date of discharge
  e) Disposition (dead/alive)
- Complete blood count—Minimum:
  a) Hematocrit
  b) Hemoglobin
  c) White blood cell count with differential
  d) Platelets
- Chest X-ray
- Oxygen saturation (if available)
- Hantavirus antibody testing (when, where, what test, what results)
- If deceased: autopsy results; record of tissue specimens/contact person
- History of rodent exposure (e.g., droppings, nests, handling mice, etc.) or close contact with another HPS case within eight weeks prior to symptom onset
- History of travel in the last six weeks

EXAMPLE OF AN EPIDEMIOLOGICAL SURVEILLANCE FORM FOR HPS

Suggested Minimum Epidemiological Surveillance Form for Hantavirus Pulmonary Syndrome (HPS)

Date of investigation: _____/_____/_____ Identification Nº: _____
Name of person completing this form: _____ Occupation: _____ Contact information: _____

Institutional Information:
Date of symptom onset: _____/_____/_____
Was patient hospitalized? ☐ Yes ☐ No ☐ Unknown Number of times hospitalized since onset of illness: _____

	First Hospitalization		Second Hospitalization	
Name of hospital:	_____		_____	
Location of hospital:	_____		_____	
Dates in hospital:	____/____/____ to ____/____/____		____/____/____ to ____/____/____	
Record number:	_____		_____	
Disposition:	☐ Alive	☐ Dead	☐ Alive	☐ Dead
Autopsy performed?	☐ Yes	☐ No	☐ Yes	☐ No
If yes, are tissue specimens available?	☐ Yes	☐ No	☐ Yes	☐ No
Contact person/tel. no. for specimens:	_____		_____	

If not hospitalized, name and address of clinic/primary care center: _____

Patient Information:
First name: _____ Family name: _____ Age: _____ Sex: ☐ Male ☐ Female
Race/ethnicity:_____ Residential address: _____ City: _____
County: _____ State: _____ ☐ Urban ☐ Periurban ☐ Rural
Occupation: _____ Place of work: _____

EXAMPLE OF AN EPIDEMIOLOGICAL SURVEILLANCE FORM FOR HPS, CONT.

Clinical Information:

Symptom	*Condition*	*Value/Comment*
Fever >38.3 °C	☐ Yes ☐ No	
Adult respiratory distress syndrome or ARDS-like illness	☐ Yes ☐ No	
Supplemental oxygen required	☐ Yes ☐ No	
Bilateral interstitial infiltrates	☐ Yes ☐ No	
Unexplained illness resulting in death	☐ Yes ☐ No	
Autopsy examination showing noncardiogenic pulmonary edema without an identifiable specific cause of death	☐ Yes ☐ No	

Diagnostic Test	*Performed?*	*Results*
Hematocrit	☐ Yes ☐ No	
Hemoglobin	☐ Yes ☐ No	
White blood cell count with differential	☐ Yes ☐ No	
Platelets	☐ Yes ☐ No	
Chest X-ray	☐ Yes ☐ No	
O_2 saturation	☐ Yes ☐ No	
Other:	☐ Yes ☐ No	

Risk Factor	*Exposure?*	*Description*
History of rodent exposure within 8 weeks of symptom onset	☐ Yes ☐ No	
Close contact with another HPS case within 8 weeks of symptom onset	☐ Yes ☐ No	
Other:	☐ Yes ☐ No	

Confirmed Case:

Confirmed Case—Requires ONE of the following:

Laboratory Test	*Performed?*	*Test Center*	*Results*
Presence of hantavirus-specific IgM or ≥ 4-fold rise in IgG antibody titers	☐ Yes ☐ No		
Positive RT-PCR results for hantavirus RNA	☐ Yes ☐ No		
Positive immunohistochemical results for hantavirus antigens	☐ Yes ☐ No		

ANNEX 3. GUIDELINES FOR THE SAFE TRANSPORT OF INFECTIOUS SUBSTANCES AND DIAGNOSTIC SPECIMENS[1]

Prepared by the World Health Organization, Emerging and Other Communicable Diseases, Surveillance and Control

[1] WHO/EMC/97.3. Distr.: General. Orig.: English.

INTRODUCTION

These guidelines are applicable to the transport of infectious substances and diagnostic specimens both nationally and internationally. They provide information for identifying and classifying the material to be transported and for its safe packaging and transport. The guidelines stress the importance of developing a working relationship between the groups involved—the sender, the carrier and the receiver—in order to provide for the safe and expeditious transport of this material.

Postal, airline and other transport industry personnel hold concerns about the possibility of their becoming infected as the result of exposure to infectious microorganisms that may escape from broken, leaking or improperly packaged material. The packaging of infectious materials for transport must therefore address these concerns and be designed to minimise the potential for damage during transport. In addition, the packaging will serve to ensure the integrity of the materials and timely processing of specimens.

There are no recorded cases of illness attributable to the release of specimens during transport, although there are reported incidents of damage to the outer packaging of properly packaged materials. The shipment of unmarked and unidentified infectious materials, improperly packaged, obviously increases the overall potential for exposure to all persons.

The international regulations for the transport of infectious materials by any mode of transport are based upon the Recommendations of the United Nations Committee of Experts on the Transport of Dangerous Goods (UN). The Universal Postal Union (UPU) reflects these recommendations in its regulations, particularly for packaging. The International Civil Aviation Organization (ICAO) and the International Air Transport Association (IATA) have also incorporated the UN Recommendations in their respective regulations, as have other international transport organizations. The World Health Organization serves in an advisory capacity to these bodies. This document provides practical guidance to facilitate compliance with current international regulations. If, at a future date, any modification is made in the section of the UN Recommendations on the Transport of Dangerous Goods dealing with infectious substances and diagnostic specimens, these guidelines will be updated accordingly.

DEFINITIONS

For the purpose of describing transport safety measures the terms “infectious substances” and “infectious materials” are considered synonymous. The term “infectious substances” will be used in this document.

Infectious substances

An infectious substance is defined as a substance containing a viable microorganism, such as a bacterium, virus, rickettsia, parasite or fungus, that is known or reasonably believed to cause disease in humans or animals.*

With respect to packaging and transport situations, infectious substances include:

1. all cultures containing or suspected of containing an agent which may cause infection;
2. human or animal samples that contain such an agent in quantities sufficient to cause infection, should an exposure to them occur due to a transport mishap;
3. sample(s) from a patient with a serious disease of unknown cause;
4. other specimens not included above and designated as infectious by a qualified person, e.g., a physician, scientist, nurse, etc.

* This definition is taken from the current UN Recommendations on the Transport of Dangerous Goods. Prions are not included in this definition, although they are considered to be infectious agents.

Diagnostic specimens

A diagnostic specimen is defined as any human or animal material including, but not limited to, excreta, blood and its components, tissue and tissue fluids collected for the purposes of diagnosis, but excluding live infected animals.

Diagnostic specimens resulting from medical practice and research are considered a negligible threat to the public health.

Diagnostic specimens obtained from patients with suspected infectious diseases may contain limited quantities of an infectious agent. There are very few agents which may be the source of an infection as a result of a transport mishap. *If exposure to the specimen due to transport mishap could result in an infection, the diagnostic specimen must be packaged, labelled and transported as an infectious substance.* Diagnostic specimens collected during an investigation of an outbreak of a serious disease of unknown cause must be handled as infectious substances.

PACKAGING, LABELLING AND DOCUMENTATION FOR TRANSPORT

Because of the distinction of risks between infectious substances and diagnostic specimens, there are variations to the packaging, labelling and documentation requirements. The packaging requirements are determined by the UN and are contained in ICAO and IATA regulations in the form of Packaging Instructions (PI) 602 and 650. The requirements are subject to change and upgrade by these organisations. The current packaging requirements are described below. UN-approved packaging systems are available commercially.

Basic triple packaging system

The system consists of three layers as follows (Figure A3.1).

