Rodent control programmes in areas affected by Bolivian haemorrhagic fever

RODOLFO MERCADO R.[1]

Bolivian haemorrhagic fever (BHF) caused by Machupo virus is acquired by contact with the excretions and secretions of Calomys callosus, *an indigenous cricetine rodent which is preadapted to peridomestic habitats. It competes successfully with* Mus musculus, *but not with* Rattus rattus. *A successful disease control programme has functioned in Beni Department since 1964. It is based on trapping surveys and the detection of splenomegaly in* Calomys *rodents as an index of chronic virus infection. Mass trapping and poisoning are used initially, and regular trapping is employed to control* Calomys *populations in towns where disease has occurred. More than 1000 cases of BHF were recorded from 1960-1964, but less than 200 in the past 10 years. The cost of this programme is approximately $30 000 annually.*

The salient ecological features of Bolivian haemorrhagic fever (BHF) caused by Machupo virus have been reviewed previously (1, 2). At present the only known natural host of the virus is the cricetine rodent *Calomys callosus*. This small mouse is principally an animal of tropical American grasslands, with the highest population densities concentrated along the borders of grasslands and forests. Although the exact geographic range of this species has not been determined, available evidence indicates that it includes the plains of eastern Bolivia and the northern portion of Paraguay as well as the contiguous western fringe of Mato Grosso State in Brazil.

Within that region animals infected with Machupo virus have so far been found in portions of Itenez, Mamoré, and Yacuma provinces of the Department of Beni, Bolivia. Another arenavirus, Latino, which is presumed to be nonpathogenic for man, has been recovered from *C. callosus* in Santa Cruz Department, Bolivia, and near Corumba, Brazil (P. A. Webb, unpublished observations, 1972). Thus, as a public health problem, control of *C. callosus* is restricted to a portion of the Department of Beni measuring about 28 000 km^2 and inhabited by approximately 50 000 persons (Fig. 1). Cattle raising and subsistence agriculture are the principal occupations. Transportation is by river, air, and either horse or ox-cart, although roads into Beni are at present under construction by the Bolivian government. There are 4 main towns in the Machupo virus enzootic area, all with populations of 2000–5000 persons: Magdalena, San Joaquin, San Ramón, and Santa Ana. My purpose here is to review briefly the estimated human morbidity and mortality caused by Machupo virus since 1959, the year when BHF was first recognized (3), and to trace the evolution, the cost, and the successes and failures of the specific disease control programme at present maintained by the Ministry of Health in Bolivia.

From 1959 until July 1964 an estimated 1028 cases of BHF with 245 fatalities (22%) occurred in Itenez and Mamoré provinces. Through 1962, the disease was confined to Itenez province, and it was notable that the capital town, Magdalena, was spared completely (4). Beginning in mid-1962, BHF was reported in the general area of San Joaquin, Mamoré, and from early 1963 until mid-1964 a major epidemic unfolded in the town itself. This disastrous plague, which affected about one out of every three persons and killed 5% of the population, was abruptly terminated with mouse traps and oil-grain baits containing zinc phosphide. Fifteen traps and 10–20 baits per house were used. Nearly 3000 *C. callosus* (about 10 per house) were captured in the first 3 weeks of this programme. Many more undoubtedly died from the poison. Thereafter, a regular programme was maintained, each house having 15 traps set for 3 consecutive nights each month. The team operated by the Bolivian Commission for Haemorrhagic Fever consisted of 7 persons: the medical director, a field supervisor, 4 trappers, and a secretary. From 1965 through 1969, this effort cost

[1] Chief, Institute of Transmissible Diseases, Ministry of Health, La Paz, Bolivia.

Fig. 1. Map of Bolivia showing the approximate distribution of *C. callosus* (stippled areas) and of BHF (hatched area).

approximately $15 000 per year for personnel, supplies, and transportation.

Captures of *Calomys* rodents averaged about 80 per month from August 1964 through March 1965. Early in 1965 further cases of BHF occurred in San Joaquin (24 in all) and were strongly correlated with houses where the largest numbers of rodents were caught (5). Most the these houses were located in the northwestern area of the town. Beginning in March 1965, intensive efforts were made to eliminate rodents in these houses. The number of traps was tripled, zinc phosphide was again used briefly, and cardboards dusted with talcum were placed under curved tiles along potential rodent runs in and around houses. When untrappable *Calomys* were detected, resort was sometimes made to shooting the animals with 0.22 bird shot, by the light of head lamps.

