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ECOLOGY AND EPIDEMIOLOGY OF CRIMEAN-CONGO HEMORRHAGIC FEVER VIRUS
TRANSMISSION IN THE REPUBLIC OF SENEGAL

ANNUAL/FINAL REPORT

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SUMMARY

The ecology and epidemiology of Crimean-Congo hemorrhagic fever (CCHF) in West Africa, a widespread, life-threatening, tick-borne, viral zoonosis, remains poorly understood despite considerable recent progress. During the five years of research represented by our study of factors that contribute to transmission of CCHF virus in Senegal, numerous observations and experiments were undertaken in the field and laboratory.

In the domain of vector ecology and behavior, we demonstrated that feeding by immature Hyalomma ticks was host-mediated, that these ticks exhibit a diel detachment rhythm, and that the survival of adult H. truncatum was temperature- and humidity-dependent. Field observations showed that that adult Hyalomma and Rhipicephalus ticks are active seasonally with annual and spatial variation, that certain rodents and birds are natural hosts for immature stages, and that adults can be found resting in rodent burrows.

Various experimental studies of CCHF virus transmission have illucidated the role of sheep in amplifying and transferring virus to H. truncatum adults, that these sheep show little disease in response to such infection, that laboratory mice may serve as appropriate models for experimental CCHF virus infection, that phenotypic changes in CCHF virus result from different types of host-passage.

Studies of the vector competence and vectorial capacity of ticks have compared different species for their epidemiological potential as CCHF virus vectors in Senegal, documented the prevalence of infection in nature, and demonstrated the existance of sexual and transovarial transmission in H. truncatum. Experimental infection of H. truncatum and Amblyomma variegatum resulted in CCHF virus replication, whereas the argasid tick Ornithodoros sonrai was found incompetent as a vector for CCHF virus.

The epidemiology and epizootiology of CCHF in West Africa was studied by serological demonstration of the spatio-temporal pattern of antibody in Senegal, by correlation of environmental and vectorial variables, and through analysis of a fatal case of CCHF in Mauritania. An extensive questionnaire-based study uncovered human risk factors for CCHF in rural northern Senegal.

As a complement to these studies on CCHF virus, other arboviruses that simultaneously circulate in the region were investigated. Most notably, studies of Rift Valley fever (RVF) virus transmission in southern Mauritania and Senegal were undertaken: we documented antibody prevalence in domestic animals during the 1987 outbreak, a decline in RVF virus transmission following that epidemic, and human risk factors for RVF and associated mosquito vectors in Senegal.

FOREWORD

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals" prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 86-23, Revised 1985).

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I. INTRODUCTION and OBJECTIVES

Crimean-Congo Hemorrhagic Fever (CCHF), is a member of a group of arthropod-borne viral zoonosis producing acute, sometimes fatal febrile and hemorrhagic symptoms. Human disease often involves initially the nervous system and in severe cases may progress to vascular disorders such as profuse diapedetic hemorrhages, brain edema, general malaise, and ultimately cardiac arrest. The first recognized epidemic occurred in the Crimea, U.S.S.R. in 1945 (Chumakov 1945, 1947) after which the viral agent was isolated from ixodid ticks (reviewed by Chumakov 1974). CCHF virus, family Bunyaviridae, genus Nairovirus, was later found to be identical to that of "Congo virus" from Africa (Casals 1969).

Transmission of CCHF virus occurs over an extremely large area of the world, including the southern U.S.S.R, central Asia, southern Europe, the Middle East, and the entire African continent (Hoogstraal 1979, Watts et al. 1988). In West Africa, studies prior to ours in Senegal and southern Mauritania have demonstrated CCHF virus and evidence of infection in certain vertebrate and tick species (Saluzzo et al. 1984, 1985a, 1985b, 1986, Camicas et al. 1986). CCHF virus transmission was well-known in this region before our project was begun.

More than 30 species of ixodid ticks have been shown to be capable of supporting infection by CCHF virus (Hoogstraal 1979, Watts et al. 1988) however, only a few species may be important in maintaining the natural transmission cycle. Epidemiological reports have implicated certain Hyalomma species that vary according to geographic region, particularly H. marginatum rufipes which has been associated with intense transmission in western Africa (Hoogstraal 1979). Whether this association is justified requires studies of host associations and vectorial capacity such as those that we have undertaken. CCHF virus has also been isolated from H. truncatum and H. impeltatum, species that are abundant in our region. The hosts associated with these ticks had been surveyed previously (e.g. Camicas et al. 1986, Gueye et al. 1986, 1987, 1989); however, much less was known about the ecology, population dynamics and host-associations of the immature stages of any of the Hyalomma species. Similarly, the vertebrates that might serve as maintenance reservoirs of the virus needed to be defined. Furthermore, the importance of transovarial transmission of the virus between tick generations in nature, relative to that of horizontal transmission, deserved study. Finally, the manner in which the numerous individual components of the CCHF virus cycle interact in nature is poorly understood.