1. Primary receptacle. A labelled primary watertight, leak-proof receptacle containing the specimen. The receptacle is wrapped in enough absorbent material to absorb all fluid in case of breakage.
2. Secondary receptacle. A second durable, watertight, leak-proof receptacle to enclose and protect the primary receptacle(s). Several wrapped primary receptacles may be placed in one secondary receptacle. Sufficient additional absorbent material must be used to cushion multiple primary receptacles.
3. Outer shipping package. The secondary receptacle is placed in an outer shipping package which protects it and its contents from outside influences such as physical damage and water while in transit.

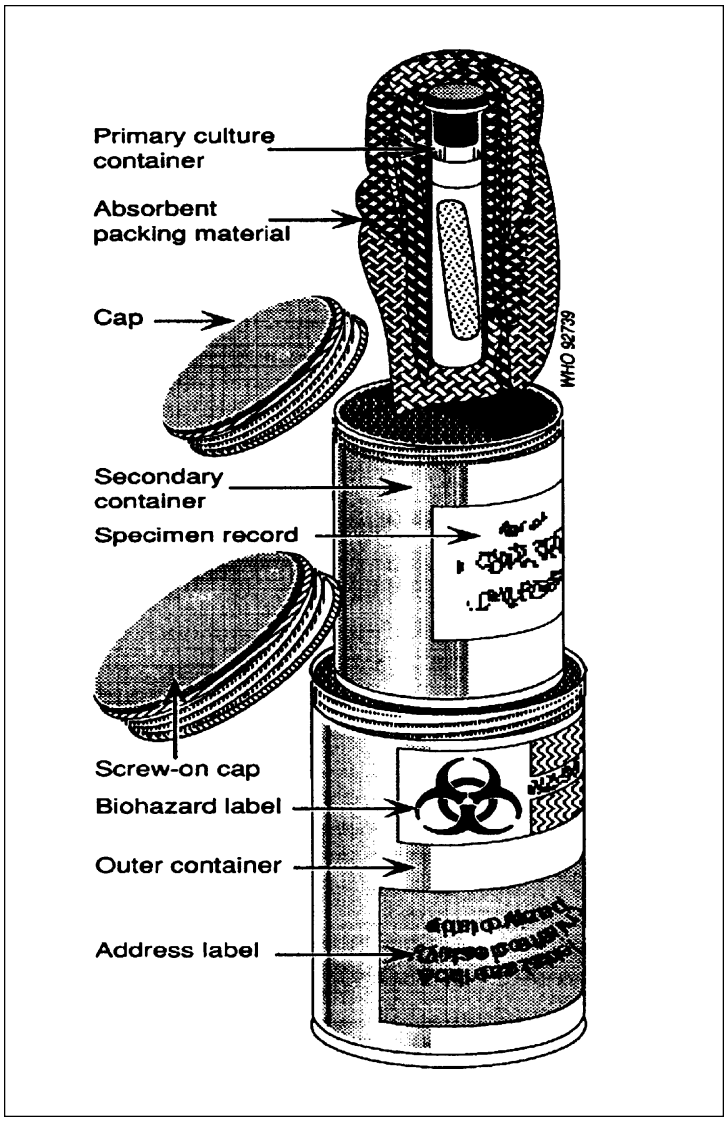
Specimen data forms, letters and other types of information that identify or describe the specimen and also identify the shipper and receiver should be taped to the outside of the secondary receptacle.

Requirements for infectious substances

The basic triple packaging system is used with the following additional specifications and labelling and documentation requirements.

Infectious substances may only be transported in packaging which meets the UN class 6.2 specifications and packaging instruction (PI)602. This ensures that strict performance tests which include a nine metre drop test and a puncture test have been met. The outer shipping package must bear the UN Packaging Specification Marking (Figure A3.2). UN-approved packaging supplier listings may be

FIGURE A3.1. Triple packaging system.



obtained from carriers or from the appropriate national ministry or department, e.g., the Ministry of Transport, etc.

Hand carriage of infectious substances is strictly prohibited by international air carriers, as is the use of diplomatic pouches for that purpose.

The maximum net quantity of infectious substances which can be contained in an outer shipping package is 50 mL or 50 g if transport is by passenger aircraft. Otherwise, the limit per package is 4 L–4 Kg for transport by cargo aircraft or other carriers. Primary receptacles exceeding 50 mL in combination packing must be oriented so the closures are upward, and labels (arrows) indicating the "UP" direction must be placed on two opposite sides of the package. The passenger aircraft quantity limits do not apply to blood or blood products for which there is no reason to believe they contain infectious substances, when in receptacles of not more than 500 mL each and with a total volume of not more than 4 L in the outer package.

FIGURE A3.2. Packaging specification marking.

Example:

4H"/Class 6.2/94 GB/2470

The packaging markings consists of:
- the United Nations symbol
- type of packing
- the text "Class 6.2"
- the last two digits of the year of manufacture of the packaging
- state authority
- manufacturer's code.

In case shipments include only freeze-dried cultures the quantity should be given in g or mg, not in mL. The "PACKAGE ORIENTATION" labels should be affixed to avoid any delay.

Labelling of the outer package for shipment of infectious substances must include the elements listed hereafter.

1. The International Infectious Substance Label.
2. An address label with the following information:
   - the receiver's (consignee) name, address and telephone number
   - the shipper's (consignor) name, address and telephone number
   - the UN shipping name (Infectious Substances Affecting Humans or Animals as the case may be) followed by the scientific name of the substance
   - the UN Number (Humans—UN2814, Animals—UN2900)
   - temperature storage requirements (optional).
     If the outer package is further packed in an overpack (with dry ice for instance) both outerpack and overpack must carry the above information, and the overpack must have a label stating "INNER PACKAGES COMPLY WITH PRESCRIBED SPECIFICATIONS."
3. Required shipping documents—these are obtained from the carrier and are fixed to the outer package:
   - the shipper's Declaration of Dangerous Goods (Figures A3.4 and A3.5 are examples)
   - a packing list/proforma invoice which includes the receiver's address, the number of packages, detail of contents, weight, value (note: state that there is "no commercial value" as the items are supplied free of charge)
   - an airwaybill if shipping by air.
4. An import and/or export permit and/or declaration if required.
5. If the outer package contains primary receptacles exceeding 50 mL in combination, at least two "Orientation Labels" (arrows) must be placed on opposite sides of the package showing correct orientation of the package.

Requirements for diagnostic specimens

The basic triple packaging system is used with the following specifications and labelling requirements.

Diagnostic specimens may be transported in packaging which meets the packaging instruction (PI)650. The UN specification marking is not required.

Primary receptacles may contain up to 500 mL each, the total volume in the outer package not to exceed 4 L.

Labelling of the outer package for the shipment of diagnostic specimens must include the following.

1. An address label with the following information:
   - the receiver's (consignee) name, address and telephone number
   - the shipper's (consignor) name, address and telephone number
   - the statement "Diagnostic Specimen, Not Restricted, Packed in Compliance with Packing Instruction 650."
2. Required shipping documents—these are obtained from the carrier and are fixed to the outer package:
   - a packing list/proforma invoice which includes the receiver's address, the number of packages, detail of contents, weight, value (note: state that there is "no commercial value" as the items are supplied free of charge)
   - an airwaybill if shipping by air.
3. An import and/or export permit and/or declaration (if required).

Note: The infectious substance label and the shipper's declaration of dangerous goods are not required for diagnostic specimens.

Requirements for Air Mail

Infectious substances and diagnostic specimens may be shipped by registered air mail. The basic triple packaging system is used with the same requirements as for other means of conveyance.

The address label must display the word "LETTRE" and the green Customs Declaration Label for Postal Mail is required for international mailing. Diagnostic specimens are to be identified with the violet UPU "PERISHABLE BIOLOGICAL SUBSTANCES" label. Infectious substances are to be identified with the International Infectious Substance label (see Figure A3.3). Infectious substances must also be accompanied with a shipper's Declaration of Dangerous Goods form (see Figures A3.4 and A3.5 at the end of the document).

Because of local/international restrictions, prior contact should be made with the local post office to ascertain whether the packaged material will be accepted by the postal service.

