CONTROL OF VEE EPIZOOTIC-EPIDEMIC BY VACCINE DEVELOPED AT USAMRIID

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Venezuelan equine encephalomyelitis (VEE) is a zoonotic arbovirus disease affecting both Equidae and man. Infection in equine animals may be subclinical, but more often it assumes one of the following clinical forms: (a) mild illness consisting primarily of anorexia, fever, and depression; (b) severe illness characterized by anorexia, high fever, stupor, staggering, and blindness, followed by recovery with or without permanent sequelae; or (c) fatal disease with a similar sequence of signs, but terminating in death (1). Overall mortality rate in equines probably exceeds 75% of those infected.

In man, VEE commonly occurs as an influenza-like illness characterized by generalized muscular pains, severe frontal headache and high fever; overt signs of encephalitis are rare, occurring primarily in children (1). Severity of disease appears to vary with virus subtype; overall mortality in humans probably is no more than 1%.

In VEE epizootic-epidemic situations, the horse is the major amplifying host providing the principal source of infected blood meals for mosquitoes; following incubation in the mosquito vector, the virus is then transmitted to uninfected Equidae or other nonhuman hosts. Because of feeding habits of the common vectors, man is only an incidental target, and it is generally agreed that prevention of the disease in man is best accomplished by controlling and preventing disease in Equidae.

VEE was first recognized as a separate disease entity following a major epizootic-epidemic of encephalitis in Venezuela in 1936. From 1936 to 1968, devastating outbreaks occurred in Venezuela, Colombia, Peru and Ecuador. In January, 1969, a major epizootic-epidemic of VEE erupted in Ecuador and spread into Peru. Untold thousands of Equidae are reported to have died and thousands of humans became ill; more than 1,200 cases of encephalitis were attributed to the disease. This outbreak was caused by a highly virulent variant, designated 1B, of VEE virus.
Later in 1969, a disease in horses characterized by encephalitis, resulting frequently in death, reached major epizootic proportions in Guatemala, El Salvador, Honduras and Nicaragua (2). Before the etiology was established, a presumptive diagnosis of VEE was made, based on clinical signs and knowledge of the equine encephalitides present in the area. Subsequently, isolations of the 1B variant of the virus were made from man, horses, mosquitoes, and wild rodents. The following year the epizootic extended into Costa Rica and into Mexico (3); and within another year, into the United States.

As part of the effort to control these outbreaks, a live attenuated virus vaccine (TC-83) developed at the U. S. Army Medical Research Institute of Infectious Diseases (USAMRIID) was administered to horses, burros, and mules. Attenuation was obtained by the serial passage of a virulent (Trinidad VE-1) strain of VEE virus in cell culture (4,5). The TC-83 vaccine was originally developed for protection of laboratory personnel working in high-risk areas and subsequently has been administered to more than 6,000 human beings (5,6,7). During developmental studies, limited evidence suggested that the vaccine might be suitable for use in Equidae (7,8).

At the time of the outbreak in Guatemala in 1969, the first equine deaths occurred in the early spring. The true extent of the problem was not realized for almost two months and VEE was not confirmed until midsummer. Immediately upon confirmation, a request for technical assistance and vaccine was submitted from the Governments of Guatemala and El Salvador through the State Department to the Department of Defense (DOD). When the disease spread to the Pacific Coastal Plain of Honduras and Nicaragua, these governments also requested vaccine and technical assistance. Because of the type of terrain and certain administrative and logistical difficulties, eradication of insect vectors by aerial spraying was considered to be impractical. Control of the movement of horses and other equines was instituted, but was difficult to enforce. It very rapidly became apparent that if spread of disease was to be controlled, a major emphasis would have to be placed on use of the vaccine. There appeared to be little or no hope of aborting the epizootic by immunizing animals in areas where the disease was already present, since antibodies do not develop until 7 to 10 days after vaccination. Therefore, to establish a barrier of immune animals for containing the epizootic, it would be necessary to administer vaccine to animals at least two weeks prior to appearance of VEE in a given area.

When the initial vaccine request was received, there was considerable reservation regarding the advisability of using a vaccine originally developed for human use in an attempt to stop the spread of an epizootic in horses: (1) the vaccine had never been used for control of a major outbreak in equines, although limited use of the vaccine had been made in Colombia in 1968; (2) we could not be absolutely sure that the disease was VEE; (3) it was not known if the countries making the request had personnel and equipment to conduct such a mass
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vaccination campaign; and (4) one of the countries, El Salvador, was at war with its neighbor, Honduras. Thus, the possibility existed that the vaccine could be discredited for reasons entirely unrelated to its effectiveness in protecting equines against VEE infection. Nevertheless, the decision was made to supply the vaccine and materials for preparing diluent. In addition, personnel thoroughly familiar with the vaccine and its use were sent to both Guatemala and El Salvador. The first shipment of TC-83 vaccine arrived in Guatemala just 4 days after receipt of the request in the United States.