In 1966–1967, fewer than 40 *Calomys* were captured. During 1968 and 1969, increased numbers of these rodents were trapped, 138 and 121 respectively. In this 5-year interval only 2 unconfirmed, nonfatal, cases of BHF occurred in San Joaquin. These gratifying results may be explained on the basis of the following facts and hypotheses and in turn tend to confirm them:

1. The principal and perhaps the only natural reservoir of Machupo virus is *C. callosus*.

2. Virus infection of all neonatal *Calomys* and of a significant fraction of adults is chronic, with persistent viraemia and the shedding of large amounts of virus in the urine (6, 7).

3. *C. callosus* is preadapted for peridomestic living, readily entering houses and gardens, and reaching population densities under these circumstances that are never observed in the absence of man.

4. Once *Calomys* densities have been severely reduced by intensive trapping and poisoning, 45 trap-nights per house per month appear to be sufficient to maintain populations below the threshold of virus contamination necessary for transmission to man in a town.

It is important to mention here that San Joaquin, situated about one mile from its small port on the Machupo River, had no *Rattus rattus* and virtually no *Mus musculus*. More than 95% of all mammals taken were *C. callosus*. Thus, the problem posed was ecologically rather simple, namely to control the density of a species that occupies the entire terrestrial habitat in the town and that constantly threatens to invade it from the rural periphery.

The years 1966 through 1968 comprised a period of low Machupo virus activity. Few *Calomys* were found in San Joaquin and only two possible, but unproven, cases of BHF occurred there. Thirteen patients were admitted to hospital in 1966 from 4 small localities south of the town. Eight of these were from the village of Rio Negro. Subsequent investigation revealed that 30% of a sample population of 60 had neutralizing antibodies to the virus. Most of these persons denied having had a recent severe illness, and there was no history of any outbreak compatible with BHF prior to 1966. *C. callosus* were numerous and 11 of 35 tested had specific antibodies. Intensive trapping and poisoning stopped further disease transmission. It is noteworthy that this is the only outbreak of this size in which no fatalities occurred.

SECOND PHASE

The year 1969 marked the advent of the second phase in the development of our control programme. Workers at the Middle America Research Unit had discovered in 1967 that chronically infected *Calomys* developed persistent splenomegaly; the spleens of adult animals weighed 0.17 g to nearly 1.0 g and were at least 20 mm in length. Field studies done in 1968 at Cabrera, a large ranch near Rio Negro,

confirmed this relationship in a small number of animals. In January and February of 1969, 10 cases of BHF with 6 deaths occurred in the community of La Cayoba, an area of rice cultivation 40 km north of Magdalena. Machupo virus was recovered from each of 3 patients tested. By the time our control team arrived from San Joaquin, many persons had fled the community. Only one of 139 sera obtained from healthy persons had Machupo virus antibodies. But virus was recovered from 12 of 48 *C. callosus*, nearly always from those with enlarged spleens. The usual control measures were instituted, but quickly became of doubtful value when all remaining people were moved to a government-owned farm about 5 km from Magdalena. Residents of the town became concerned that these "infected" refugees would bring the virus into Magdalena. They were assured by the Commission that this was very unlikely because Magdalena, unlike San Joaquin, was infested with *Mus musculus* (a fact discovered in 1964 during a survey undertaken to determine why only the latter town had suffered epidemic BHF).

Nevertheless, beginning in March 1969, the disease appeared in Magdalena. There were 22 cases in that year and 12 in 1970. Since infections were contracted initially in houses at the edge of the town and since *C. callosus* captures predominated in the 24 peripheral blocks while *Mus musculus* were much more numerous in 23 inner blocks, it was decided to base control measures on Sherman live-traps, releasing all *Mus* and killing all *Calomys*. Zinc phosphide and kill-traps were used sparingly, and only in houses where BHF occurred or more than a single *Calomys* was found.

