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EPIDEMIOLOGICAL AND EPIZOOTIOLOGICAL INVESTIGATIONS
OF FILOVIRUSES IN THE CENTRAL AFRICAN REPUBLIC

ANNUAL REPORT

A.J. GEORGES, J.P. GONZALEZ, C.C. MATHIOI

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<p>→ The 1987 field studies have focused on 2 villages, Gordil and Ouandja. The main results of these prospective studies begun in 1985 show a higher prevalence in Ouandja females than in males, several high titered seroconversions a higher rate of seropositivity in outlying areas (close to croplands) than in areas with high density population, a low prevalence in rodents and high prevalence in dogs. These meaningful results must be confirmed and extended so that we can accurately define the epidemiology, ecology and pathogenicity of the filoviruses in the CAR. Key words:</p>									
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SUMMARY

The collaborative program of sero-epidemiological investigations on Filoviruses has been focused in 1987 on two cooperative villages, Gordil and Quandja, of the Vakaga district (Northern part of the country), which have been studied since 1985.

We have mainly observed: a high (25.4 and 27.8%) and relatively stable seroprevalence in human population; a lowest prevalence in Quandja males than in females (18.7 versus 35.9%); a high rate of seroconversions, for instance 10 high titered seroconversions (0 to ≥ 128) in Quandja from 1986 to 1987; a high frequency of double positivities with Ebola (strains Zaire and Sudan), but also a few high titered seropositivities with Marburg; mainly in Quandja, a lowest seroprevalence in areas with highest human densities, and also with large grain storing, and therefore numerous dwelling rodents, the prevalence is higher in outlying areas, close to croplands areas; a low seroprevalence in rodents (4.5%) and a high seroprevalence in dogs (34.5%).

Further investigations are necessary: accurate characterization and identification of individuals who have seroconverted, establishment of a profile with high infection risk (females, households with high rate of positivity ...), question each seroconversion about previous illnesses, survey children of less than 5 years, who have not been tested yet, resurveying dog populations and extending ecological studies to the croplands surrounding the village.

These investigations will help us to accurately define the epidemiology, ecology and pathogenicity of the filoviruses.

FOREWORD

For the protection of human subjects, the investigators have adhered to policies of applicable Federal Law 45CFR46.



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BODY OF REPORT

A. STATEMENT OF THE PROBLEM

In the past, the filoviruses, a new group of pathogenic agents, were not adequately or thoroughly studied in Africa. The current Intitute Pasteur/USAMRIID filovirus field program was established to systematically study these agents and accurately assess and reduce their natural threat by defining their epidemiology, ecology, and pathogenicity, and by developing procedures to control disease.

The current field program, as outlined in previous reports (1,2), was divided into three phases. Phase one consisted of cross-sectional serosurveys conducted in different ecological or phytogeographic areas to locate areas of virus activity as measured by the prevalence of filovirus reactive antibody. Phase two consisted of prospective studies conducted in well defined populations to document active virus transmission by identifying seroconversions. Phase three consisted of in depth studies to identify the occurrence of clinical diseases associated with antibody prevalence and define the local ecology of filovirus activity. Phase one was completed and phase two started in 1986. The results of the phase one studies on the epidemiology of filoviruses in CAR (Central African Republic) suggested that the research efforts should be formed on the Vakaga district in the northern part of the country: 1. The filovirus activity as measured by antibody prevalence was highest in this region; 2. Virus activity was confined to select villages; 3. The antibody prevalence was highest

among the female population; 4. Both Ebola virus and Marburg virus were active in the Vakaga district; and 5. The numerous double seropositives (Ebola virus and Marburg virus reactive antibody positives) suggested shared risk factors for the filoviruses.

Unfortunately, our follow-up study revealed that conducting long term prospective studies in the Vakaga would be difficult. Many villages, Amardjedi and Sikikede for example, were not willing to participate in additional studies. (The reluctance of Amardjedi and Sikikede residents to participate in long term studies was due to their support of illegal poaching and their fear that outsiders would notify the authorities of their activities).

In light of the reluctance of many villages to cooperate and the logistical problems encountered in traveling deep into the Vakaga district, two cooperative villages, Gordil and Ouandja, were selected for detailed studies in 1987. The results of cross sectional studies revealed that the antibody prevalence in villages that neighbored Gordil and Ouandja did not significantly differ from the antibody prevalence in Gordil and Ouandja indicating that the results generated from studies in these two villages would reflect the epidemiology and ecology of the region (Tables I and II).

Table I.

Comparison of filovirus reactive antibody prevalence in village surveyed in different areas of the Vakaga (a).