Several factors hindered the disease control programs. Accurate delineation of epizootic areas was extremely difficult because of poor case-reporting. In sparsely settled areas where animals were allowed to roam freely, they frequently died without the owner's knowledge. In some instances, owners submitted false reports of disease in an attempt to obtain vaccine; in others, they failed to report equine deaths because the animals were not recorded for tax purposes. Heavy rains and flooding of major rivers delayed or prevented vaccination teams from reaching critical areas. Shortage of serviceable vehicles and inadequate road conditions compounded these naturally occurring obstacles.

By September the epizootic had subsided in Guatemala and apparently was contained in the eastern half of the country. In El Salvador, equine traffic was never effectively controlled and when the disease appeared to be on the decline, control efforts including vaccination were relaxed. As a result, VEE spread across the country into Honduras, where it was confined to the Pacific Coastal Plain. In Nicaragua the epizootic was limited to the southwestern portion of the country adjacent to Honduras.

In May, 1970, a group of concerned scientists, each of whom was involved in one capacity or another in the 1969 epizootic, met to pool accumulated knowledge and to prepare for 1970 outbreaks which all predicted were bound to come. It was the opinion of this group that VEE would most likely spread into Costa Rica and westward into that area of Mexico adjacent to Guatemala. From this meeting a plan was evolved to concentrate study efforts in Costa Rica and to prepare for the anticipated 1970 outbreaks.

Almost on schedule, during mid-August, 1970, VEE did appear in horses in the northwest corner of Costa Rica. If, as is postulated, the source of this infection was from Nicaragua, VEE infection had breached a 100-mile-wide barrier zone in which more than 90% of the Equidae had been vaccinated the previous summer, and which was free of reported cases of VEE in both 1969 and 1970. In late August, restriction of the movement of Equidae was instituted and an intensive and effectively administered vaccination program was initiated. Again, vaccine and technical assistance were supplied by USAMRIID. The epizootic was confined to a small area adjacent to Nicaragua and by mid-September, the disease appeared to be under control. Losses were
limited to approximately 300 animals.

Also as predicted for 1970, cases of equine encephalitis began to occur in Mexico, near the headwaters of a river valley adjacent to Guatemala. Specific identification of VEE virus (1B) as the etiologic agent was obtained in early July. In about one month the epizootic extended almost 200 miles to the west, into the Pacific Coastal Plain, as well as north into the state of Veracruz.

In Mexico, disease was widespread before a control program was initiated. Control of equine traffic was never very effective and vaccination rarely was accomplished prior to the appearance of disease in an area. Thus, while the number of horses infected was reduced, virus spread was not significantly slowed; as a consequence, VEE continued to spread throughout Mexico. By early June, 1971, equine cases were occurring within 35 miles of Brownsville, Texas.

The vaccination campaigns conducted in Central America in 1969 represented the first large-scale field use of the attenuated TC-83 vaccine for immunization of horses. The urgent need to protect the equine populations, coupled with a variety of other factors, precluded establishing controlled studies for assessment of vaccine efficacy. Observations made in the field, however, did serve to indicate that the vaccine was effective. Seven to 10 days after completion of the vaccination campaign in a particular area, clinical equine VEE ceased, even on ranches where some horses in the area were ill at the time of vaccination. Complete protection occurred in certain well-delineated areas, e.g., isolated valleys where disease was known to be absent at the time of vaccination, or large ranches where vaccination was completed 7 to 10 days prior to the initial cases of the disease in the area. In Guatemala, an immune barrier of vaccinated horses, about 50 kilometers in width, was established on the Pacific Coastal Plain. This barrier prevented the spread of VEE to the west. Similar vaccination barriers prevented direct extension of the epizootic into other areas of Central America. These were particularly effective in areas which were somewhat isolated geographically and in which horse movement was limited (2).

The effectiveness of the vaccine was well illustrated by the results of its administration to two herds of horses in El Salvador. In one herd, 35 of 40 horses were vaccinated. When disease appeared in that area about a month later, none of the 35 vaccinated animals became ill, but all five unvaccinated horses died. In the other herd which also was located outside the initial epizootic zone, no disease was reported in approximately 400 previously vaccinated horses following the appearance of the disease in that area.