Refrigerants

Ice or dry ice when used in a shipment must be placed outside the secondary receptacle. If wet ice is used it should be in a leak-proof container and the outer package must also be leak-proof.

The secondary receptacle must be secured within the outer package to prevent damage after the refrigerant has melted or dissipated. Dry ice must not be placed inside the primary or secondary receptacle because of the risk of explosions. An overpack (a specially designed insulated outer package) may be used to contain dry ice. The outer package must permit the release of carbon dioxide gas if dry ice is used. UN Packing Instruction 904 must be observed.

If dry ice is used for infectious substances, the details must appear on the shipper's Declaration for Dangerous Goods. In particular, the outermost packing must carry the "MISCELLANEOUS" hazard label for dry ice (see Figure A3.3).

If liquid nitrogen is used as a refrigerant, special arrangements must be made in advance with the carrier. Primary receptacles must be capable of withstanding extremely low temperatures and appropriate packaging requirement of the carrier must be observed. In particular, the outermost packing must carry the "NON-FLAMMABLE GAS" label for liquid nitrogen (see Figure A3.3).

LOCAL SURFACE TRANSPORT

Examples include transport of specimens from a doctor's office/surgery to a laboratory, from a hospital to a diagnostic laboratory or from one laboratory to another. Such courier services

FIGURE A3.3. Hazard labels for dangerous goods.

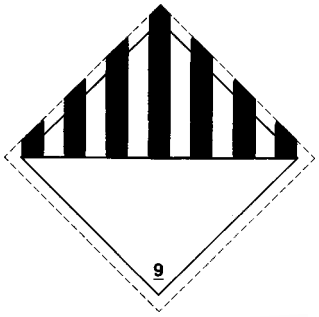
For all dangerous goods to be shipped by airfreight, specific hazard label(s) must be affixed to the outside of each package. The following hazard labels are of importance for culture collections or other institutions shipping biological substances.

Hazard labels for infectious substances and for genetically modified micro-organisms which meet the IATA definition of an infectious substance:

Name: Infectious Substance
Minimum dimensions: 100 x 100 mm
For small packages: 50 x 50 mm (black and white)

Hazard label for noninfectious genetically modified microorganisms and for carbon dioxide, solid (dry ice):

Name: Miscellaneous
Minimum dimensions: 100 x 100 mm
For small packages: 50 x 50 mm (black and white)

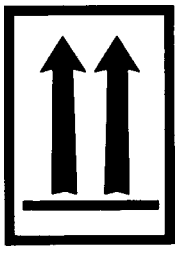


Hazard label for liquid nitrogen:

Name: Non-flammable gas
Minimum dimensions: 100 x 100 mm
For small packages: 50 x 50 mm (green and white)

Packages containing liquid cultures of infectious organisms and genetically modified microorganisms must be packed so that the closure(s) of the inner packaging(s) are upward; the upright position of the packaging must be indicated by two "Package Orientation" labels (black or red arrows). The labels must be affixed on opposite sides of the packaging. A label "THIS SIDE UP" or "THIS END UP" may also be displayed on the top cover of the package:

Name: Package Orientation
Minimum dimensions: 74 x 105 mm (black or red and white)
For small packages of infectious substances dimensions may be halved.



may be operated by a hospital, a laboratory, a health service or other approved agency or organisation.

The principle of safe transport by this means is the same as for air or international transport—the material should not have any possibility of escaping from the package under normal conditions of transport.

The following practices should be observed:

1. specimen containers should be watertight and leak-proof;
2. if the specimen container is a tube, it must be tightly capped and placed in a rack to maintain it in an upright position;
3. specimen containers and racks should be placed in robust, leak-proof plastic or metal transport boxes with secure, tight fitting covers;
4. the transport box should be secured in the transport vehicle;
5. each transport box should be labelled appropriately consistent with its contents;
6. specimen data forms and identification data should accompany each transport box;
7. a spill kit containing absorbent material, a chlorine disinfectant, a leak-proof waste disposal container and heavy duty reusable gloves should be kept in the transport vehicle.

Note: The practices 1–7 described above are not intended to supersede local or national requirements.

TRANSPORT PLANNING

It is the responsibility of the sender to ensure the correct designation, packaging, labelling and documentation of all infectious substances and diagnostic specimens.

The efficient transport and transfer of infectious materials requires good coordination between the sender, the carrier and the receiver (receiving laboratory), to ensure that the material is transported safely and arrives on time and in good condition. Such coordination depends upon well-established communication and a partner relationship among the three parties.

All have specific responsibilities to carry out in the transport effort.

The sender

1. makes advance arrangements with the receiver of the specimens including investigating the need for an import permit;
2. makes advance arrangements with the carrier to ensure:
   - that the shipment will be accepted for appropriate transport
   - that the shipment (direct transport if possible) is undertaken by the most direct routing, avoiding arrival at weekends;
3. prepares necessary documentation including permits, dispatch and shipping documents;
4. notifies the receiver of transportation arrangements once these have been made, well in advance of expected arrival time.

The carrier

1. provides the sender with the necessary shipping documents and instructions for their completion;
2. provides advice to the sender about correct packaging;
3. assists the sender in arranging the most direct routing and then confirms the routing;
4. maintains and archives the documentation for shipment and transport;
5. monitors required holding conditions of the shipment while in transit;
6. notifies the sender of any anticipated (or actual) delays in transit.

The receiver

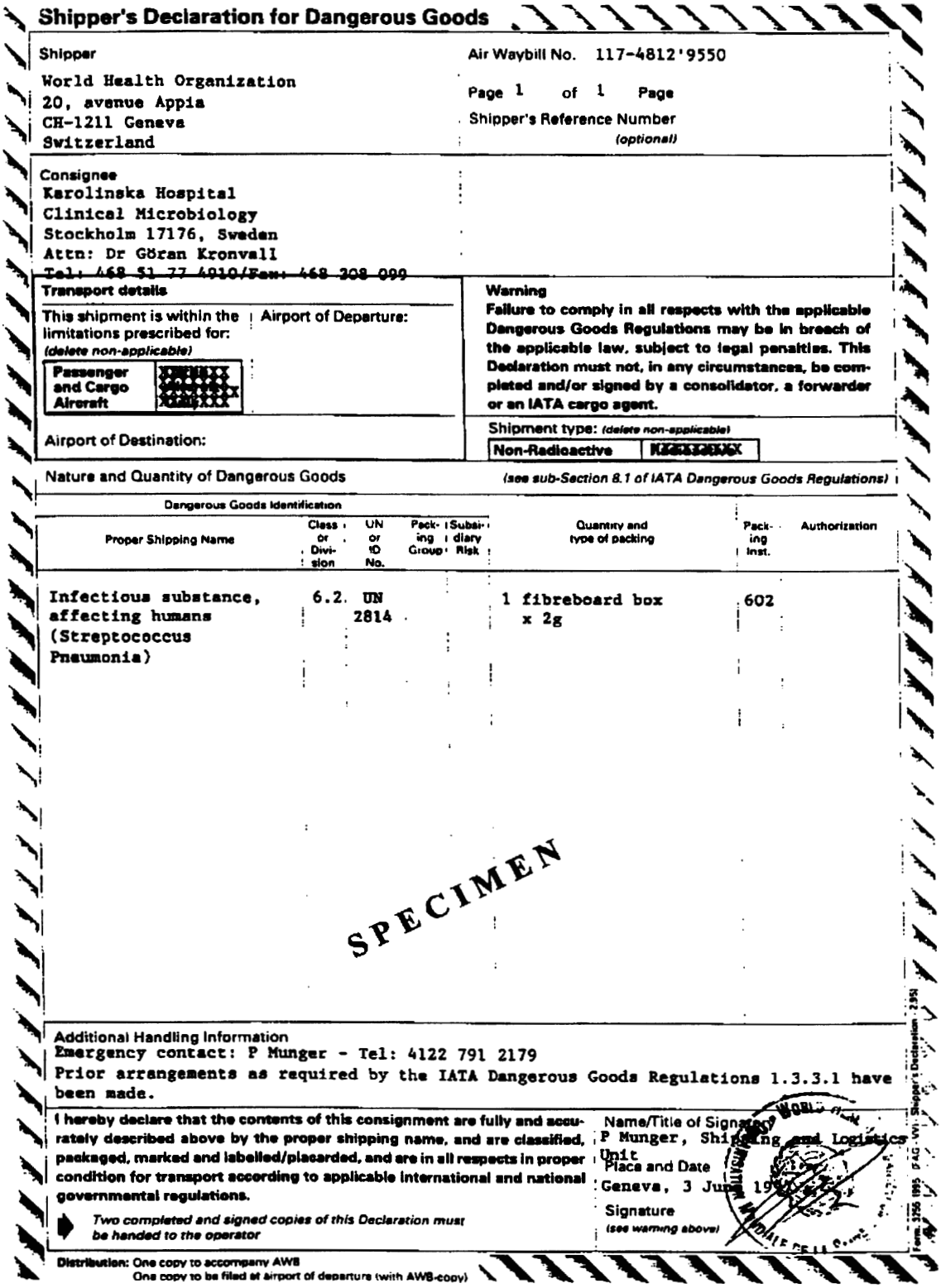
1. obtains the necessary authorisation(s) from national authorities for the importation of the material;
2. provides the sender with the required import permit(s), letter(s) of authorisation, or other document(s) required by the national authorities;
3. arranges for the most timely and efficient collection on arrival;
4. immediately acknowledges receipt to the sender.