Survey Area	Village	Total. N°.	N°. Pos.	% Pos.
Bira0	Toumou(b)	128	29	22.6
	Takalama	95	14	14.7
Gordil	Gordil(c)	147	30	20.4
	Ndiffie	97	19	19.6
Quandja	Quandja(c)	135	40	29.6
	Tirongoulou	68	14	20.5
	Tahala	61	9	14.8
	Serengobo	42	7	16.6

a. Villages in the Bira0, Gordil and Quandja Areas were screened in 1986 and the antibody prevalence was compared to previous results in villages of the same Area.

b. 1984 results

c. 1985 results.

Table II.

Sex distribution of filovirus activity in Vakaga district villages.

Village Survey	General			Male			Female		
	Total Screen.	N° Pos.	% Pos.	Total Male	N° Pos.	% Pos.	Total Female	N° Pos.	% Pos.
Takalama	95	14	14.7	47	6	12.7	48	8	16.7
Ndiffie	97	19	19.6	54	8	14.8	43	11	25.6
Tahala	61	9	14.8	33	5	15.2	28	4	14.3
Serengobo	42	7	16.6	25	4	16.0	17	3	17.6
Tirongoulou	68	14	20.5	32	7	21.8	36	7	19.4

B. METHODS

1. Sampling procedures:

In brief, the following sampling procedure was implemented. In each village, volunteers were selected, questionnaires consisting of general background questions were completed for each individual, blood samples were drawn, and each participant was given an identification number, medical examination, and treated for illnesses. In each village a preliminary census has been conducted, maps drawn and heads of all households identified.

2. Serological procedures:

Blood samples were drawn and allowed to clot and the resulting serum specimen was divided into two aliquots. One aliquot was screened at the Institute Pasteur and one aliquot was tested at USAMRIID. The serum samples were thawed and separated into three aliquots. Two aliquots were stored frozen at -20°C , while the remaining aliquot was diluted and screened double blind by IFA for hemorrhagic fever virus reactive antibodies. The samples were screened at a 1:16 dilution on CRELM slides and the seropositives were screened and titrated on hemorrhagic fever virus infected and uninfected Vero cell monospecific spot slides. Specimens were considered positive if they reacted with virus infected and not virus uninfected Vero cells. The endpoints for the serological titrations were recorded as the reciprocal of the last dilution which produced a positive react with infected cells.

C. RESULTS

1. Filovirus antibody prevalence:

The filovirus antibody prevalence in Gordil (Table III) and Quandja (Table IV) seems to be stable though a lower antibody prevalence was observed in 1986 than in either 1985 or 1987. The overall prevalence for the two villages seem to be similar (25.2% in Gordil and 26.1% in Quandja). However, as previously observed, sex and age related factors seem to influence exposure to the filoviruses (Tables V and VI). The male population of Quandja has a significantly low filovirus antibody prevalence suggesting a lower exposure to the filoviruses (Table VI). The low prevalence in Quandja males was consistently observed. Age also influences exposure. However, the effect seems to be more apparent in Gordil than in Quandja. The youngest age groups in both villages seem to have a significant antibody prevalence.

2. Seroconversions:

Seroconversions are common in Gordil and Quandja. 18.4% (26/141) of the seronegative and 39.3% (22/56) of the seropositive populations participating in our prospective studies have seroconverted. 26 seroconversions (negative to positive) occurred between 1986 and 1987 (Table VII). The majority of the study population remained either seronegative (81.6%, 115/141) or seropositive (60.7%, 34/56). The antibody titer seems to be relatively stable since 44.6% of the seropositives (25/56) maintained equivalent antibody titers between 1985 and 1987.

Table III.

Filovirus reactive antibody prevalence in 1985, 1986 and 1987 previously unsurveyed Gordil populations.

Survey Year.	General			Male			Female		
	Total Screen.	N° Pos.	% Pos.	Total Male	N° Pos.	% Pos.	Total Female	N° Pos.	% Pos.
1985	147	30	20.4	92	19	20.6	55	11	20.0
1986	62	10	16.1	27	3	11.1	35	7	20.0
1987	89	34	38.2	33	12	36.4	55	20	36.6
Summary:	298	75	25.2	152	34	22.4	145	38	26.2

a. Only those individuals not surveyed in previous years are represented in this table.

Table IV.

Filovirus reactive antibody prevalence in 1985, 1986 and 1987 previously unsurveyed Ouandja populations.