Detailed clinical observations and serologic evaluations following administration of the TC-83 vaccine were carried out in Nicaragua by Walton and his colleagues (9) from the Middle America Research Unit in Panama. No adverse effects were observed in vaccinated...
animals on four different ranches located outside of the epizootic area. Four months after vaccination, 83 of 89 horses (93%) had neutralizing antibody to VEE virus.

Prior to the outbreak of disease in one area in Mexico, a carefully planned and well-executed study provided additional data regarding TC-83 vaccine effectiveness under field conditions. Paired serum samples were collected prevaccination and 30 to 45 days post-vaccination from 163 horses, mules, and burros. Six horses in the survey group had significant prevaccination hemagglutination inhibition (HI) titers, indicating previous infection, probably with an endemic strain. Of the remaining 157 animals without demonstrable evidence of previous infection, 96% responded to immunization by developing significant titers (7). Statistical analysis of the data failed to reveal significant differences in antibody titers between sexes, or among species. When the epizootic subsequently spread into this area, none of the immunized horses developed disease, while horses on neighboring ranches sickened and died with a VEE-like illness. The excellent (96%) serologic conversion is similar to that obtained by Walton (93%) in Nicaragua (11) and the subsequent protection against natural infection was similar to the observations made elsewhere in Central America (10,7).

During the Costa Rican outbreak, which had been predicted and for which some preliminary planning was done, teams of U. S. scientists collected data on human and equine disease and TC-83 vaccine safety and efficacy. In one study by personnel from the Middle America Research Unit, clinically well horses were vaccinated in an area where active disease was occurring (11). Equine deaths ceased abruptly within 8 days of vaccination. Virulent virus was isolated from prevaccination serum samples from five horses in one study subgroup; two of these horses died, one developed a late (8 days) clinical illness but survived, and two showed no signs of disease. An additional 28 animals in the subgroup remained healthy throughout and developed neutralizing antibodies to VEE.

No sound data exist to calculate rates for infection, morbidity or mortality for either equines or human beings in Central America. An estimated 3,000 horses died in Guatemala, but very little human disease was reported. Hinman and his co-workers from the Center for Disease Control in Atlanta, Georgia reported serologic evidence of infection in humans ranging from 0 to 50% (12). Those areas having the lower incidence of human infection correlated well with areas in which vaccination of equines was accomplished rapidly and coincident with or prior to the onset of equine cases. The overall low incidence of human VEE infection in Guatemala contrasts markedly with the hundreds of cases of encephalitis reported during the 1969 Ecuadoran VEE epidemic, during which TC-83 vaccine was not used (13).

In Costa Rica, very little human illness was observed except in one isolated village with about 200 inhabitants where the disease
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in horses appeared early, but vaccination was started late in the course of the epizootic. It was concluded: "The rapid curtailment of the Costa Rican VEE epizootic in a susceptible equine population with adequate numbers of mosquito vectors could only have been due to the vaccine" (9). Walton, in an analysis of the Nicaraguan and Costa Rican studies, concludes: "It is our opinion that the TC-83 vaccine is highly effective. Horses are protected in the field against threatening epizootics and even in the presence of active horse disease the vaccine will protect within 3 days with cessation of deaths within 9 days" (11). Thus, events observed in Costa Rica and Nicaragua provided confirmation by a different laboratory of observations made in Guatemala and El Salvador the previous year.

Only 50,000 doses of vaccine (25,000 each for Guatemala and El Salvador) were initially requested. With the extension of the epizootic, this quantity was quickly exhausted and more vaccine was requested. Before the epizootic subsided in 1969, more than 690,000 doses of TC-83 vaccine had been supplied. All vaccine had been provided from research stock held by DOD. By the end of 1969, however, this stock was nearly exhausted.

Following the 1969 epizootic in Central America, a request was submitted by a commercial biologic company in this country for a license to produce live VEE vaccine for export. Experts on VEE urged to no avail that this license be granted. When it became apparent that no other source of vaccine would be available for the predicted outbreaks, a decision was made to replenish the DOD stock of TC-83 vaccine.