The objectives of our project were to address many of the unknowns mentioned above by investigating certain poorly understood variables that were likely to be important in the CCHF virus transmission cycle. Ultimately, we hoped to develop a more complete understanding of the complex interactions of the

dynamics of the enzootic cycle and the epidemiology of human disease. This effort was a collaborative one involving scientists and technicians from numerous institutions. Our collaboration included expertise in the areas of virology, entomology, immunology, ecology, and epidemiology. The many people who participated in this project and their associated organizations are listed in Table 1. Numerous presentations at scientific congresses, reports, and publications have resulted from research under the grant; the most significant of these are described in Table 2.

This final report summarizes accomplishments during the five year period from 1 January, 1987 through 31 December, 1991. Details of this effort may be found in each of the 4 previous Annual Reports or in publications listed in Table 2. This summary of our project is grouped into 5 sections: a) tick ecology and behavior, b) experimental transmission studies, c) vector competence and vectorial capacity, d) epidemiology and epizootiology, and e) studies of other associated arboviruses. Within each section, a summary of various projects is provided, followed by a corresponding citation of an article that is in preparation or has been published.

II. TICK ECOLOGY and BEHAVIOR

Among the arboviruses that cause zoonotic disease in humans, CCHF virus is noteworthy for the ecological diversity of potential vectors with which it is associated. Either by inference or direct evidence of infection, nearly 20 species of African ticks have been implicated as potential CCHF virus vectors (reviewed by Hoogstraal 1979). In Senegal, at least 7 such ticks are found (Camicas et al. 1986), including 5 species of the genus Hyalomma, 2 species of Rhipicephalus and Amblyomma variegatum. Various studies undertaken through this project have examined aspects of the ecology and behavior of certain potential vectors.

II.A. Host-Mediated Feeding by Immature Hyalomma Ticks.

Foremost among factors that influence the transmission of vector-borne disease agents are the frequency of vector feeding and the diversity of vertebrate hosts. The ixodid ticks that transmit numerous human and animal pathogens typically take a blood-meal once each as a larva, nymph and adult. Thereby, horizontally-acquired pathogens may be transmitted to vertebrates solely by nymphs or adults, while simultaneous or subsequent feeding of a preceding stage is needed for the maintenance of transmission. We studied certain components of these interactions using larval and nymphal Hyalomma ticks and various African mammals and birds that they naturally infest. H. truncatum and H. marginatum rufipes parasitising rodents (4 spp), hedgehogs, hares and birds (6 spp) exhibited host-specific differences in the pattern of attachment, duration of

feeding, and dropoff. An unusual "2-host" pattern of parasitism, whereby larvae remain attached to feed again as nymphs on the same individual host, was seen in ticks engorging on certain vertebrates. However, the typical "3-host" response predominated with other host species. The vectorial capacity of these ticks for horizontally-transmitted pathogens, thereby, would depend upon the vertebrate host on which they fed. When fed on guinea pigs, a animal frequently used in laboratory studies, these ticks behaved unlike those feeding on natural hosts. Multiple feeding did not appear to evoke "resistance" in natural hosts, unlike that which has been observed with guinea pigs. These results are discussed as they may influence laboratory experiment design and the maintenance of pathogen transmission in nature.

* Wilson, M.L., Dykstra, E.A., Cornet, J.P., Schmidt, E.A. Camicas, J.L., Gonzalez, J.P. Host-regulated feeding and detachment of Hyalomma ticks (Acari:Ixodidae). J. Med. Entomol. (in preparation).

II.B. Environment-Dependent Survival of H. truncatum.

The survival of unfed adult H. truncatum held under different regimes of constant temperature (5, 17, 24, 30° C) and relative humidity (RH) (10, 50, 80%) was monitored during >1yr. Longevity of this tick was shortest at the highest temperature and lowest RH (100% dead at week 25). Conversely, H. truncatum lived longest at lower temperatures and higher RH (<100% dead at week 64). The survival of males and females was similar and, curiously, was independent of the weight of ticks. These findings have implications for the maintenance and study of laboratory colonies of H. truncatum, and for the development of tick control strategies to reduce vectorial capacity.

* Wilson, M.L., Dykstra, E.A., Schmidt, B.A. Temperature- and humidity-dependent longevity of unfed adult Hyalomma truncatum J. Med. Entomol. (in press)

II.C. Diel Detachment Rhythm of H. truncatum.

The diurnal detachment pattern of immature and adult H. truncatum infesting natural and laboratory hosts was studied. Larval ticks were allowed to feed on guinea pigs as well as 3 species of West African rodents that serve as hosts in nature. Adults fed on domestic sheep. Responses to these hosts were studied at ambient temperature and humidity as well as natural daylight. Larvae, attached, engorged and detached within 3 to 7 days post-infestation (PI). The majority of ticks dropped off during the daylight or crepuscular hours; relatively fewer engorged larvae detached during the night. A similar pattern was observed when larval H. truncatum fed on multimammate rats, slender gerbils and Nile rats. This tick behaved as a "3-host"

species in this context, i.e. all larvae detached from their host after the first blood meal. This "3-host" feeding pattern and a predilection for daytime dropoff may have implications for the design of laboratory studies of H. truncatum as well as for the vectorial capacity of this tick in nature.