Shipments should not be dispatched until:

- advance arrangements have been made between the sender, carrier and receiver
- the receiver has confirmed with the national authorities that the material may be legally imported
- the receiver has confirmed that there will be no delay incurred in the delivery of the package to its destination.

Detailed information on response and emergency safety measures in transport-associated accidents can be found in *Laboratory Biosafety Manual*, Second edition (1993). Geneva: World Health Organization: (pp. 52–54).

FIGURE A3.4. Standard shipment of infectious substances.



Shipper's Declaration for Dangerous Goods

Shipper
World Health Organization
20, avenue Appia
CH-1211 Geneva
Switzerland

Air Waybill No. 117-4812'9550

Page 1 of 1 Page

Shipper's Reference Number (optional)

Consignee
Karolinska Hospital
Clinical Microbiology
Stockholm 17176, Sweden
Attn: Dr Göran Kronvall
Tel: 468 51 77 4910/Fax: 468 308 099

Transport details

This shipment is within the limitations prescribed for: (delete non-applicable)

Passenger and Cargo Aircraft

Airport of Departure:

Airport of Destination:

Warning
Failure to comply in all respects with the applicable Dangerous Goods Regulations may be in breach of the applicable law, subject to legal penalties. This Declaration must not, in any circumstances, be completed and/or signed by a consolidator, a forwarder or an IATA cargo agent.

Shipment type: (delete non-applicable)
Non-Radioactive

Nature and Quantity of Dangerous Goods (see sub-Section 8.1 of IATA Dangerous Goods Regulations)

Dangerous Goods Identification					Quantity and type of packing	Packing Inst.	Authorization
Proper Shipping Name	Class or Division	UN or ID No.	Packing Group	Subsidiary Risk			
Infectious substance, affecting humans (Streptococcus Pneumonia)	6.2.	UN 2814			1 fibreboard box x 2g	602	

SPECIMEN

Additional Handling Information
Emergency contact: P Munger - Tel: 4122 791 2179
Prior arrangements as required by the IATA Dangerous Goods Regulations 1.3.3.1 have been made.

I hereby declare that the contents of this consignment are fully and accurately described above by the proper shipping name, and are classified, packaged, marked and labelled/placarded, and are in all respects in proper condition for transport according to applicable international and national governmental regulations.

Name/Title of Signatory
P Munger, Shipping and Logistics Unit

Place and Date
Geneva, 3 June 19[illegible]

Signature (see warning above)

Two completed and signed copies of this Declaration must be handed to the operator

Distribution: One copy to accompany AWB
One copy to be filed at airport of departure (with AWB-copy)

Form 1756 (1995) (FAG-VV) Shipper's Declaration (2/95)

FIGURE A3.5. Shipment of infectious substances using dry ice.

Shipper's Declaration for Dangerous Goods

Shipper
World Health Organization
20, avenue Appia
CH-1211 Geneva
Switzerland

Air Waybill No. 117-4812'9550

Page 1 of 1 Page

Shipper's Reference Number *(optional)*

Consignee
Karolinska Hospital
Clinical Microbiology
Stockholm 17176, Sweden
Attn: Dr Göran Kronvall
~~Tel: 468 51 77 4010/Fax: 468 308 099~~

Transport details

This shipment is within the limitations prescribed for: *(delete non-applicable)*

Passenger and Cargo Aircraft	XXXXXXX

Airport of Departure:

Airport of Destination:

Warning

Failure to comply in all respects with the applicable Dangerous Goods Regulations may be in breach of the applicable law, subject to legal penalties. This Declaration must not, in any circumstances, be completed and/or signed by a consolidator, a forwarder or an IATA cargo agent.

Shipment type: *(delete non-applicable)*

Non-Radioactive	XXXXXXXXX

Nature and Quantity of Dangerous Goods *(see sub-Section 8.1 of IATA Dangerous Goods Regulations)*

Dangerous Goods Identification							
Proper Shipping Name	Class or Division	UN or ID No.	Packing Group	Subsidiary Risk	Quantity and type of packing	Packing Inst.	Authorization
Infectious substance, affecting humans (Streptococcus Pneumonia)	6.2	UN 2814			1 fibreboard box x 2g	602	
Dry Ice	9	UN 1845	III		10 kg	904	
		OVERPACK USED					

SPECIMEN

Additional Handling Information
Emergency contact: P Munger - Tel: 4122 791 2179
Prior arrangements as required by the IATA Dangerous Goods Regulations 1.3.3.1 have been made.

I hereby declare that the contents of this consignment are fully and accurately described above by the proper shipping name, and are classified, packaged, marked and labelled/placarded, and are in all respects in proper condition for transport according to applicable international and national governmental regulations.

Two completed and signed copies of this Declaration must be handed to the operator

Name/Title of Signatory
P Munger, Shipping and Logistics Unit

Place and Date
Geneva, 3 June 1997

Signature *(see warning above)*

Distribution: One copy to accompany AWB
One copy to be filed at airport of departure (with AWB-copy)

ANNEX 4. BIOSAFETY GUIDELINES (*79*)

GENERAL PRINCIPLES

Laboratories are designated according to their design features and constriction and containment facilities (safety precautions and equipment) as Basic—Biosafety Level 1, Basic—Biosafety Level 2, Containment—Biosafety Level 3, and Maximum Containment—Biosafety Level 4.

Table A4.1 describes the risk groups and Table A4.2 relates them to the laboratory designations. Table A4.3 gives a summary of the four biosafety level requirements.

TABLE A4.1. Classification of infective microorganisms by risk group.

Risk Group 1 (no or very low individual and community risk)	A microorganism that is unlikely to cause human or animal disease.
Risk Group 2 (moderate individual risk, low community risk)	A pathogen that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock, or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spread of infection is limited.
Risk Group 3 (high individual risk, low community risk)	A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.
Risk Group 4 (high individual and community risk)	A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.

TABLE A4.2. Relationship of risk groups to biosafety levels, practices, and equipment.

Risk Group	Biosafety Level	Examples of labs	Lab practices	Safety equipment
1	Basic—Biosafety Level 1 (BSL-1)	Basic teaching	GMT[a]	None; open bench work
2	Basic—Biosafety Level 2 (BSL-2)	Primary health services; primary level hospital; diagnostic, teaching, and public health	GMT plus protective clothing; biohazard sign	Open bench plus BSC[b] for potential aerosols
3	Containment—Biosafety Level 3 (BSL-3)	Special diagnostic	As BSL-2 plus special clothing, controlled access, directional air flow	BSC and/or other primary containment for all activities
4	Maximum Containment—Biosafety Level 4 (BSL-4)	Dangerous pathogen units	As BSL-3 plus airlock entry, shower exit, special waste disposal	Class III BSC or positive pressure suits, double-ended autoclave, filtered air

[a] GMT = good microbiological technique.
[b] BSC = biological safety cabinet.