During the summer of 1970, USAMRIID was again called upon to supply vaccine to combat the new outbreaks, and with the extent of the spread in Mexico the stock was quickly exhausted and additional vaccine had to be produced. Experts on VEE within and without the Government were unanimous in their opinion that, with the introduction into Central America of the highly equine-virulent VEE variant IB, an entirely new and decidedly more dangerous threat of the spread of VEE into the United States had developed during 1969 and 1970. With the outbreaks in Costa Rica and Mexico, the VEE virus had demonstrated its ability to spread, even crossing barriers of immune horse populations. At a meeting of the U. S. Animal Health Association in Philadelphia in October, 1970, the senior author of this paper accurately predicted that VEE would spread into South Texas prior to 4 July 1971. Again a recommendation was made for approval of commercial production of TC-83 vaccine—but for probable use within the United States and no longer solely for export. Again it became apparent that efforts in this direction would not be successful in time to meet the anticipated need in Texas. The Commanding General, U. S. Army Medical Research and Development Command, approved a recommendation to prepare 2.7 million doses of vaccine for possible emergency use within the United States.
The spring of 1971 brought a culmination of all the predictions of the previous year; within a period of three months the disease spread more than 350 miles in Mexico, and by early June was reported to be 35 miles south of Brownsville. Although not reported until 30 June, the first horse in South Texas with encephalitis became sick on 23 June; virus was isolated from the brain and confirmed as VEE on 9 July. The disease in Equidae spread rapidly and by mid-July, horses were dying of VEE as far north as Harris County (Houston), which is 300 miles north of Brownsville (14). Figure 1 indicates the location of the officially reported suspect equine cases by week of onset of illness through 31 July. Progression of the disease westward and northward from the Brownsville area is readily apparent. It must be emphasized that the figure depicts reported suspect cases, rather than laboratory-confirmed cases. In many instances, specimens for laboratory submission were not collected. Also, the pattern of VEE disease in horses and the time and method of sample collection frequently minimized the chances for positive diagnosis. However, the majority of reported cases of Equidae with symptoms compatible with VEE infection were located in counties along the Rio Grande River and the first two tiers of counties along the Gulf Coast; the clustering of cases in these areas was not due to lack of surveillance elsewhere within Texas, since a statewide equine encephalitis surveillance and reporting system was placed in effect. Also, virulent VEE virus was isolated from the blood of many of these horses indicated in Figure 1, including one in Harris County. The lack of supportive evidence for VEE, the sparsity of cases and the known endemic status of Eastern and Western encephalomyelitis virus in the panhandle and north central parts of Texas would suggest the suspect cases in those areas were not VEE.

Even when VEE was known to be present within 35 miles of Brownsville, Texas, U. S. officials were somewhat hesitant to allow the vaccine to be used in the United States, but equine vaccination was begun on a voluntary basis on 25 June in a 13-county area of South Texas. In late June, all of the horses of the King Ranch and neighboring ranches were vaccinated, but elsewhere in the 13-county area initial vaccination coverage was not as complete. Although vaccination was not made compulsory and extended statewide until 13 July, horses with suspect encephalitis were reported beyond the allowable vaccine area by 10 July. In early July, vaccine administration was most intense in the southernmost two counties, and the sharp cessation of equine cases in this area followed. Statewide vaccination reached peak intensity by 24 July, with approximately 80% of the horses vaccinated. Note in Figure 2, the epizootic apparently reached its maximum extent by 24 July. Both the number of cases reported and the distribution of cases by county were greater prior to 24 July (Figure 2A) than they were the five weeks following 24 July (Figure 2B). This marked decline in number of cases and the apparent cessation of spread into new areas can only be attributed to the effectiveness of the vaccine program, since heavy rains occurred throughout this area in mid-July and mosquito populations were increasing. In addition, note the
absence of disease in one coastal county of South Texas. This county and adjacent portions of the neighboring counties appeared to be free of VEE in animals and man, although surrounding areas had confirmed VEE infections in horses and/or man. This "disease-free" area corresponds to the King Ranch area in which early and complete equine vaccination was accomplished.

Counties in which laboratory-confirmed VEE in horses was obtained (Figure 3) correlate very nicely with the distribution of reported cases through 24 July except for counties north and east of Houston. However, the cessation of new cases within 10 days following vaccination in these counties, except in unvaccinated animals, is most suggestive of a VEE etiology. Only two previously uninfected counties in Southwest Texas reported VEE-positive horses after 4 September. Since VEE continued to occur immediately south of the Texas border, it is most likely that infection spread once more into those counties from Mexico.