- * Wilson, M.L., Logan, T.M., Dykstra, E.A., Cornet, J.P., Ba, K., Camicas, J.L. Detachment rhythm of Hyalomma truncatum (Acari: Ixodidae): natural and laboratory hosts elicit dissimilar patterns. J. Med. Entomol. (in preparation).

II.D. Adult Tick Seasonal Activity and Population Dynamics.

The seasonal pattern of activity and population density of the principal tick species in the Sahelo-sudanian savannah of northern Senegal were characterized. From May 1987 through December 1991, monthly samples of grazing sheep were made systematically near Yonofere and Dahra, Senegal. From each of 5 grazing herds chosen by chance about every month, 10 randomly selected sheep were carefully examined for the presence of ticks. Thereby, >5,000 sheep were been examined. Additionally, individually tagged, privately-owned sheep and cattle in Yonofere (15°14'N, 14°29'W) and Bandia (14°37'N, 17°01'W) that were maintained as part of their original herds were studied. More than 50 tagged sheep, goats and cattle in Bandia and about 200 animals in Yonofere were sampled at regular intervals. From these sheep >20,000 adult H. truncatum, H. impeltatum, H. m. rufipes, H. dromedarii, Rhipicephalus evertsi evertsi, and R. guilhoni were removed and identified. Three species predominated: H. truncatum, H. impeltatum, and R. guilhoni. Seasonal patterns of activity were difficult to discern, however H. truncatum appeared to be more abundant during the dry season. H. impeltatum, found only at Dahra, also exhibited most activity during the dry season. The pattern for R. guilhoni was less clear: little variation was obvious at Yonofere, while this tick was somewhat more active during the dry season at Dahra. R. e. evertsi also was most abundant during the dry season. These results are discussed in terms of the long-term temporal dynamics of CCHF virus transmission and the focal nature of epizootics.

- * Wilson, M.L., Camicas, J.L., Cornet, J.P., Diouf, A., Ba, K., Samb, I., Dykstra, E.A., Schmidt, B.A. Seasonal and population dynamics of adult ticks (Acari: Ixodidae) infesting domestic ungulates in northern Senegal. J. Med. Entomol. (in preparation).

II.E. Natural Host Associations of Immature Hyalomma Ticks.

Available evidence indicates that larval and nymphal stages of most Hyalomma and Rhipicephalus ticks feed primarily on birds and small mammals; they are rarely or never found on the

ungulates that serve as hosts to adults. Because of the importance of this general pattern to the transmission dynamics of CCHF virus, we undertook studies of the host associations of immature ticks by systematically trapped and examined birds, rodents, hedgehogs and hares in northern Senegal. We also sought to determine the seasonal activity and population dynamics of these stages. Ticks removed from hosts were placed into live vials until molting, and then were identified. During monthly observations covering >3 years, 1615 birds were examined at Yonofere, of which 2.2% harbored ticks. The predominant species was H. m. rufipes, of which there were 158 larva or nymphs. Most of these ticks appeared after the rainy season, particularly during the months of December and January; a few immature H. m. rufipes were present at other times of the year. Of nearly 50 bird species examined, ticks infested only 9, including grey-headed and golden sparrows (Passer spp.), village, slender-billed and vitelline masked weavers (Ploceus spp.) chestnut-bellied and long-tailed starlings (Lamprotornis caudatus, Spreo pulcher) yellow-fronted canary (Serinus mozambicus), and the Red-beaked Hornbill (Tockus erythrorhynchus). In addition, 9 larval H. truncatum were found on 3 birds, as were a few Argus sp.

From June 1987 through November 1990, a total of 274 small mammals were examined, including 184 rodents, 41 hedgehogs (Erinaceus albiventris) and 41 hares (Lepus crawshawi). Of the 499 larval and nymphal H. truncatum removed, 97.4 % were found on hares. Little seasonal variation was evident, although fewer ticks were found during the rainy season from June through October. In addition, 28 immature H. m. rufipes were found, again primarily on hares; the period of greatest activity corresponded with that from birds. These results are discussed in the context of environmental constraints on immature tick feeding, and in transmission of CCHF virus in West Africa.

* Wilson, M.L., Cornet, J.P., Ba, K., Dykstra, E.A., Camicas, J.L. Natural host associations of immature Hyalomma ticks. J. Med. Entomol. (in preparation).

II.F. Recovery of Ticks from Rodent Burrows.

To investigate whether immature ticks might use underground rodent burrows as a refuge from extreme temperatures and low humidity in the Sudano-Sahelian region northern central Senegal, we systematically examined such burrows during May 1987 through August 1988. Six burrows were chosen about monthly in each of 2 sites: Yonofere and Bandia. A total of 144 burrows were carefully excavated while the contents were suctioned using a gasoline motor-powered aspirator modified from a commercial leaf-blower. A series of filters separated pebbles and sand from arthropods. The rodent species that most recently inhabited each burrow was recorded, and included those of the multimammate rat (Mastomys erythroleucus (N=64), the gerbil (Taterillus sp.) (N=55), the Nile rat (Arvicanthus niloticus (N=13), Geoffroy's

ground squirrel, (Yerus erythropus) (N=5). About half of these burrows contained the Argasid tick Ornithodoros (Alectorobius) sonrai (Morel), sometimes numbering >100 per burrow. All Ixodidae that were recovered were adults and included 8 H. truncatum (in 6 burrows), 4 Rhipicephalus guilhoni (3 burrows) and 1 Rhipicephalus sulcatus (1 burrow). The immature stages of these ticks typically feed on rodents, suggesting that engorged nymphs may have detached from such hosts while they were in their burrows, and subsequently molted to adults. Thereby, the distribution and behavior of rodent hosts could influence the spatial pattern over which newly molted nymphs and adults would emerge and quest.