Each country should draw up a classification by risk group of the microorganisms encountered within its boundaries, based on the following factors:

- Pathogenicity of the organism.
- Mode of transmission and host range of the organism. These may be influenced by existing levels of immunity, density and movement of the host population, presence of appropriate vectors, and standards of environmental hygiene.
- Availability of effective preventive measures. These may include prophylaxis by immunization or administration of antisera; sanitary measures, e.g., food and water hygiene; control of animal reservoirs or arthropod vectors; and restrictions on the importation of potentially infected animals or animal products.
- Availability of effective treatment. This includes passive immunization, postexposure vaccination, and use of antimicrobials and chemotherapeutics, taking into consideration the possibility of the emergence of resistant strains.

In assessing the various criteria for classification, it is also important to take into account conditions prevailing in the geographical area in which the microorganisms are handled. Individual governments may decide to prohibit the handling or importation of certain pathogens except for diagnostic purposes.

In the preparation of lists it is recommended that, where appropriate, additional information be given about the advisability of wearing gloves and eye protection and, in the case of some Risk Group 3 pathogens, whether or not a biological safety cabinet is required.

Existing classifications, made by different countries and official organizations, may be useful for the preparation of new classifications and guidelines. One such set of guidelines for hantavirus pulmonary syndrome is available from the U.S. CDC.

Genetically engineered microorganisms may be placed in the risk groups that are appropriate for their recipients and donors, and handled at the relevant biosafety level. Various national and international codes and guidelines for work with genetically engineered organisms are available and can help guide local efforts.

TABLE A4.3. Summary of biosafety levels.

	Biosafety Level			
	1	2	3	4
Isolation of laboratory	No	No	Desirable	Yes
Room sealable for decontamination	No	No	Yes	Yes
Ventilation:				
Inward air flow	No	Desirable	Yes	Yes
Mechanical via building system	No	Desirable	Desirable	No
Mechanical independent	No	No	Desirable	Yes
Filtered air exhaust	No	No	Yes	Yes
Double-door entry	No	No	Yes	Yes
Airlock	No	No	No	Yes
Airlock with shower	No	No	No	Yes
Effluent treatment	No	No	No	Yes
Autoclave:				
On site	Yes	Yes	Yes	Yes
In laboratory room	No	No	Yes	Yes
Double-ended	No	No	Desirable	Yes
Biological safety cabinets:				
Class I or II	No	Yes	Yes	Desirable
Class III	No	No	Desirable	Yes

ANNEX 5. EDUCATIONAL MATERIALS AVAILABLE FROM THE U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

The following materials are available free of charge from the U.S. Centers for Disease Control and Prevention. Copies may be requested by calling (1-404) 639-1510, faxing (1-404) 639-1509, or through e-mail at dvd1spath@cdc.gov. Requests may also be sent by regular mail to Special Pathogens Branch, Centers for Disease Control, Mail Stop A26, 1600 Clifton Road, Atlanta, Georgia 30333. Please include your postal mailing address in your request.

PREVENTING HANTAVIRUS DISEASE

The purpose of this video (running time 27 minutes) is to provide information to the general public on hantavirus pulmonary syndrome (HPS). Doctors and scientists who have had firsthand experience with HPS discuss symptoms, transmission, risk factors, treatment, and prevention. The video also focuses on how to prevent the disease by using rodent control measures and safety precautions. Additionally, people who have survived HPS describe what it is like to have this illness. A Spanish version is also available.

A NEW HANTAVIRUS

This videotape (running time 57 min) provides information on hantavirus pulmonary syndrome to health professionals and covers the 1993 outbreak in the southwestern United States, clinical description, laboratory diagnosis, treatment, surveillance, and prevention.

METHODS FOR TRAPPING AND SAMPLING SMALL MAMMALS FOR VIROLOGIC TESTING

This manual is intended as a guide for those persons performing ecologic and epidemiologic studies involving populations of rodents which are potentially infected with hantavirus. The manual covers the following major topics in detail: selection of appropriate collection sites; trapping methods that provide a representative sample of the rodent population; handling, operation, and placement of traps for small mammals; safe and humane techniques for trapping and handling rodents; selection of appropriate sample fluids and tissues and detailed methods for obtaining these samples; proper storage, packaging, and shipment of specimens to the laboratory; effective decontamination and cleaning of traps and other materials; safe disposal of infectious wastes; and careful collection and recording of all pertinent data.

HANTAVIRUS: INFORMATION ABOUT THE DISEASE AND HOW TO HELP PREVENT IT

This packet of prevention materials includes a poster, multiple copies of a concise informational brochure (may be ordered separately), a "Frequently Asked Questions" sheet, and "The Essential Facts" sheet.

PREVENT HANTAVIRUS PULMONARY SYNDROME

This brochure is a public information guide for tourists, campers, and hikers.

LABORATORY MANAGEMENT OF AGENTS ASSOCIATED WITH HPS: INTERIM BIOSAFETY GUIDELINES

This *Morbidity and Mortality Weekly Report* (*MMWR*) issue contains the following information on biosafety:

precautions for handling specimens from humans; precautions for handling tissue samples and viral cultures; and precautions for work with host species.

HANTAVIRUS INFECTION—SOUTHWESTERN UNITED STATES: INTERIM RECOMMENDATIONS FOR RISK REDUCTION

This *MMWR* issue contains the following information on risk reduction: general household precautions in affected areas; eliminating rodents inside the home and reducing rodent access to the home; cleanup of rodent-contaminated areas; special precautions for homes of persons with confirmed hantavirus infection or buildings with heavy rodent infestation; precautions for workers in affected areas who are regularly exposed to rodents; precautions for other occupational groups who have potential rodent contact; and precautions for campers and hikers in the affected areas.

CDC HANTAVIRUS INTERNET WEB SITE

http://www.cdc.gov/ncidod/diseases/hanta/hps/index.htm.

The "All About Hantavirus" Internet Web site offers information on HPS. Contents are divided into general and technical information areas. Subjects covered in the general information area include carriers and transmission, a description of at-risk groups, symptoms, treatment, prevention methods for various situations, and the history of HPS in the United States. The technical information area is written as a standard research article, with topics ranging from clinical subjects through ecology, epidemiology, and virology. Additional offerings include case information, data on HPS in South America, a listing and description of other information resources, state epidemiology contacts, and special reports. One article, for example, discusses the potential impact of El Niño on the occurrence of HPS. A text-only version of the entire site is also available to make access easier for persons with slow Internet connections.

ANNEX 6. PREVENTION CAMPAIGN AGAINST HANTAVIRUS PULMONARY SYNDROME IN ARGENTINA

In Argentina, the first cases of hantavirus pulmonary syndrome (HPS) were identified in the central area of the country. Prevention strategy for HPS was incorporated into the existing, well-developed campaign against Argentine Hemorrhagic Fever (AHF), another severe rodent-borne viral disease. Using the same materials, the health officials introduced the idea of another rodent-borne disease to both the general public and health personnel. Differences between the two diseases, such as the fact that AHF is vaccine preventable while HPS is not, were highlighted. Surveillance for HPS and AHF was carried out simultaneously.

In May 1995, HPS emerged in the Andean-Patagonian area of the provinces of Chubut and Río Negro. Local, regional, provincial, and national health authorities were contacted, and health education efforts were developed. Materials provided by the U.S. Centers for Disease Control and Prevention and the Instituto Maiztegui were used and adapted to the local geographic and social conditions.

Media sources such as newspapers, TV, and radio instructed the general public on basic information about HPS and prevention measures. Other communication channels, such as health workers, primary and secondary schools, universities, firemen, janitorial staff of schools, trash collectors, forestry workers, park rangers, municipal employees, and public and private businesses, were used to communicate messages about HPS. Brochures were mass distributed door-to-door by health workers. A local education video was also developed and shown at schools and tourist information sites.

