**Table 1. Smallpox vaccination and deaths from postvaccination reaction, Venezuela, 1968-1979.**

| Year | Total | Vaccinations (in thousands of doses) | | Deaths |
|---|---|---|---|---|
| | | Primary | Revaccinations | |
| 1968 | 1,592.8 | 663.7 | 929.1 | 1 |
| 1969 | 1,378.7 | 598.1 | 780.6 | — |
| 1970 | 1,119.2 | 890.1 | 229.1 | 3 |
| 1971 | 870.0 | 630.6 | 239.4 | 2 |
| 1972 | 786.0 | 568.1 | 217.9 | 2 |
| 1973 | 691.7 | 480.0 | 211.7 | — |
| 1974 | 617.9 | 385.8 | 232.1 | — |
| 1975 | 526.2 | 311.3 | 214.9 | 1 |
| 1976 | 429.1 | 202.9 | 226.2 | — |
| 1977 | 387.0 | 177.1 | 209.9 | — |
| 1978 | 133.0 | 68.1 | 64.9 | — |
| 1979 | 66.6 | ... | ... | — |

*Source*: Morbidity Section, Epidemiology Division, Ministry of Health and Social Welfare.)

try of Health and Social Welfare and studying the legal basis for amending the Vaccination Law in order to establish a policy in keeping with the WHO recommendations.

(*Source*: *Boletín Epidemiológico Semanal* No. 32, 3-9 August 1980. Division of Epidemiology, Ministry of Health and Social Welfare, Venezuela.)

# Argentinian Hemorrhagic Fever

Argentinian hemorrhagic fever (AHF) is an endemo-epidemic anthropozoonosis that has gradually spread in the pampas of Argentina, as shown in Figure 1.

The etiologic agent of AHF is the Junín virus, one of the four arenaviruses that are pathogenic for man, the other three being the virus of lymphocytic choriomeningitis (LCM), that of Lassa fever, and the Machupo virus, which causes Bolivian hemorrhagic fever.

With the exception of the Lassa fever virus and the Tamiami virus, all the other arenaviruses are found in different geographic areas of Latin America. These viruses are associated with different rodent species in which they produce persistent infections that ensure their maintenance in nature. Each of these agents is found in autochthonous rodents of geographic regions that are usually far removed from one another. However, in the AHF endemic region, the simultaneous activity of two arenaviruses pathogenic for man—the Junín and the LCM—has been confirmed.

This report covers various statistical aspects of the AHF, the results of recent studies that will contribute to the diagnosis and treatment of this disease, and an account of research for the development of a vaccine.

Figure 2 shows the total number of cases reported annually with a presumptive clinical diagnosis of AHF since 1958, when official records of this disease were begun.

Table 1 shows the distribution of the cases studied in Pergamino since 1965. As may be seen, an etiologic diagnosis of AHF was established in approximately 70 per cent of the cases reported in Pergamino in that 15-year period. Most of the remaining 30 per cent of the cases reported on the basis of a clinical diagnosis of AHF were patients who possibly suffered from virus infections of a different etiology.

Table 2 shows the distribution by sex and age group of the cases with an etiologic diagnosis of AHF that were studied in Pergamino. The marked predominance of males and of middle-aged persons is evident.

Table 3 shows the results of a controlled therapeutic study, which clearly demonstrates the effectiveness of immune plasma in reducing AHF case-fatality ratio if it is administered within eight days of onset of the disease. This study showed that immune plasma acts by neutralizing the viremia of the acute period of AHF. These results show that, for the treatment of AHF patients, it is essential to use plasma units containing specific Junín antibodies. So far, this has not been possible for two main reasons: first, because in some medical care