* Logan, T.M., Wilson, M.L., BA, K. & Cornet, J.P. Association of ticks (Acari: Ixodidae) with rodent burrows in Senegal. J. Med. Entomol. (in preparation).

III. EXPERIMENTAL INFECTIONS OF VERTEBRATES

III.A. Transmission of CCHF Virus from Sheep to H. truncatum.

CCHF virus was inoculated into West African sheep that were simultaneously infested with adult H. truncatum ticks. The sheep developed a viremia and antibodies, indicating virus infection and replication; however, the length and magnitude of the viremia and serological response corresponded to the animals immunological status. Tick attachment and feeding was not influenced by sheep infection. CCHF virus infection was acquired by 11-33% of female and 0-60% of male ticks. Infection in the ticks did not influence their feeding success as judged by weight at drop-off, and the weight of eggs produced by infected and non-infected ticks was similar. Transovarial transmission of CCHF virus was demonstrated in 2 of 12 (17%) egg batches from infected female ticks, but in none of 19 egg batches from ticks that tested negative for CCHF virus. Our results suggest that under certain ecological conditions, sheep may serve to amplify CCHF virus in nature through horizontal transmission and that the maintenance cycle also may be influenced by transovarial transmission to the next generation of ticks.

* Wilson, M.L., Gonzalez, J.P., Cornet, J.P. & Camicas, J.L. (1991) Transmission of CCHF virus from experimentally infected sheep to Hyalomma truncatum ticks. Res. Virol. 142: 395-404.

III.B. Experimental CCHF Virus Infection of Laboratory Mice.

The serological, virological and pathogenic impact of CCHF virus infection was studied using laboratory mice as a model. Mice of various ages and sexes were inoculated intracranially, intraperitoneally or subcutaneously with different virus titers. The effects of age, route of infection, and concentration of

inoculum on viral pathogenicity and the development and transfer of viremia and antibody were investigated. Inoculation of day-old mice was similarly fatal at high titers, but the percentage of these mice that survived increased as the initial virus titer declined. Older mice better survived higher titer inoculation. Thus, we observed a dose-response-like pattern that was age-dependent. Adult mice which survived infection produced IgG beginning 3-5 days post-inoculation. Antibodies of pregnant mice that were infected subcutaneously from 1 to 6 days prior to giving birth apparently were transferred to the infants who were not found to be viremic. Our results suggest that certain aspects of transmission and pathogenicity of this widespread, sometimes fatal, zoonosis may be studied in the laboratory by use of model vertebrates such as mice.

* Keyes, L.E., Wilson, M.L., & Gonzalez, J.P. Experimental infections with CCHF virus using laboratory mice. Res. Virol. (submitted).

III.C. Response of Sheep to CCHF Virus Infection.

To further clarify the role of sheep in the maintenance cycle CCHF virus, we studied biological and clinical aspects of animals that were experimentally infected with the virus. A total of 17 sheep were infected either by intra-peritoneal inoculation or by infestation with experimentally infected ticks. These adults, as well as 5 lambs born of infected females were monitored. Among clinical symptoms, only a moderate fever was observed ($39.7^{\circ}\text{C} \pm 0.3$) during the period of viremia. CCHF virus was reisolated after intra-cranial inoculation into suckling mice from blood samples taken on days 3 to 9 p.i. at a mean titer of 3.3 log LD₅₀/ml. Circulating virus was detected during 7 days in naive sheep and for less than 4 days in previously infected sheep. Antibody production was demonstrated by a direct ELISA (IgG) and by an IgM-capture ELISA. In non-immune sheep, IgM was first observed on day 7 p.i. and IgG appeared 1 day later. Among 5 sheep studied for liver and kidney functions, all showed hepatic dysfunction with a moderate elevation of serum aspartate transferase (210 U./l). Two of 4 sheep tested for blood responses had abnormal cell counts with a marked neutrophilia (up to 63%) lasting for two weeks beginning day 5 p.i. None of these changes in biological factors could be directly related to CCHF virus infection. Ewes infected when pregnant produced post-partum antibodies in their milk at a significant titer (1/1,000); antibodies were recovered in the sera of nursing lambs from the first meal to 50 days after birth with a decreasing titer.

* Gonzalez, J.P., Camicas, J.L., Cornet, J.P. & Wilson, M.L. Biological and clinical responses of west African sheep to CCHF virus infection. Res. Virol. (in preparation).

III.D. Host-passage Induced Phenotypic Changes in CCHF Virus.