Health education efforts were extended beyond the general public and health professionals. Work was done in collaboration with the national parks in the region and the provincial tourism authority to carry out health/sanitation assessments and inspections in tourist areas: cabins, hotels, and campgrounds. Rodent eradication and fumigation were conducted in areas considered to be at risk.

Among the Spanish-language educational materials developed were:

- Síndrome pulmonar por hantavirus: Información para profesionales
- Síndrome pulmonar por hantavirus: Información para la población
- Mensajes para la difusión radial y televisiva

For more information on these materials, contact:

Instituto Nacional de Enfermedades Virales Humanas
(INEVH—ANLIS)
Monteagudo 2510
2700 Pergamino
Provincia de Buenos Aires
Argentina
Telephone: (54-477) 33044; Fax: (54-477) 33045
E-mail: postmaster@inevh.sld.ar

A national meeting is held annually for physicians, laboratory workers, and public health personnel involved in the HPS program. Materials are available in Spanish from the last two meetings:

- Recomendaciones de la 1ª Reunión Anual sobre SPH en Argentina
- Recomendaciones de la 2ª Reunión Anual sobre SPH en Argentina

For details on these materials, contact:

ANLIS Dr. Carlos Malbrán
Vélez Sársfield 563
Buenos Aires, Argentina
Telephone: (54-1) 303-1804/10

For more information about Argentina's health education program in Chubut and Río Negro, contact:

Dirección de Zona Sanitaria Noroeste (Siprosalud)
Rivadavia 826
9200 Esquel
Provincia de Chubut
Argentina
Telephone: (54-945) 51422/50922
Fax: (54-945) 51428/51426

ANNEX 7. PREVENTION CAMPAIGN AGAINST HANTAVIRUS IN CHILE: NONOUTBREAK AND OUTBREAK SITUATIONS

A PREVENTION CAMPAIGN FOR NONOUTBREAK SITUATIONS

In 1995, the first case of hantavirus pulmonary syndrome (HPS) appeared in Region X of Chile, in a village near El Bolsón, Argentina. Due to the proximity of HPS cases in Argentina, a communication campaign was implemented in southern Chile. Every health service in the southern region produced a campaign addressing its own regional needs, which mostly included the production of posters and pamphlets.

A PREVENTION CAMPAIGN FOR OUTBREAK SITUATIONS

In 1997, an outbreak of HPS occurred in Aysén, Region XI of Chile, and provoked panic among the population. In response, the Ministry of Health established a communication strategy at the national level.

The objectives of the communication strategy were to obtain prevention techniques culturally appropriate to the rural population, to calm and protect the urban and rural population, and to educate health care workers.

A number of actions were taken. Daily reports on the epidemiologic situation were disseminated through the media. A relationship was established between the National Commission on Hantavirus and the press. Educational materials were distributed in schools, bus terminals, and other public places. A scientific conference was held for journalists, with participation from epidemiologists, virologists, and a rodent specialist. A "hantavirus radio day" was produced, which established communication between specialists and the population. Special programs about hantavirus were televised. Finally, a Hantavirus Prevention National Campaign was designed and implemented.

The Hantavirus Prevention National Campaign was divided into two stages, general prevention and summer prevention.

In the first stage, the general objectives included reducing and preventing hantavirus infection in the country and promoting in-home hygiene habits, especially in rural zones. Specific objectives included promoting the adoption of prevention measures in the population and informing the population of the mechanisms of transmission and characteristics of the virus in order to calm their fears.

Media and material support were extensive. They included:

- radio: two messages (rural and urban), for four weeks in September and October
- television: two commercials (rural and urban), for four weeks in September and October
- posters: two (rural and semiurban zones), 50,000 copies, distributed in September
- notes: for general information, 500,000 copies, distributed in September
- notebook for public sector heath group: 16,000 copies, distributed in October
- notebook for private sector health group: 14,000 copies, distributed in October
- notebook for hospital professionals: 1,000 copies, distributed in October
- notebook for basic education teachers: 80,000 copies, distributed in October
- posters for schools (rural and urban): 10,000 copies, distributed in October

The second stage of the national campaign focused on summer prevention. Its general objectives included promoting a safe summer through the adoption of prevention measures for camping and staying in summer homes and promoting the adoption of prevention measures by persons who work or have contact with rural areas.

Media and material support was comprehensive and included:

- radio: two messages (cabins and camping), for a month, from December to January
- television: two commercials (cabins and camping), for a month, from December to January

- posters: two (cabin and camping sectors), 50,000 copies, distributed December to January
- notes: two (cabin and camping sectors), 500,000 copies, distributed December to January
- Material for those who work with National Forests Corporation: for visitors, notes (500,000) and posters (700); for employees: small notebooks for park rangers (400); for volunteers: small notebooks (1,200)

COMMUNICATION STRATEGY FOR MAINTENANCE (NONOUTBREAK PERIOD)

During this period, the Ministry of Health strategy was to maintain prevention measures, especially in the previously affected areas of the Ninth through the Eleventh regions.

Accomplished and planned future actions include:

- reporting new cases to the population regularly
- maintaining a permanent level of caution in the public, in order to maintain good hygiene habits, especially in the rural regions
- continuing commercials on television aimed specifically at rural residents.

Also to be produced are a video and book to be distributed at the central level. Both pieces will summarize all the work accomplished by the Hantavirus Taskforce. The materials will also serve as a registry of the experience that may be useful for future generations of health care workers. National campaign officials will also work to obtain new sponsors to contribute to the production of other educational materials, especially in regard to personal risk.

For more information about Chile's health education program, contact:

María Elina Barrera
Jefe de Comunicaciones y Relaciones Públicas
Ministerio de Salud de Chile
Mac Iver 541, Oficina 201
Santiago
Chile
Telephone: (56-2) 630-0301; Fax: (56-2) 639-7292

ANNEX 8. HANTAVIRUS PREVENTION IN THE UNITED STATES OF AMERICA

RAPID RESPONSE DURING THE 1993 OUTBREAK

At the United States Centers for Disease Control and Prevention (CDC), educational efforts were primarily focused on educating medical and public health professionals. Since this was a newly recognized disease, the physicians and nurses needed to be informed about the disease, and the state epidemiologists needed to know what to do if their states had any cases. Therefore, the first educational materials and activities were planned for this target audience. A comprehensive video was developed and aggressively disseminated to this group and used in other, subsequent educational activities. These activities included training courses for state public health laboratories on diagnostic testing of hantavirus and an audio conference for physicians, nurses, laboratorians, epidemiologists, and pathologists.

For the public, CDC developed and then promoted a video in both English and Spanish versions, set up a telephone hot line to answer the public inquiry calls, provided materials on request, and developed an Internet site. One major goal was to work with public health professionals from the most affected states to generate locally appropriate programs in their areas. As additional states recognized cases, this material was shared with them and they further disseminated it to local health departments. A similar pattern has been useful with other countries undergoing their first experiences with hantavirus pulmonary syndrome (HPS).

CDC also worked with the private sector in raising the public awareness of HPS. In this collaboration, CDC provided the content, arranged for interviews with HPS experts, and reviewed draft news releases and materials. The private sector provided the financial and human resources in marketing and advertising. Video and audio news releases were produced for broadcast stations to use across the nation. Print materials targeting the general public and prevention articles for newspapers and magazines were also developed.

CURRENT PREVENTION MEASURES

Information on HPS control and prevention measures is disseminated regularly as part of ongoing educational efforts. State health departments are updated periodically by mail on a variety of subjects. Mailings communicate news or information (e.g., the increased possibility of an outbreak of HPS during an epizootic related to El Niño climate changes), provide materials such as case investigation kits or treatment guidelines, and offer information about CDC services and resources, such as what diagnostic testing is available, how to submit samples for testing, and what prevention materials are available.

In 1998, the CDC hosted the Fourth International Conference on Hemorrhagic Fever with Renal Syndrome and Hantaviruses in Atlanta, Georgia. Much recent data on hantavirus research and prevention coming out of that meeting are available on the Internet at http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/intro.htm.