Another control team was organized along lines similar to those used in San Joaquin. Because Magdalena had nearly 30% more houses than San Joaquin, and because fewer of the more expensive Sherman traps were employed, total trap-nights per house per month were slightly less than half those used in San Joaquin. This fact, plus the lack of an initial mass campaign of trapping and poison, probably accounts for the pattern of rodent captures depicted in Table 1. The reasoning was that extermination of *Mus musculus* might open the way for penetration of *Calomys* into the densely populated town centre. The slight increase in more sylvatic rodents and the appearance of opossums during 1970 show that migration into the edge of the town does represent a recurrent phenomenon.

Finally, late in 1970 when *Mus* populations were seen inexplicably to fall more rapidly than those of *Calomys*, with the persistent finding of about 10–15% enlarged spleens in the latter and with the appearance of 3 cases of BHF in the inner city, an intensive clean-up was done using kill-traps and poison. Since then *Calomys* populations have been kept at low levels by as little as 10 trap-nights per house per month.

Table 1. Rodents and marsupials captured in Magdalena, Bolivia, July 1969—December 1970

Species	Jul.-Dec. 1969	Jan.-Jun. 1970	Jul.-Dec. 1970
Calomys callosus	472	348	152
Mus musculus	662	225	127
All others	134	48	173

During 1969 and 1970, it became evident that the events in Magdalena did not represent an isolated disease outbreak but were part of a more generalized increase in virus-infected *Calomys* rodents in the Itenez Province. Forty-five patients living in 16 small localities outside Magdalena were admitted to the hospital during that time, compared to 34 from the town itself. Ten of these cases occurred between April and early June in 4 closely spaced hamlets some 30 km north of the town. Census, serological survey, and rodent-trapping data obtained during a two-week campaign in mid-June were as follows: The human attack rate by Machupo virus was 12 of 84 (15%) including 2 wild infections; an average of 9.5 *C. callosus* were captured in each of 16 houses, and 48% of these rodents had spleens greater than 20 mm in length. Trapping was supplemented with zinc phosphide, and there were no further cases of disease and no rodents captured on a return visit 3 months later.

CURRENT PROGRAMME

Experiences such as these have convinced us of the basic value of rodent control measures. At the present time, the Bolivian haemorrhagic fever control programme employs very few people. In addition to a chief medical officer, personnel comprise two teams consisting of a medical officer, a field supervisor, and three trappers, located in San Joaquin and Magdalena. The total annual budget is about $30 000. The medical officers, in addition to managing control operations and caring for sus-

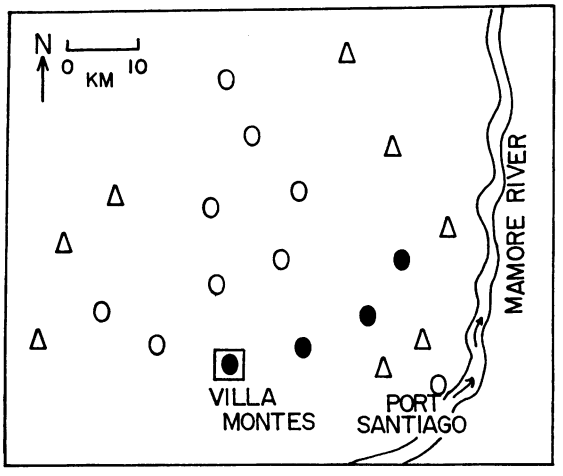

Fig. 2. Part of Yacuma Province, Beni Department, Bolivia, showing the distribution of *C. callosus* in the area of Villa Montes where BHF occurred, June, 1971. The solid and open circles represent, respectively, the occurrence of Machupo virus infected and uninfected *C. callosus*, the triangles show sites where no *C. callosus* were found, and the square indicates cases of BHF.

Table 2. *Calomys callosus*, splenomegaly, and human haemorrhagic fever in three provinces of Bolivia, 1971-1974

Localities with:	No. of localities in province of:			Totals
	Mamoré	Itenez	Yacuma	
Normal or no *Calomys*	32	180	16	228
Splenomegalic *Calomys*	7	69	12	88
Splenomegalic *Calomys* and BHF cases	11	12	2	25

pected BHF patients in their respective hospitals, are available to help physicians in other towns whenever disease occurs, and may call on the Ministry of Health for reinforcements in the form of physicians, nurses, laboratory technicians, and supplies, depending on the potential severity of any given outbreak.