The pathogenicity to suckling mice (SM) of intra-cerebrally CCHF virus has been used as a measure of virus phenotype. We studied potential phenotypic changes associated with different host passage histories. Two strains isolated from different hosts (human and tick) were passaged into other hosts (vertebrates and ticks) then reisolated and tested for pathogenicity in SM. More than 5,700 SM were inoculated with 13 viral suspensions with different passage histories. Survival curves were established using the actuarial lifetime table and differences were evaluated with the log rank test. Regardless of the origin of the strain, viruses exhibited the same phenotype when passaged from mice to mice. However, the viral phenotype radically changed when another vertebrate- or tick-passage occurred. The last host appears to be the major influence on SM pathogenicity. Because CCHF virus strains appear to vary little in their antigenic phenotype, perhaps hosts can induce phenotypic changes that modulate viral pathogenesis without producing detectable genotypic change.

- * Gonzalez, J.P., Camicas, J.L., Cornet J.P. & Wilson M.L.
Host-passage induced phenotypic changes in CCHF virus.
Res. Virol. (submitted).

IV. VECTOR COMPETANCE and VECTORIAL CAPACITY for CCHF VIRUS

IV.A. Comparison of Ticks as Vectors of CCHF Virus in Senegal.

At least 30 tick species, from 7 genera have been found naturally infected with CCHF virus worldwide. To this list we added R. guilhoni. In the sub-Saharan Africa, 17 tick species have been implicated as vectors, of which 12 are present in Senegal or Mauritania. We studied the five principal species that appear to be the most important in CCHF virus transmission in Senegal, namely A. variegatum, H. impeltatum, H. m. rufipes, H. truncatum, and R. guilhoni. We reported on the distribution, host associations, seasonal activity patterns and CCHF virus infection of these ticks, as well as the epidemiological implications for human disease. Despite similarities in ecological characteristics, not all of these species seem equally likely to be important in the transmission cycle. The most important vectors in enzootic and epidemic transmission throughout Senegal appear to be H. truncatum and A. variegatum.

- * Camicas, J.L., Wilson, M.L., Cornet, J.P., Digoutte, J.P., Calvo, M.A., Adam, F., Gonzalez, J.P. (1990) Relative potential of ticks as vectors of Crimean-Congo hemorrhagic fever virus in Senegal: ecological and epidemiological implications.
Archiv. Virol. [Suppl 1]: 303-322.

IV.B. Natural Prevalence of CCHF Virus in Ticks.

The intensity of infection in populations of ticks is an important component of their capacity as vectors of CCHF virus. In order to characterize the prevalence of naturally-acquired CCHF virus infection in adult ixodid ticks feeding on domestic ungulates, ticks were collected and analysed from numerous sites throughout Senegal and southern Mauritania. Ticks from sheep, goats and cattle were identified, pooled by species and collection site, then frozen at -70°C until being tested for the presence of arboviruses. From 1984 through 1991, more than 40,000 ticks comprising 5 genera and 11 species were sampled and tested by suckling mouse inoculation and cell culture. The identity of viruses from positive pools was determined by complement fixation following mouse passage. Numerous strains of CCHF virus were identified from pools of H. m. rufipes (28), H. truncatum (6), H. impeltatum (2), A. variegatum (3), and Boophilus geigy (3). In addition one strain of CCHF virus was isolated from Boophilus decoloratus, the first such isolation in Senegal. Finally, CCHF virus was isolated from Rhipicephalus guilhoni, the first time this tick has ever been shown to be infected. Other viruses also were isolated from various species of ticks including Dugbe (2) Bhanja (1), Jos, and more than 100 strains of Wad Medani. These results are analysed for the minimum infection rates and the possible implications for maintenance of transmission in nature.

* Wilson, M.L., Camicas, J.L., Zeller, H.G., Cornet, J.P., Saluzzo, J.F., Calvo-Wilson, M.A., Adam, F., Digoutte, J.P. Prevalence of Crimean-Congo hemorrhagic fever virus in ticks (Acari: Ixodidae) from hosts in Senegal: infection of adults. J. Med. Entomol. (in preparation).

IV.C. Sexual and Transovarial Transmission in H. truncatum.

Male H. truncatum ticks were inoculated with CCHF virus, hypostomectomized, and then allowed to mate with uninfected females feeding on a naive rabbit. After mating, CCHF virus was reisolated from 2 of 3 males tested and from 4 of 6 mated engorged females (titer $\leq 2.2 \log \text{LD}_{50}/\text{ml.}$). Vertical transmission was then demonstrated by virus reisolation from a portion of two of the six egg batches laid by the positive females. From these 2 positive egg batches, 6 larvae pools were tested, yielding virus reisolation from one. Attempts to reisolate CCHF virus from 15 nymph pools from this positive batch of larvae did not succeed. Virus reisolation from gonopore-closed females which cofed with preinfected males, demonstrated transmission in the absence of copulation. Rabbits that served as blood meal sources seroconverted after infestation by infected male ticks. However virus was not reisolated from 3 gonopore-closed, engorged females, nor from their eggs, after a feeding with hypostomectomized preinfected males. Transmission of CCHF virus during mating or cofeeding of

adult H. truncatum., and subsequent transovarian transmission, appears to be another way to increase infection in the tick population, and may contribute to the maintenance of transmission in nature.