ANNEX 9. PREVENTION MATERIALS FOR REPRODUCTION AND DISTRIBUTION

This annex contains reference materials on personal risk reduction that can be produced and distributed easily and quickly.

HANTAVIRUS PULMONARY SYNDROME

Rationale for Surveillance

Hantavirus pulmonary syndrome (HPS) in the Americas is a rare but usually severe disease transmitted through close contact with the urine, feces, or saliva of infected rodents. Although HPS cases have only been reported from Argentina, Brazil, Canada, Chile, Paraguay, United States of America, and Uruguay, the potential for disease exists throughout the Americas due to the widespread distribution of existing rodent reservoirs. Surveillance is therefore essential for all countries.

Recommended HPS Case Definition

Clinical Case Definition:

- A febrile illness (i.e., temperature greater than 38.3 °C [101 °F]) occurring in a previously healthy person characterized by bilateral diffuse interstitial edema that may radiographically resemble adult respiratory distress syndrome (ARDS) with respiratory compromise requiring supplemental oxygen developing within 72 hours of hospitalization; **OR**
- An unexplained illness resulting in death in conjunction with an autopsy examination demonstrating noncardiogenic pulmonary edema without an identifiable specific cause of death.

Laboratory Criteria for Diagnosis:

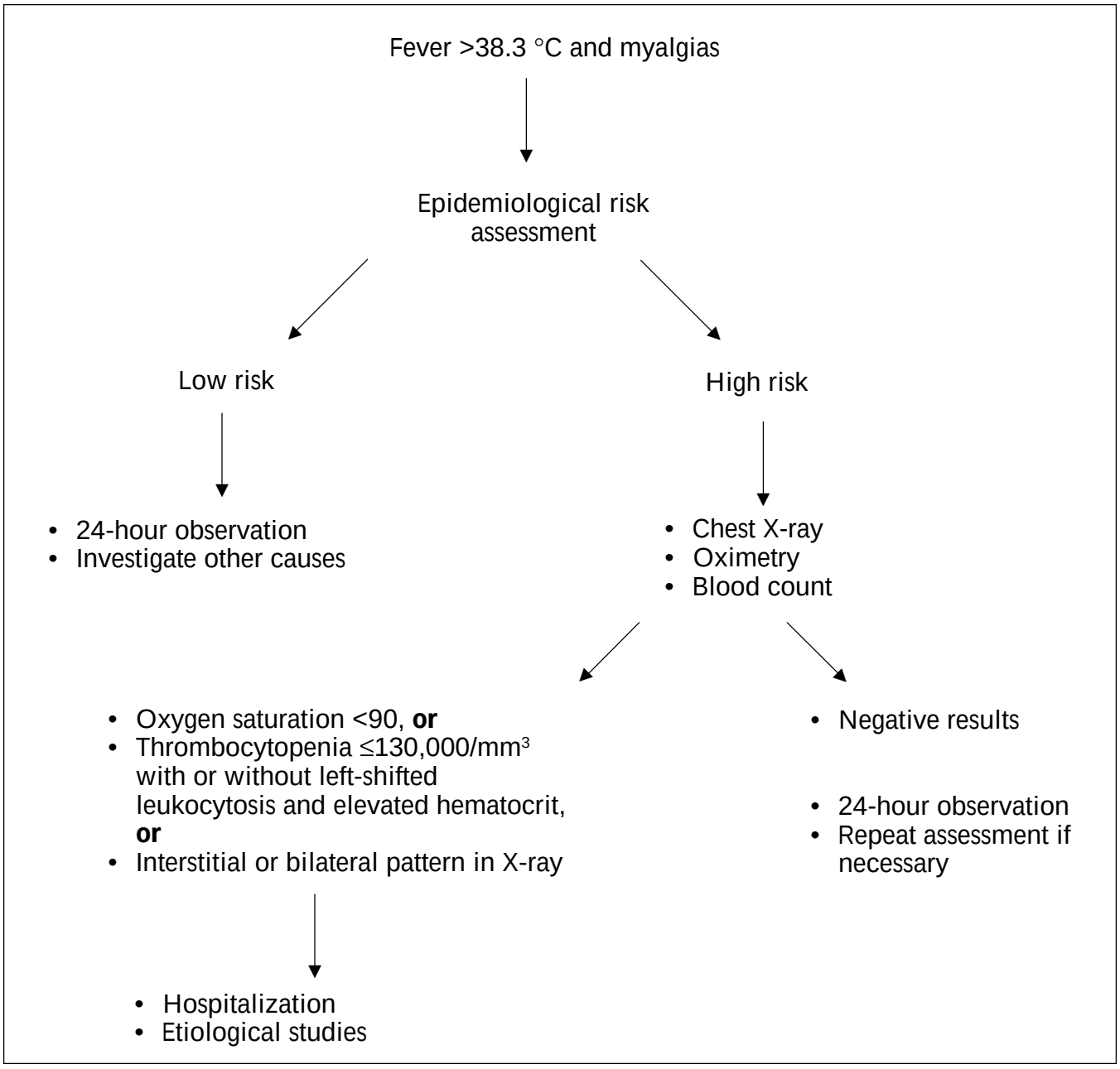
- Presence of hantavirus-specific IgM antibodies or a 4-fold or greater increase in IgG antibody titers; **OR**
- Positive reverse transcriptase-polymerase chain reaction (RT-PCR) results for hantavirus RNA; **OR**
- Positive immunohistochemical results for hantavirus antigens.

Case Classification:

Suspected: A case compatible with the clinical description.

Confirmed: A suspected case that is laboratory confirmed.

FIGURE A9.1. Hantavirus pulmonary syndrome algorithm.



Recommendations for Surveillance

- Establish HPS as a reportable (compulsory reporting) disease in all PAHO Member Countries.
- Develop a case report form that identifies standard minimum data elements to be collected by all countries of the Region.
- If HPS is suspected, a blood count, chest X-ray, oxygen saturation, and hantavirus serology should be performed. Rodent exposure should be evaluated.
- Postmortem blood, fresh frozen tissue, and formal fixed tissue should be collected from deceased HPS patients and properly transported to the nearest laboratory capable of HPS confirmation.
- If hantavirus infection not meeting the case definition of HPS is suspected, specimens may also be submitted for testing along with a description of clinical manifestations.

General Precautions for Residents of Affected Areas

- Reduce the availability of food sources and nesting sites used by rodents inside the home.
- Eliminate rodents inside the home.
- Discourage children from playing with rodents or their nests, and advise them to tell their parents if they see rodents or their nests.
- Keep food (including pet food) and water covered and stored in rodent-proof metal or thick plastic containers with tight-fitting lids.
- Store garbage inside homes in rodent-proof metal or thick plastic containers with tight-fitting lids.
- Wash dishes and cooking utensils immediately after use and remove all spilled food.
- Dispose of trash and clutter.
- Use spring-loaded rodent traps in the home continuously.
- As an adjunct to traps, use rodenticide with bait under a plywood or plastic shelter (a covered bait station) on an ongoing basis inside the house.

General Practices for the Prevention of Rodent-infested Homes

- Use steel wool or cement to seal, screen, or otherwise cover all openings into the home that have a diameter of 0.5 cm or more.
- Place metal roof flashing as a rodent barrier around the base of wooden, earthen, or adobe dwellings up to a height of 30 cm and buried in the soil to a depth of 15 cm.
- Place 10 cm of gravel under the base of homes or under mobile homes to discourage rodent burrowing.
- Reduce rodent shelter and food sources within 30 m of the home.
- Cut grass, brush, and dense shrubbery within 30 m of the home.
- Use raised cement foundations in new construction of sheds, barns, outbuildings, or woodpiles.
- When possible, place woodpiles 30 m or more from the house and elevate wood at least 30 cm off the ground.
- Store grains and animal feed in rodent-proof containers.
- Near buildings, remove food sources that might attract rodents, or store food and water in rodent-proof containers.
- Store hay on pallets, and use traps or rodenticide continuously to keep hay free of rodents.
- Do not leave pet food in feeding dishes.
- Dispose of garbage and trash in rodent-proof containers that are elevated at least 30 cm off the ground.
- Haul away trash, abandoned vehicles, discarded tires, and other items that may serve as rodent nesting sites.
- Place spring-loaded rodent traps at likely spots for rodent shelter within 30 m around the home, and use continuously.
- Use a nationally approved rodenticide certified for outside use in covered bait stations at places likely to shelter rodents within 30 m of the home.