Survey Year.	General			Male			Female		
	Total Screen.	N° Pos.	% Pos.	Total Male	N° Pos.	% Pos.	Total Female	N° Pos.	% Pos.
1985	135	40	29.6	64	12	18.8	71	28	39.4
1986	105	14	13.3	47	4	8.5	58	11	18.9
1987	251	73	29.1	103	24	23.5	116	49	40.5
SUMMARY:	491	128	26.1	214	40	18.7	245	88	35.9

a. Only those individuals not surveyed in previous years are represented in this table.

Table V.

Age and Sex specific filovirus reactive antibody prevalence in the Gordil population surveyed in 1985, 1986 and 1987(a).

Age Group.	Females			Males			General		
	Total N°.	N° Pos.	% Pos.	Total N°.	N° Pos.	% Pos.	Total N°.	N° Pos.	% Pos.
1-10	58	8	13.7	74	15	20.2	132	23	17.4
11-20	27	9	33.3	30	6	20.0	57	15	26.3
21-30	23	7	30.4	17	3	17.6	30	10	33.3
≥ 31	28	12	42.8	20	8	40.0	48	20	41.6
Total:	136	36	26.4	141	32	22.6	267	68	25.4

a. Prevalence is summary of the 1985, 1986, 1987 results on unsurveyed populations.

Table VI.

Age and Sex specific filovirus reactive antibody prevalence in the Ouandja population surveyed in 1985, 1986 and 1987(a).

Age Group.	Females			Males			General		
	Total No.	N° Pos.	% Pos.	Total No.	N° Pos.	% Pos.	Total No.	N° Pos.	% Pos.
1-10	50	18	36.0	84	16	19.0	134	34	25.3
11-20	62	16	26.0	76	12	15.7	138	28	20.2
21-30	39	7	17.9	10	4	40.0	49	11	22.4
≥ 31	90	43	46.7	44	9	20.4	134	51	38.0
Total:	245	88	35.9	214	40	18.7	459	128	27.8

a. Prevalence is the summary of the 1985, 1986, 1987 results on unsurveyed populations.

Table VII.

Filovirus seroconversions in Gordil and Quandja CAR between May 1985 and April 1987(a).

1986 Serosurvey:						1987 Serosurvey:							
Household		Ind.	Ab.Reactivity			Household		Ind.	Ab.Reactivity				
No.	Res.	Pos.	S.Age	EboZ	EboS	MBG	No.	Res.	Pos.	S/Age	EboZ	EboS	MBG
Gordil:													
B24*	10	2	F/13	128	128	-	A7	3	1	M/7	64	-	-
							A21*	8	1	M/08	32	128	-
							A28	3	1	M/25	32	64	-
							A37	9	2	F/8	-	128	-
							A40*	8	3	M/10	32	256	-
							A45	2	2	M/6	128	-	-
							B17	4	1	F/10	-	-	-
Quandja:													
32	6	1	M/10	-	16	-	05	5	2	M/11	-	64	-
							12*	17	6	M/6	256	32	-
							12*	17	6	F/32	2048	2048	-
							13*	7	3	M/10	128	128	-
							17	8	2	F/12	32	32	-
							33*	7	4	F/38	512	128	-
							39*	9	4	F/40	128	64	-
							45	4	4	F/35	-	32	64
							47	11	5	M/8	-	32	-
							48	5	4	M/12	-	32	-
							55*	3	3	M/9	128	128	-
							58	9	2	F/10	32	-	-
							59*	15	6	F/45	128	32	-
							68	7	1	F/30	32	32	-
							72*	6	3	M/14	512	128	-
							83*	5	2	M/70	512	128	-
							84*	12	6	F/10	256	1024	-
							85	3	1	M/8	32	32	-

a. Seronegatives were annually rescreened.

* Strong (high tittered) seroconversions.

3. Double positives:

The high frequency of double positives (individuals positive to Ebola virus and Marburg virus) in the Vakaga districts remains an unique unexplained observation (Table VIII). 81.3% (13/16) of the Marburg virus antibody seropositives are also seropositive for Ebola virus reactive antibody. In contrast, only 10.2% (13/127) of the Ebola virus antibody seropositives are seropositive for Marburg virus reactive antibody. There are several plausible explanations for this observation. The most likely is that both Marburg virus and Ebola virus are active in northeastern CAR.

Table VIII.

Filovirus reactive antibody specificity of 1987 Gordil and Quandja seropositive specimens(a).

Filovirus Reactivity	Number Positive Specimens		
	Gordil	Quandja	Total
MBG	2	1	3
MBG/EBD	7	6	13(b,c)
EBD	9	11	20
EBD/EBD	37	57	94

- a. abbreviations: MBG = Marburg virus; MBG/EBD = Marburg and Ebola viurs;
EBD = Ebola virus; EBD/EBD = Ebola virus Sudan Strain
and Ebola virus Zaire strain.
- b. 81.3% (13/16) MBGpositives are also positive to Ebo.
- c. 10.2% (13/127) Ebo positives are MBG positive.