With one exception, only sporadic equine cases were reported during August and September. The exception involved a ranch in a county bordering the Rio Grande River. On 20 July, 38 horses in one pasture were vaccinated, but the owner considered it too much trouble to round up the remaining horses. In mid-August, at the height of the epizootic in that area, all vaccinated animals remained healthy but 40 of 67 unvaccinated horses on that ranch sickened and died. A decision was made to vaccinate the other unvaccinated horses on the ranch including, at the owner's insistence, some which were symptomatic, e.g., fever 103-105.5. Virulent VEE virus was isolated from three of three prevaccination blood samples. Although not anticipated that vaccination of a VEE-infected horse would in any way alter the outcome, eight of nine horses, known to be sick at time of vaccination, survived; three horses with fever 103-105 that were unvaccinated died. This degree of survival was not expected, since mortality with VEE generally exceeds 75%. These findings, along with the results in Costa Rica in which three of five horses infected with virulent VEE virus at vaccination survived, suggest the vaccine affords some protection to already-infected horses. Although these observations are limited, such protection could be a contributory factor in the dramatic cessation of new illness when TC-83 vaccine is applied in an area where horses are already dying with VEE.

The first human infection with VEE in Texas was recognized on 5 July, two weeks following the first recognized equine case. The clinical syndrome seemed relatively constant and preliminary information indicates very little evidence of subclinical infection (15). This is in agreement with the studies of Hinman et al. during the Guatemalan epizootic (12). The number of human cases increased rapidly, with a majority occurring in Cameron and Hidalgo Counties, near Harlingen and Brownsville. Characteristically, in each county, disease in man followed shortly after the appearance of disease in horses. Case incidence seemed to peak in mid-July and the epidemic was
essentially over by 24 July. A county-by-county occurrence of human and equine infection is shown in Table I. Equine cases are reported for only those counties with confirmed human infection. In each county, equine cases occurred approximately 10 days prior to the first human infection, and the decline in human disease was preceded by a marked decline in equine cases.

In addition to vaccination and equine quarantine, a mosquito-control program, consisting of low-volume aerial spraying of Malathion or Dibrom, was employed for a distance of 5 to 30 miles inland, along the coastal counties of Texas. This procedure effectively killed adult mosquitoes, but in most areas only one coverage was applied. The continued appearance or decrease in equine disease in these counties correlated more closely with the vaccination program than with mosquito-abatement measures.

On 16 July, the VEE epizootic was declared a national emergency, and on 17 July the vaccination program was extended to four additional states (New Mexico, Oklahoma, Arkansas and Louisiana). One week later the vaccine area was extended to California, Arizona and the Gulf Coast states, and subsequently to eight additional states and the District of Columbia, extending the area to Tennessee, Kentucky, and the Atlantic Coast states as far north as New Jersey (14).

With the abundance of data collected from the Texas epizootic, additional laboratory data on lack of reversion to virulence and the pressure of necessity, a commercial license for attenuated vaccine production was granted in August, 1971. Seed virus and production methodology were supplied by DOD as a product of USAMRIID research and developmental activities.

Experts on VEE expect the 1B virus to establish itself in Texas, as well as to spread to other areas of North America. Lack of knowledge concerning the epidemiology of VEE in a temperate climate precludes predicting the extent and direction of spread. However, this virus is potentially capable of infecting a wide range of hosts and vectors. Fortunately, additional commercial sources of vaccine are anticipated and an emergency supply is being maintained by an official U. S. Government agency.

Thus the story may end—a story which began with "just another" VEE epizootic-epidemic in South America. The etiologic agent of that epizootic, a highly virulent strain of VEE virus, gained entry into Central America and predictably spread quickly into the United States. Fortuitously, a vaccine was available in sufficient quantity to ameliorate the effects of the epizootic-epidemic in Central America, Mexico and the United States. This vaccine, developed by USAMRIID for human use, was used to break the host-mosquito-host cycle, and ultimately to protect man by immunization of the amplifying host—the horse.
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REFERENCES


TABLE I. Incidence of Laboratory-Confirmed Human and Reported Equine VEE Infections in Seven Texas Counties

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<th>County</th>
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* Reports combined for Cameron and Hidalgo Counties.
Figure 1. Reported cases of suspect equine encephalitis in Texas. Each dot represents one animal. Numbers are used in counties where cases were too numerous to be shown individually. A.—Period of 23 June to 10 July. Harris County in East Central Texas and the initial 13-county vaccination area in South Texas are indicated by outline. B.—Week of 11 July. C.—Week of 18 July. D.—Week of 25 July.
Figure 2. Summation of reported suspect equine encephalitis cases. Each dot represents one animal. Numbers are used in counties where cases were too numerous to be shown individually. Note the absence of cases in one county in Southeastern Texas (King Ranch area). A.--Period of 23 June to 24 July. B.--Period of 25 July to 5 September.
Figure 3. Counties in which human or equine cases of VEE were confirmed by virus isolation and/or specific rise in antibody titer.