Eliminating Rodent Infestation: Guidance for Residents of Affected Areas

- Before rodent elimination work is begun, ventilate closed buildings or areas inside buildings by opening doors and windows for at least 30 min. Use an exhaust fan or cross ventilation if possible. Leave the area until the airing-out period is finished. This airing may help remove any aerosolized virus inside the closed-in structure.
- Seal, screen, or otherwise cover all openings into the home that have a diameter of 0.5 cm or more. Then set rodent traps inside the house, using peanut butter, fruit, sugarcane, or other substitutes as bait. Use only spring-loaded traps that kill rodents.
- Next, treat the interior of the structure with an insecticide labeled for flea control, following label instructions. Insecticide sprays or powders can be used in place of aerosols if they are appropriately labeled for flea control.
- Rodenticides may also be used while the interior is being treated, as outlined below:
  - Remove dead rodents from the traps. Wear rubber or plastic gloves while handling rodents. Place the carcasses in a plastic bag containing a sufficient amount of a general-purpose household disinfectant to thoroughly wet the carcasses. Seal and double-bag the carcasses, then dispose of them by burying them in a hole 0.5–1 m deep or by burning. If burying or burning is not feasible, contact your local or state health department about other appropriate disposal methods. Rebait and reset all sprung traps.
  - Before removing the gloves, wash gloved hands in a general household disinfectant and then in soap and water. A hypochlorite solution prepared by mixing 3 tbsp of household bleach in 4.5 L of water may be used in place of a commercial disinfectant. When using the solution, avoid spilling the mixture on clothing or other items that could be damaged.
  - Thoroughly wash hands with soap and water after removing the gloves.
  - Leave several baited spring-loaded traps inside the house at all times as further precaution against rodent reinfestation. Examine the traps regularly.
  - Disinfect traps no longer in use by washing in a general household disinfectant or the hypochlorite solution and ***rinsing*** clean. Disinfect and wash gloves as described above, and wash hands thoroughly with soap and water before beginning other activities.

Cleanup of Rodent-contaminated Areas: Guidance for Residents of Affected Areas

- Persons involved in the cleanup should wear rubber or plastic gloves.
- Spray dead rodents, rodent nests, droppings, and foods or other items that have been tainted by rodents with a general-purpose household disinfectant.
- Soak the material thoroughly and place in a plastic bag.
- When cleanup is complete (or when the bag is full), seal the bag, then place it into a second plastic bag and seal.
- Dispose of the bagged material by burying in a hole 0.5–1 m deep or by burning. If these alternatives are not feasible, contact the local or state health department concerning other appropriate disposal methods.
- After the above items have been removed, ***mop*** floors with a solution of water, detergent, and disinfectant. To avoid generating potentially infectious aerosols, do not vacuum or sweep dry surfaces before mopping.
- Spray dirt floors with a disinfectant solution. A second mopping or spraying of floors with a general-purpose household disinfectant is optional.
- Carpets can be effectively disinfected with household disinfectants or by commercial-grade steam cleaning or shampooing.
- Disinfect countertops, cabinets, drawers, and other durable surfaces by washing them with a solution of detergent, water, and disinfectant, followed by an optional wiping-down with a general-purpose household disinfectant.
- Rugs and upholstered furniture should be steam cleaned or shampooed. If rodents have nested inside furniture and the nests are not accessible for decontamination, the furniture should be removed and burned.
- Launder potentially contaminated bedding and clothing with hot water and detergent. (Use rubber or plastic gloves when handling the dirty laundry, then wash and disinfect gloves.) Machine-dry laundry on a high setting or hang it to air-dry in the sun.

Special Precautions for Cleanup in Homes of Persons with Hantavirus Infection or Buildings with Heavy Rodent Infestation

- A baseline serum sample, preferably drawn at the time these activities are initiated, should be available for all persons conducting the cleanup of homes or buildings with heavy rodent infestation. The serum sample should be stored at –20 °C.
- Persons involved in the cleanup should wear coveralls (disposable if possible), rubber boots or disposable shoe covers, rubber or plastic gloves, protective goggles, and an appropriate respiratory protection device, such as a half-mask air-purifying (or negative-pressure) respirator with a high-efficiency particulate air (HEPA) filter or a powered air-purifying respirator (PAPR) with HEPA filters. Respirators (including positive-pressure types) are not considered protective if facial hair interferes with the face seal, since proper fit cannot be assured. Respirator practices should follow a comprehensive user program and be supervised by a knowledgeable person. Personal protective gear should be decontaminated upon removal at the end of the day. If the coveralls are not disposable, they should be laundered on site. If no laundry facilities are available, the coveralls should be immersed in liquid disinfectant until they can be washed.
- All potentially infective waste material (including respirator filters) from cleanup operations that cannot be burned or deep-buried on site should be double-bagged in appropriate plastic bags. The bagged material should then be labeled as infectious (if it is to be transported) and disposed of in accordance with local requirements for infectious waste.
- Workers who develop symptoms suggestive of HPS within 45 days of the last potential exposure should immediately seek medical attention. The physician should contact local health authorities promptly if hantavirus-associated illness is suspected. A blood sample should be obtained and forwarded with the baseline serum through the state health department to the appropriate reference laboratory for hantavirus antibody testing.

Precautions for Workers in Affected Areas Who Are Exposed to Rodents

- A baseline serum sample, preferably drawn at the time of employment, should be available for all persons whose occupation involves frequent rodent contact. The serum sample should be stored at –20 °C.
- Workers in potentially high-risk settings should be informed about the symptoms of HPS and be given detailed guidance on prevention measures.
- Workers who develop a febrile or respiratory illness within 45 days of the last potential exposure should immediately seek medical attention and inform the attending physician of the potential occupational risk of hantavirus infection. The physician should contact local health authorities promptly if hantavirus-associated illness is suspected. A blood sample should be obtained and forwarded with the baseline serum to the appropriate reference laboratory for hantavirus antibody testing.
- Workers should wear a half-face air-purifying (or negative-pressure) respirator with eye protection or a power air-purifying respirator equipped with high-efficiency particulate air filters when removing rodents from traps or handling rodents in the affected area. Respirators (including positive-pressure types) are not considered protective if facial hair interferes with the face seal, since proper fit cannot be assured. Respirator use practices should be in accord with a comprehensive user program and should be supervised by a knowledgeable person. Workers should wear rubber or plastic gloves when handling rodents or handling traps containing rodents. Gloves should be washed and disinfected before removal.
- Traps contaminated by rodent urine or feces or in which a rodent was captured should be disinfected with a commercial disinfectant or bleach solution. Dispose of dead rodents.
- Persons removing organs or obtaining blood from rodent-affected areas should follow published safety guidelines.

Reducing Risk of Hantavirus Infection: Guidance for Hikers and Campers

- Avoid coming into contact with rodents and rodent burrows or disturbing dens, such as pack rat nests.
- Do not use cabins or other enclosed shelters that are rodent infested until they have been appropriately cleaned and disinfected.
- Do not pitch tents or place sleeping bags in areas in proximity to rodent feces or burrows or near possible rodent shelters (e.g., garbage dumps or woodpiles).
- If possible, do not sleep on the bare ground. Use a cot with the sleeping surface at least 30 cm above the ground. Use tents with floors.
- Keep food in rodent-proof containers.
- Promptly bury (or—preferably—burn, followed by burying, when in accordance with local requirements) all garbage and trash, or discard in covered trash containers.
- Use only bottled water or water that has been disinfected by filtration, boiling, chlorination, or iodination for drinking, cooking, washing dishes, and brushing teeth.

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