In addition to the basic control efforts in San Joaquin and Magdalena, which utilize about 10 trap-nights per house per month, regular visits are made to as many smaller localities as possible once each year, during which 50–150 Sherman traps are operated for two nights. If *Calomys* are found but none have enlarged spleens, supplies of warfarin are left and the people instructed in its use. Results have been somewhat variable in this approach, since in the absence of human disease the people often employ the poison in their fields rather than in their homes. BHF has eventually occurred in a few instances.

If *Calomys* with enlarged spleens are found, zinc phosphide baits are distributed. Follow-up visits are made in 2 or 3 months and continued at this interval until no animals with large spleens or no *Calomys* are found. Sometimes as many as 3 repeat applications of poison are needed to achieve this result. A similar approach is used where human disease has occurred, but repeat observation is carried out more frequently: 3 months, 6 months, and then annually after all *Calomys* have been eliminated.

Wherever a case of BHF occurs, all neighbouring farms and ranches are surveyed until a perimeter of *Calomys*-negative places is documented. An example is shown in Fig. 2, a portion of Yacuma Province, 1971. The positive localities are systematically poisoned and checked by trapping until cleared of infected *Calomys*. Over the past 5 years we have never failed to find *Calomys* with enlarged spleens when a new focus of BHF was reported. As shown in Table 2, 341 distinct localities have been examined. *Calomys* with enlarged spleens were found in 113 of these, and 25 (7%) were sources of BHF cases. Although far from perfect, we believe that this control programme has saved many lives. Since subclinical human infection by Machupo virus has proved to be uncommon, the number of susceptible persons in the enzootic region is increasing each year. Nevertheless, we have not had more than 50 cases of BHF in any year since 1964. Rodent control, particularly during 1969–1971 when all signs pointed to a major population increase in *Calomys*, deserves much of the credit.

In addition, the presence of an organized campaign has proved crucial to the maintenance of confidence on the part of the people of Beni Department who are now embarked on a major development scheme destined to make the region one of the leading beef-producing areas of Latin America. With such development, the danger of BHF will probably increase; thus the lessons we are learning should be of even greater value in the future.

RÉSUMÉ

PROGRAMMES DE LUTTE CONTRE LES RONGEURS DANS LES ZONES OÙ SÉVIT LA FIÈVRE HÉMORRAGIQUE BOLIVIENNE

La fièvre hémorragique bolivienne est due au virus Machupo, dont le réservoir naturel est un cricétiné, *Calomys callosus*. Ce rongeur vit dans les plaines tropicales du nord et de l'est de la Bolivie. Des cas de fièvre hémorragique bolivienne chez l'homme ont été observés dans les provinces de Mamoré, d'Itenez et de Yacuma dans le Département de Beni en Bolivie. Le virus Latino, qui est un autre arénavirus, a été isolé de *C. callosus* dans le Département de Santa Cruz près de Corumbá au Brésil mais on pense qu'il n'est pas pathogène pour l'homme. La répartition de *C. callosus* n'a pas été très clairement établie mais le rongeur a été observé dans une zone de quelque 28 000 km² regroupant 50 000 habitants. D'après des estimations, 1 028 cas de fièvre hémorragique bolivienne dont 245 mortels (25%) se seraient produits dans les provinces d'Itenez et de Mamoré entre 1959 et juillet 1969.

L'épidémie la plus importante a sévi en 1963-64 dans la ville de San Joaquín (Province de Mamoré): la maladie a frappé une personne sur trois et le taux de mortalité a été de 5%. On est parvenu à enrayer cette épidémie en capturant et en détruisant les rongeurs au moyen de pièges et d'appâts empoisonnés. Ce succès ainsi que les autres résultats remarquables des opérations de lutte menées contre des poussées épidémiques moins importantes peuvent s'expliquer sur la base des faits et des hypotèses suivants:

1. *C. callosus* est le principal — voire l'unique — réservoir naturel du virus Machupo.