4. Distribution of virus activity:

Filovirus activity in Gordil and Quandja does not seem to be strongly associated with select areas or households suggesting that virus activity is not clustered within the villages. However, an interesting observation was made concerning the distribution of virus activity in Gordil and Quandja. A relatively low antibody prevalence seems to be associated with higher population densities. This is most apparent in Quandja where the prevalence ranges from 29.1% (67/230) in central Quandja to 40% (72/179) and 40.5% (17/42) in outlying areas (Table IX). A similar association is seen in Gordil, but the association is much smaller. In Gordil the highest antibody prevalence is in the eastern section (40.2%, 35/87) or the area adjacent to the Manou/Gordil croplands. The relatively low antibody prevalence in the centers of these villages is surprising since the center of Quandja and to a lesser extent the center of Gordil is densely populated and large quantities of grain are stored in this area. In West Africa, the ecology of Lassa virus is strongly associated with rodent populations which live on the grain stored within villages and/or households. As the human population density increases the amount of grain stored, the density of the rodent population, and the number of Lassa virus infections also increases. A similar association would be expected should village dwelling rodents be associated with the ecology of the filoviruses in central Africa. However, the low prevalence in more densely populated areas would suggest village rodents are not important in the ecology of the filoviruses. The low antibody prevalence found in rodent populations collected in Gordil and Quandja would also support the lack of importance of village dwelling rodents.

Table IX.

Distributions of seropositives living in Gordil and Quandja between 1985 and 1987.

Total Area No.	No. Pos.	% Pos.	Total Area No.	No. Pos.	% Pos.	Total Area No.	No. Pos.	% Pos.			
GORDIL (a)											
Northwest:	110	79	17.2			Southwest:	114	29	25.4		
Northeast:	75	29	38.6			Southeast:	12	6	50.0		
North:	185	48	25.9			South:	126	35	27.8		
East:	87	35	40.2(b)			West:	224	48	21.4		
QUANDJA (c)											
Northeast:	103	40	38.8	North Central:	130	42	32.3				
Southeast:	76	32	42.1	South Central: (d)	100	25	25.0	Southwest:	42	17	40.5
East:	179	72	40.0	Central:	230	67	29.1	West:	42	17	40.5

- a. Gordil is oriented east/west with the southern houses bordering the park.
- b. Eastern Gordil borders Manou/Gordil croplands.
- c. Quandja is oriented North/South with southern houses bordering the river.
- d. South Central and southwest Quandja are the most densely populated areas of Quandja.

5. Seroprevalence in select animal populations:

664 animal specimens were collected in Gordil and Quandja in 1987. 379 specimens were from rodents associated with the villages. 4.5% (17/379) of the rodents were found to be seropositive for filovirus reactive antibody (Table X). The lack of a significant prevalence in the rodent populations suggest an urban filovirus cycle does not exist. The possibility of a cropland/rodent filovirus cycle can not be ruled out. The high antibody prevalence in dogs (34.5%, 10/29) may support the possibility of a cropland cycle since dogs are used to keep monkeys and other animals out of the fields during the growing season. Dogs may be an intermediate host which is infected by contaminated animals and passes the infections on to the human population. The practice of living among the fields during the growing season may promote the cropland cycle.

Table X.

Filoviruses reactive antibody prevalence in select animal populations collected in Gordil and Ouandja CAR in 1987.

Survey Species	Filoviruses antibodies		
	Total No.	No. Pos.	% Pos.
Cattle	20	2	10.0
Chickens	131	5	3.8
Dogs	29	10	34.5 b
Donkeys	13	3	23.1
Goats	75	0	0.0
Sheep	17	0	0.0
Rodents:	379	17	4.5
Mastomys	265	12	4.5
Arvicanthis	98	9	9.2
Musaraigne	5	0	0.0
Taterillis	4	0	0.0
Praomys	3	0	0.0
Other. a	4	0	0.0

a. Myomys, Gerbil, Lemniscomys, Grapiusus.

b. Village prevalence: 2/7 (28.%) Gordil, 8/22 (36.4%) Ouandja.

D. DISCUSSION

Collectively, our serological data indicate that the filoviruses (Ebola virus, Marburg virus, or a serologically related member of the group) are active in the Central African Republic. Significant antibody prevalences are consistently observed in select populations (Tables III and IV). The numerous seroconversions from seronegative to high tittered (512 or greater) seropositives (Table VII) suggest these agents are more active than previously thought. Exposure seems to occur early in life and may result in the production of persistent antibodies (Tables III and IV).