- * Gonzalez, J.P., Camicas, J.L., Cornet J.P. & Wilson M.L. (1992) Sexual and transovarian transmission of CCHF virus in Hyalomma truncatum ticks. Res. Virol. 143: 23-28.

IV.D. CCHF Virus Replication in H. truncatum and A. variegatum.

CCHF virus replication was studied in two potential vectors from West Africa. H. truncatum is an important tick species in CCHF virus ecology, and A. variegatum represents another common tick that feeds on a variety of hosts and is a potential vector. Ticks were infected by intra-anal inoculation. CCHF virus was reisolated 5 days p.i. from 100% of ticks tested by suckling mice inoculation. During the early phase of virus replication the virus titer increased in H. truncatum but not in A. variegatum. Virus titer increased gradually to more than 6 log LD50/ml at 100hrs. p.i. for H. truncatum, then slowly decreased on day 7 p.i. to a plateau until day 12 p.i. Antigen was first detected in H. truncatum hemocytes 4 hours p.i. at a low level of cell-infection ($\geq 1\%$); The rate of infected cells then increased through day 12 p.i. CCHF virus titer in A. variegatum reached a plateau in 5 days, and remained at a moderate level of 2 ± 0.5 log LD50/ml up to 70 days p.i. When we explored the distribution of the virus in A. variegatum, infection in the leg and hypostome hemolymph increase in a similar way through day 115 p.i. Despite exhibiting a lower titer, A. variegatum still remained infected with CCHF virus at 4 months p.i. when tested by suckling mice inoculation. Long-term infection was seen in other studies on H. truncatum where virus was reisolated 11 months p.i. with a mean titer of 2.3 log LD50/ml (unpublished). The stability of CCHF virus titer after about 15 days of intrinsic incubation suggests that life-long, stable persistence of this virus may occur in certain susceptible adult ticks.

- * Gonzalez, J.P., Cornet J.P., Wilson M.L, & Camicas J.L. (1991). CCHF virus replication in adult Hyalomma truncatum and Amblyomma variegatum ticks. Res. Virol. 142: 483-488.

IV.E. Incompetence of an Argasid Tick for CCHF Virus Transmission.

Adults and nymphs of the Argasid tick, Ornithodoros sonrai were allowed to feed on suckling mice that had been experimentally infected with CCHF virus. The mean viral titer of mouse blood at the time of tick feeding was $10^{3.2}$ plaque-forming units (PFU)/ml. Samples of ticks were assayed on 12

occasions between days 0-31 after the viremic blood meal. Mean viral titers were $10^{2.1}$ PFU/tick immediately after the viremic meal. This declined to $10^{1.2}$ PFU/tick after 2 days, and no virus was detected after 11 days. The percentage of ticks with detectable virus was 92% (22/24) immediately after the viremic blood meal, but declined to 20% (2/10) after 4 days and to 0% (0/44) after 11 or more days. Ticks were allowed to feed on sets of 3 naive suckling mice on days 0, 2, 5, 8, 11, 14, 21 and 28 after the viremic blood meal but no transmissions occurred. Similarly, no transovarial transmission of virus from CCHF virus-exposed O. sonrai to their progeny was observed. These results suggest that O. sonrai may not serve as a natural vector of CCHF virus.

- * Durden, L.A., Logan, T.M., Wilson, M.L., Linthicum, K.J. Vector incompetence of a soft tick, Ornithodoros sonrai, for Crimean-Congo hemorrhagic fever virus under laboratory conditions.
J. Inf. Dis. (submitted)

V. EPIDEMIOLOGY and EPIZOOTIOLOGY of CCHF VIRUS TRANSMISSION

V.A. Spatio-temporal Patterns of CCHF in Senegal.

Aspects of the spatial and temporal patterns of transmission of CCHF virus were studied in Senegal. A country-wide serological survey of domestic animals indicated that transmission was most intense in the northern dry Sahelian zone and least in the southern, more humid Guinean zone. Human IgG prevalence, ranging from nearly 20% to <1% among 8 sites throughout the region, also was greatest in the north. A fatal human case of CCHF from Rosso, Mauritania in 1988 was studied and an accompanying serosurvey of human contacts and domestic animals indicated epidemic transmission during that period. Systematic samples of adult ixodid ticks on domestic animals allowed us to analyse the distribution and relative abundance of potential CCHF virus vectors, demonstrating that Hyalomma spp. predominated in those biotopes where transmission was most intense. A prospective study of CCHF virus infection and tick infestation in sheep exposed a period of epizootic transmission in 1988 that corresponded temporally with increased abundance of adult H. truncatum and H. impeltatum. Four strains of CCHF virus were isolated from pools of these ticks and of R. guilhoni. Our results suggest that CCHF virus is focally endemic throughout the region, although highly variable in time and space, and that the relative abundance of Hyalomma ticks may be the primary determinant of endemic and epidemic transmission.