**Figure 1. Progressive extension of the endemoepidemic area of AHF in Argentina.**

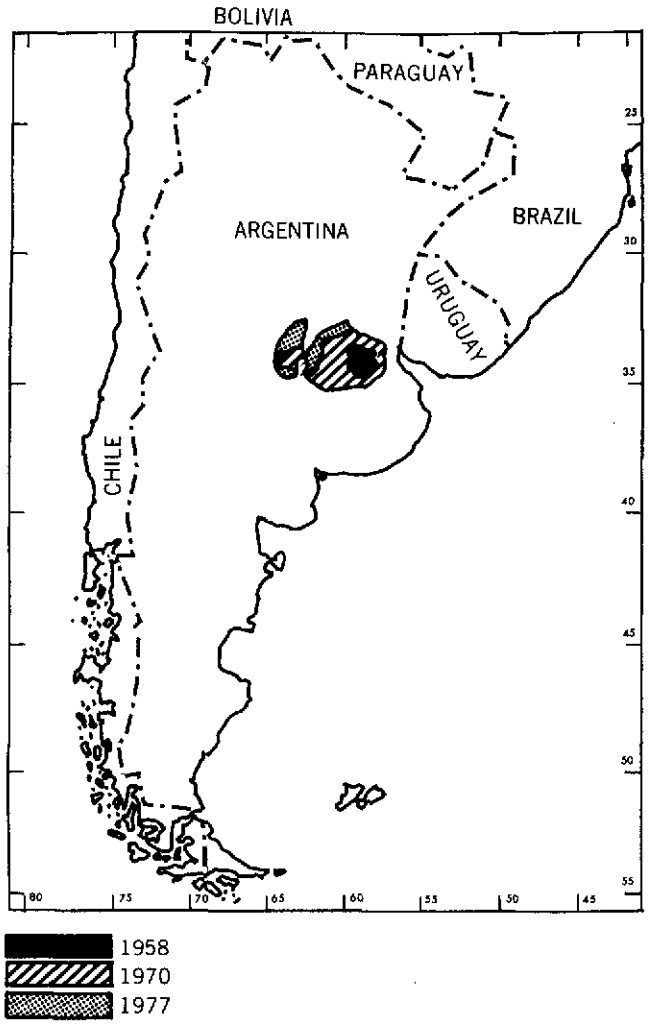
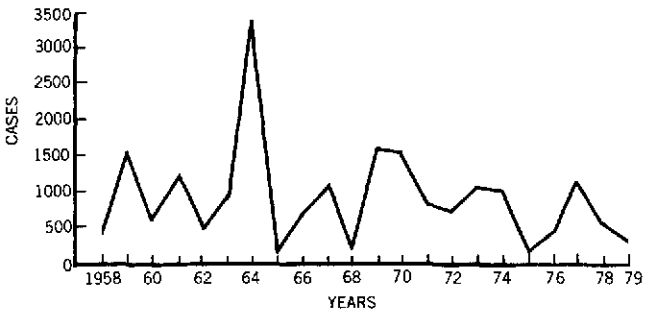



**Figure 2. Reported cases of AHF (clinical diagnosis) by year, Argentina, 1958-1979.**




centers the plasma donors used were all reported cases with a presumptive clinical diagnosis of AHF. In view of the results presented in Table 2, one third of these reported cases were clearly not useful donors of immune plasma; second, because of the serologic method routinely used, it was not possible to identify Junín antibodies in periods long after the disease. Indeed, since the viral etiology of AHF was demonstrated more than 20 years ago, etiologic diagnosis has been established in most cases by demonstrating serologic conversion in complement fixation tests (CF). Despite its usefulness, the complement fixation method has several limitations; the two most important are the late detection of Junín antibodies and their very short persistence. In some cases, the CF antibodies are not detected until 60 and even 90 days after the acute period of the disease. Furthermore, in most of these cases, these antibodies are only detectable during one or at most two years after the disease. Of course, these two facts are important limiting factors for the detection and/or selection of donors whose plasma contains Junín antibodies.

Recent studies have demonstrated the usefulness of the indirect immunofluorescence technique in the diagnosis of AHF. On the one hand, it has been found that the immunofluorescent Junín antibodies are detected earlier than the CF, 12-18 days after onset of symptoms, and their detection generally coincides with the clinical improvement of the patient. Another study has demonstrated the persistence of these antibodies in periods much more remote from the disease; they have been found in more than 90 per cent of the serum specimens obtained from 156 patients between 1 and 12 years after AHF. These results show that the indirect im-

**Table 1. Annual distribution of cases studied in Pergamino, 1965-1979.**

| Year | Clinical diagnosis | Etiologic diagnosis of AHF[a] | | |
|---|---|---|---|---|
| | Total reported | Confirmed | Negative | Doubtful[b] |
| 1965 | 63 | 20 | 41 | 2 |
| 1966 | 175 | 117 | 46 | 12 |
| 1967 | 341 | 227 | 72 | 42 |
| 1968 | 87 | 48 | 36 | 3 |
| 1969 | 549 | 356 | 152 | 41 |
| 1970 | 456 | 283 | 153 | 20 |
| 1971 | 310 | 241 | 58 | 11 |
| 1972 | 268 | 211 | 54 | 3 |
| 1973 | 435 | 330 | 89 | 16 |
| 1974 | 391 | 297 | 87 | 7 |
| 1975 | 98 | 63 | 23 | 12 |
| 1976 | 253 | 183 | 42 | 28 |
| 1977 | 553 | 396 | 79 | 78 |
| 1978 | 274 | 179 | 61 | 34 |
| 1979 | 163 | 101 | 50 | 12 |
| Total | 4,416 | 3,052 | 1,043 | 321 |