2. Tous les *Calomys* nouveau-nés et une fraction importante des adultes sont infectés à l'état chronique, avec virémie persistante et excrétion de quantités importantes de virus dans l'urine.

3. *C. callosus* manifeste une prédisposition pour la vie péridomestique; il pénètre volontiers dans les habitations et les jardins et, dans ces conditions, les populations de *C. callosus* atteignent des densités jamais observées en l'absence de l'homme.

Une fois que la densité de *Calomys* a été très fortement réduite par l'utilisation intensive de pièges et de produits empoisonnés, il semble que 45 pièges-nuits par maison et par mois suffisent pour maintenir les populations de *Calomys* au-dessous du niveau où la contamination virale est telle qu'il peut y avoir transmission à l'homme dans une ville.

REFERENCES

1. JOHNSON, K. M. ET AL. Hemorrhagic fevers of Southeast Asia and South America: a comparative appraisal. *Progr. med. Vir.*, **9**: 105-158 (1967)
2. JOHNSON, K. M. ET AL. Biology of Tacaribe-complex viruses. *In:* Lehmann-Grube, F., ed. Lymphocytic choriomeningitis virus and other arenaviruses, Berlin, Heidelberg, & New York, Springer, 1973, pp. 241-258
3. JAUREGUI, G. G. ET AL. Informe preliminar sobre el brote epidémico de Ricketziasis que se presento en el Beni, Julio 1960-Septembre 1961. *Rev. Salud pub. Bolivia*, 7: 12-30 (1961)
4. MACKENZIE, R. B. ET AL. Epidemic hemorrhagic fever in Bolivia. I. A preliminary report of the epidemiological and clinical findings in a new epidemic area in South America. *Amer. J. trop. Med. Hyg.*, **13**: 620-625 (1964)
5. MACKENZIE, R. B. ET AL. Possibilities for control of hemorrhagic fevers in Latin America. *In:* First International Conference on Vaccines against Viral and Rickettsial Diseases of Man, Washington, 7-11 November 1966, Washington, Pan American Health Organization, 1967 (PAHO Publication No. 147), pp. 260-265
6. JOHNSON, K. M. ET AL. Chronic infection of rodents by Machupo virus. *Science*, **150**: 1618-1619 (1965)
7. JUSTINES, G. & JOHNSON, K. M. Immune tolerance in *Calomys callosus* infected with Machupo virus. *Nature (Lond.)*, **222**: 1090-1091 (1969)

DISCUSSION

LORD: When I was in Bolivia a couple of years ago several government veterinarians told me that the problem of BHF had been solved by a control programme consisting of importing and releasing house cats in the affected towns. Would you tell us something about this?

MERCADO: The use of cats was a failure because, particularly in the small villages, they were considered a luxury, as they needed an additional food supply. In some of the larger towns, a market in cats developed and the wealthier people, who really needed them least, ended up with all of them.

BARNES: One of the things that intrigued me was that the epidemics of BHF occurred in the early 60s and then again in the early 70s. I wonder if anyone has considered the possibility of cycles in Machupo virus transmission in animals, like those that occur in plague. In the plague cycle in North America, it seems that every 6 years we see widespread plague epizootics; these cycles seem to be coordinated worldwide.

K. JOHNSON: I think Dr Mercado believes that the *Calomys* populations in this part of the world undergo cyclic variations of considerable magnitude and that very probably there is increased transmission of virus among such populations as their densities increase. Certainly, whenever the point is reached where human disease occurs, one finds tremendous populations of these animals, a very high percentage of which are found to be infected, even using the gross marker of splenomegaly.

BOND: As I undestand the situation, in San Joaquin, there were no competitors such as *Rattus rattus* and no cats in 1964, and so you introduced man as the principal predator. My question is, if Machupo infection has an effect on reproductive capacity of *Calomys*, what would have happened if only the virus had been the predator? Would *Calomys* populations have disappeared; was it necessary to introduce man as a principal predator in order to reduce the population?

K. JOHNSON: I do not think we really know the answer to that. I think an answer might be obtained, but there is an ethical problem. Whenever BHF begins to appear in these small human settlements, if the disease can be controlled, one is obliged to institute control. I think we have shown that for very little money, one can prevent serious and fatal human disease.