- * Wilson, M.L., Gonzalez, J.P., LeGuanno, B., Cornet, J.P., Guillaud, M., Calvo, M.A., Digoutte, J.P. & Camicas, J.L. (1990) Epidemiology of Crimean-Congo hemorrhagic fever in Senegal: temporal and spatial patterns. Archiv. Virol. [Suppl 1]: 323-340.

V.B. Environmental and Vectorial Correlates of CCHF in Senegal.

The spatial pattern of CCHF virus transmission was studied in Senegal by analysis of human and sheep IgG antibody prevalence and the relative abundance of potential tick vectors. A systematic, country-wide serological survey of sheep demonstrated that, overall, 10.4% of sheep exhibited IgG to CCHF virus. Both sexes were infected equally. Antibody prevalence increased with the age of sheep from 2.1% during the first year to 18.2% among sheep aged 3 years or more. IgG prevalence was highest in the northern, arid Sahelian zone averaging 75.7% seropositivity and decreased to nil in the southern, moister Sudano-Guinean and Guinean zones. Human IgG prevalence ranged from 21% to <1% among 8 sites that were sampled throughout the region with a similar spatial pattern of infection: greatest in the north and least in the south. The distribution and relative abundance of ixodid ticks, most of which are potential vectors of CCHF virus, was compared with that of human and sheep IgG. Hyalomma spp. ticks predominated in those biotopes where antibody prevalence was highest. Our results suggest that CCHF virus is focally endemic throughout the region, although the highest prevalence of human and animal antibody was found in northern, more arid zones. The abundance of Hyalomma ticks may be the proximal determinant of endemic transmission.

- * Wilson, M.L., LeGuenno, B., Guillaud, M., Desoutter, D., Gonzalez, J.P. & Camicas, J.L. (1990) Distribution of Crimean-Congo hemorrhagic fever viral antibody in Senegal: environmental and vectorial correlates. Am. J. Trop. Med. Hyg. 43: 557-566.

V.C. Analysis of a Fatal Case of CCHF in Mauritania.

In sub-saharian West Africa only two human cases of CCHF, both non-fatal, have been previously reported. We documented a fatal human case of CCHF in southwestern Mauritania during May 1988 by demonstrating CCHF virus-specific class M antibodies and by isolating CCHF virus (CCHFV). Five of 7 other patients simultaneously hospitalized with haemorrhagic fever symptoms also exhibited elevated IgG. Healthy family members and contacts of these patients showed an IgG prevalence of 36%; similarly 29% of their sheep had also been infected. A serosurvey of 1,219 sheep from 14 widely dispersed sites throughout southern Mauritania demonstrated IgG prevalences ranging from 4.9% to 43.6%. IgM was found in many herds. These observations demonstrate that CCHFV is enzootic in southern Mauritania, and suggest a recent period of intense transmission in parts of the region.

- * Gonzalez, J.P., LeGuenno, B., Guillaud, M., Wilson, M.L. (1990) A fatal case of Crimean-Congo haemorrhagic fever in Mauritania: virological and serological evidence suggesting epidemic transmission. Trans. Roy. Soc. Trop. Med. Hyg. 84: 573-576.

V.D. Human Risk Factors for CCHF in Rural Northern Senegal.

To determine the extent of infection and investigate modes of transmission of CCHF virus to humans within an endemic focus, a cross-sectional seroprevalence survey was performed from February to May 1989 of 755 persons 5 years of age and older living in the rural settlement of Yonofere, in sub-Saharan northcentral Senegal. Anti-CCHF virus IgG was found in 13.0% of 284 persons who completed a standardized questionnaire and provided blood samples. Seropositivity rates were equal between sexes and increased significantly with age. Risk factors for men, but not for women, included reported contact with sick animals, tickbite during the cold-dry season when immature ticks are most active, and bite by a tick which we identified as an adult male *H. truncatum*. Prospective surveillance is needed to assess the incidence and impact of human disease.

- * Chapman, L.E., Wilson, M.L., Hall, D.B., LeGuenzo, B., Dykstra, E.A., Ba, K., Fisher-Hoch, S.P. (1991) Risk factors for Crimean-Congo hemorrhagic fever in rural northern Senegal. *J. Inf. Dis.* 164: 686-692.

VI. STUDIES of OTHER ARBOVIRUSES in SENEGAL.

VI.A. Rift Valley Fever Antibodies in Small Ruminants of Senegal.

A total of 1,715 randomly selected sheep and goat sera from Senegal were tested for antibodies against Rift Valley fever (RVF) virus using an enzyme-linked immunosorbent assay. The results suggest that transmission of RVF virus is enzootic. Antibody prevalence varied among herds, and was highly heterogeneous in space. Sheep and goats expressed comparable antibody prevalences, suggesting that both may be equally involved in RVF virus transmission cycle.

- * Guillaud, M., LeGuenzo, B., Wilson, M.L., Desoutter, D., Gonzalez, J.P. & Digoutte, J.P. (1988) Prevalence en anticorps contre le virus de la Fievre de la Vallee du Rift chez les petits ruminants du Senegal. *Ann. Inst. Pasteur/Virol.* 139: 455-459.

VI.B. Rift Valley Fever in Domestic Animals During the 1987 Outbreak.