[a]Serologic conversion (appearance of complement fixation antibodies during convalescence and/or isolation of Junín virus from blood during the acute period or from organs obtained from post mortem examination of deceased patients.

[b]Incomplete serologic studies (insufficient serum specimens).

**Table 2. Distribution by sex and by age group of cases with etiologic diagnosis of AHF studied in Pergamino, 1965-1979.**

| Age group | Male | Female | Total |
|---|---|---|---|
| 0-14 | 133 | 95 | 228 |
| 15-24 | 522 | 136 | 658 |
| 25-34 | 574 | 107 | 681 |
| 35-44 | 517 | 107 | 624 |
| 45-54 | 352 | 101 | 453 |
| 55-64 | 230 | 59 | 289 |
| 65 and over | 97 | 22 | 119 |
| Total | 2,425 | 627 | 3,052 |

**Table 3. Controlled therapeutic study of 188 cases of AHF.**

| Type of treatment | Cured | Died | Total | Case-fatality ratio (%) |
|---|---|---|---|---|
| Immune plasma | 90 | 1 | 91 | 1 |
| Normal plasma | 81 | 16 | 97 | 16 |
| Total | 171 | 17 | 188 | |

$X^2 = 13.53$; $p < 0.01$.

munofluorescence method can produce a better selection of immune plasma donors for the treatment of AHF, and also suggests its usefulness in seroepidemiological surveys.

The studies being carried out in Argentina for the purpose of developing a vaccine against AHF are well known. On the one hand, they have been aimed at developing inactivated antigens by using different methods such as heat and formol, and photodynamic inactivation. On the other, two lines of research have been followed for developing attenuated vaccines: one, by using the attenuated strain XJ clone 3 of the Junín virus, with which very important experimental studies and trials have been carried out; the other, heterologic immunization with Tacaribe virus, an arenavirus that is not pathogenic for man but is antigenically related to the Junín virus.

In 1976 an International Seminar on Hemorrhagic Fevers Produced by Arenaviruses, organized by the Ministry of Public Health with the assistance of the Pan American Sanitary Bureau, was held in Buenos Aires. This Seminar brought together outstanding national and foreign experts who agreed that priority should be assigned to the development of an AHF vaccine. Consequently, since 1977 the Argentine health authorities have increased the funds assigned to research workers active in this field. Thanks to this support the above-mentioned studies have been expanded.

In addition, in 1979 the Government of Argentina and the United Nations Development Program signed an agreement for the development of an AHF vaccine, the executing agencies being the Ministry of Public Health of Argentina and the Area VI Office of the Pan American Sanitary Bureau. This project includes research aimed at developing an attenuated vaccine, which is being carried out in collaboration with the National Institute of Research on Hemorrhagic Virus Diseases, whose headquarters are in Pergamino, and the Virology Division of the Research Institute of Infectious Diseases in Frederick, Maryland, where an Argentine scientist is working. In Pergamino the studies are aimed at obtaining attenuated strains of Junín virus from nature. For that purpose, activities include the isolation and characterization of the virulence of Junín virus strains from rodents captured in the endemic area and from patients with benign clinical forms of AHF. In addition, in the security laboratories of the U.S. Army Medical Research Institute on Infectious Diseases, the Argentine virologist is carrying out research aimed at deriving virus clones in an optimum substrate for vaccine production. His activities include the multiplication of an attenuated strain of Junín virus in certified cell lines, which he has successfully accomplished, and the derivation of clones with which he will perform general virulence tests, neurovirulence tests, and controls for eliminating the presence of foreign bodies. Finally, he will select a clone as a seed strain and use it to produce a vaccine and will repeat all the controls, genetic stability, general safety, and identity tests.

(*Source*: National Institute of Studies on Hemorrhagic Viral Diseases, Ministry of State for Public Health, Argentina.)