It is still unclear which virus strains are present in the CAR. It is possible that a less pathogenic serologically cross reacting filovirus is present and responsible for the high antibody prevalence and lack of an association between the presences of filovirus reactive antibody and severe hemorrhagic disease. However, the possibility that a less pathogenic serologically cross reacting virus is present seems unlikely. The presence of both high tittered Ebola virus and Marburg virus reactive antibody seropositives suggest that these two agents are present. In addition, the observation that 81.3% (13/16) of the Marburg virus antibody seropositives and 10.2% (13/127) of the Ebola virus antibody reactive seropositives show cross reactivity with the heterologous member of the filovirus group (Table VIII) is best explained by the presence of the two prototype filoviruses.

The most compelling evidence against the presence of the prototype filovirus strains in the CAR is the lack of an association between

illness and antibody. It is unlikely that clinical filovirus infections do not occur in the CAR since clinical cases have occurred in Sudan and Zaire. In addition, routine investigations in the Vakaga district have revealed that hemorrhagic disease is not uncommon and at least two types of diseases occur in the dry season: a recurring nondescript illness associated with nasal hemorrhage; and, a nonrecurring severe sometimes fatal disease associated with nasal hemorrhage, severe headache, chest pains and cough. At least one death has been associated with uncontrollable hemorrhage in Gordil. During January 1985, a 10 year old boy, the son of a Gordil captain, developed a severe febrile illness with chest pains and uncontrollable bleeding, and died. Similar disease syndromes have been identified in Tirongoulou and Ouandja. Therefore, it is important that a concentrated effort be undertaken to identify the agent(s) associated with clinical hemorrhagic disease and/or the development of filovirus reactive antibody in the CAR.

Establishing studies in the Vakaga district to define the association between clinical infections and the acquisition of antibody will be difficult but not impossible. The results of our previous field and laboratory work has provided us with a starting point and direction: the results of the seroepidemiology studies suggest that infections are commonly occurring in the younger residents of Gordil and Ouandja; the ecological studies indicate that an urban rodent filovirus cycle may not occur and dogs may play a role in the dissemination of virus; and, the laboratory studies suggest these agents may be transmitted by the aerosol route. Village based studies associating children and dogs during the dry season could be attempted. However, establishing cropland based field studies should not be ruled out.

E. RECOMMENDATIONS

Identifying active filovirus infections in the Central African Republic has been the major goal of the collaboration between the IP and USAMRIID. The approach that was initially taken has been successful in that preliminary data suggest that active infections occur as indicated by seroconversions. An effort must be made to confirm and extend the results so that the epidemiology, ecology and pathogenicity of the filoviruses can be accurately defined.

In the short run, the two year Vakaga prospective seroepidemiological studies started in 1986 should be completed. During the final survey, an attempt must be made to correctly identify and characterize those individuals who have seroconverted so that a profile of high risk individuals can be accurately established. Though it is unlikely that an identifiable clinical illness will be associated with seroconversions, an effort must be made to question each seroconversion about previous illnesses. Consideration must also be given to resurveying the dog populations and extending the ecological studies to the croplands surrounding Bordil and Ouandja. To minimize the effort, consideration should be given to collecting ecological specimens in cropland areas owned or visited by the seroconversions.

Though it is evident that filovirus infections are common in select Vakaga populations, the Vakaga is not the most ideal location for long term studies to identify clinical and subclinical infections and isolate agents. The logistics of such studies are prohibitive. In the long run, a study area closer to Bangui and requiring less logistical support must be established. Preliminary surveys suggest that the Lobaye district may be a potential site for long term studies (Table XI); the filovirus reactive antibody prevalence as increased dramatically over the last several years and seems to be equivalent to that which was observed in Obo (1).

Table XI.

Variation in filovirus reactive antibody prevalence in select CAR ethnic groups surveyed between 1979 and 1987.

Geographic Ethnic		Survey Year: No.Pos./No.Surveyed; (% Pos.)				
Location.	Group	1979	1984	1985	1986	1987
Lobaye	Pygmies	5/93 (5.3%)	NS(a)	45/130 (34.6%)	NS	59/120 (49.2%)
	Bantu	14/404 (3.4%)	NS	NS	NS	95/305 (31.1%)
Sangha	Pygmies	NS	2/32 (6.3%)	NS	14/80 (17.5%)	NS
	Bantu	NS	27/260 (10.4%)	NS	NS	NS

a. NS = None surveyed.

LITERATURE CITED

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