Severe hemorrhagic disease during 1987 among the human population living in the Senegal River basin was found to be caused by infections of Rift Valley fever (RVF) virus infection. As in previous RVF outbreaks, local herdsmen reported a high incidence of abortion and disease among livestock. Serum samples were obtained from domestic animal populations from areas near Rosso, the best studied focus of human infection, as

well as other areas distant from known human disease. Among animals from the area where human disease was most prevalent, antibody rates reached 85%, with ca. 80% of the sera positive for both IgG and IgM antibodies. In contrast, human populations in the same area had lower RVF virus antibodies. Thus, the detection of RVF virus-specific IgG and IgM antibodies provided evidence of recent transmission, without the requirement to establish pre-disease antibody levels in populations or individuals without virus isolation. Subsequently, detection of modest levels of IgG and IgM in the Ferlo region, 130 km south of the Senegal River flood plain, established that RVF virus transmission also occurred in another area of the basin.

* Ksiazek, T.G., Jouan, A., Meegan, J.M., LeGuenno, B., Wilson, M.L., Peters, C.J., Digoutte, J.P., Guillaud, M., Merzoug, N.O., Touray, O.I. (1989) Rift Valley Fever among domestic animals in the recent West African outbreak. Res. Virol. 140: 67-77.

VI.C. Decline in RVF Virus Transmission in West Africa Following the Mauritanian Outbreak.

During 4 years after the epidemic/epizootic of RVF in southern Mauritania, we monitored domestic ungulates at a variety of sites in West Africa to determine changes in the prevalence of RVF virus transmission there, as well as whether virus activity would persist or return to the low levels found previously. In addition to observations from sites in northern Senegal, we tested sera from animals from Burkina Faso, Togo, Cote d'Ivoire and Cameroon. Sera were tested by ELISA for both IgG and IgM anti-RVF virus antibody. Herd immunity (prevalence of IgG) generally declined throughout the period in all sites. Consistent with this, samples from hundreds of sheep and cattle in the river and savannah regions of northern Senegal, showed only 3 seroconversions (appearance of IgM) in 1989, none in 1990 or 1991, and 1 in 1992. Similarly, few new RVF virus infections were found in the sahelian and sudanian habitats of the other countries sampled. This rapid decline in incidence from 1987-88 suggests that an inter-epizootic period has occurred, and raises questions as to virus maintenance. The possible influences of immunity and climate on the intensity of RVF virus transmission are discussed.

* Zeller, H.G., Thiongane, Y., Wilson, M.L., Cornet, J.P., Camicas, J.L., Bessin, R., Teou, K., Formenty, P., Gbaguidi, M., Akakpo, J.A. & Digoutte, J.P. 1991. Rift Valley fever virus activity in West Africa following the 1987 Mauritanian outbreak, 1989-1992. Trans. Roy. Soc. Trop. Med. Hyg. (in preparation).

VI.D. Human Risk Factors for Rift Valley Fever in Senegal.

To investigate past infection and modes of transmission of Rift Valley fever (RVF) virus to humans within an endemic focus, we undertook a retrospective cohort study of the semi-nomadic Peul people living in sub-Saharan north-central Senegal. Persons 5 or more years old living in the rural settlement of Yonofere were studied during February to May 1989. Anti-RVF virus IgG was found in 22.3% of 273 persons who responded to a standard questionnaire and for whom blood was analyzed; none had IgM. Seropositivity was similar for males (25.4%) and females (21.1%), increased markedly with age for both sexes, and varied considerably among camps (0%-37.5%). The principal activities that emerged as risk factors for past RVF virus infection were nursing sick people, assisting animals during abortions/births, and treating sick animals. Females who reported treating sick animals had odds ratios (OR) for RVF viral antibody that were four to five times greater than for those who did not for all age groups. For males, the ORs for assisting with animal births/abortions and nursing sick people were five to seven times those for males not reporting these activities. Serologic studies of sheep showed that RVF viral antibody prevalence averaged 30.1% overall (0.8% IgM), but varied among camps (0%-66.7%) in a manner spatially unlike that in humans. The seasonal abundance and relative density of potential mosquito vectors were also estimated by monthly samples in CDC traps. Mosquito abundance varied seasonally with rainfall (>90% captures in 4 mo). Species diversity was large (24 spp), dominated by Aedes and Culex. RVF virus was not isolated from 62 mosquito pools tested. Results indicate that RVF is endemic in this region, people are at considerable risk of infection, and the primary risk includes transmission via contact with infected animals or humans.

* Wilson, M.L., Chapman, L.E., Hall, D.B., Dykstra, E.A., Ba, K., Zeller, H.G., Traore-Lamizana, M., Hervy, J.P., Linthicum, K.J. Rift Valley fever in rural northern Senegal: human risk factors and potential vectors Am. J. Trop. Med. Hyg. (submitted).

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VIII. APPENDICES

Table 1. Collaborators and primary institutional affiliations who have participated in the studies presented in this report.

INSTITUT FRANCAIS de RECHERCHE SCIENTIFIQUE pour le DEVELOPPEMENT en COOPERATION - (OMRSTOM)

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Table 1. Continued.

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Table 2. Presentations, reports and publications that have resulted from research under the grant.

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