

levels under the same conditions. With the addition of seven further genes recently examined (21), the fraction of genes with significantly reduced mRNA levels is 8/16 or 50% (95% confidence limits: 27 to 73%).

This effect on TFs in DM1 suggests comparisons with Huntington's disease (HD) in which huntingtin selectively binds and disrupts Sp1 (22, 23). However, this protein-protein interaction in HD is more restricted than the RNA-protein interaction in DM1, which sequesters many TFs concurrently. Correspondingly, the extent of derangement of gene transcription in HD models (estimated at ~2%) (24) is far less than seen in our DM1 sample (50%).

A common requirement for basic transcription factors in different tissues that express *DMPK* could account for the multisystemic and multisymptomatic nature of DM1 findings (e.g., myotonia, myopathy, diabetes, testicular atrophy). Notably, the clinical analogies between DM1 and DM2, in which the latter has CCUG mRNA expansions (25), may conceivably derive from a common trans-acting mechanism with trapping and depletion of similar or identical TFs.

Other examples of transcriptional dysregulation in genetic disorders are the trichothiodystrophies, a group of autosomal recessive diseases (26), and Cockayne syndrome (27). All result from phenotype-specific mutations in genes encoding TFIIH, a multicomponent complex that has been implicated in transcription and DNA excision repair. Whereas repair defects explain the skin photosensitivity seen in a subset of patients, other disease phenotypes have been attributed to transcriptional defects (26). Deletion of the variable-number tandem-repeat structure that binds transcription repressor YY1 leads to transcriptional derepression in the respective chromosomal band, to result in facioscapulo-humeral muscular dystrophy (28). This short list of genetic disorder transcription syndromes (29) can now perhaps be extended.

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vitro with all RNAs, whether mutant RNA or heterologous unrelated RNAs (12). The same discordance can be inferred for conditions used for CUGBP binding in vitro (31) that fail to reproduce the selectivity for mutant versus wild-type RNA that is evident in vivo (4, 12), (Fig. 1A).

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20. We apply the same standard of 30% change for "significantly" disturbed transcription as used in the HD study (24).
21. Seven additional genes were recently studied, of which three were significantly suppressed and four unchanged in mutant RNA-expressing cells. A total of nine genes have now been tested with TF "restorations." When Sp1 or Sp3 was overexpressed, full or partial recovery was seen in three out of four of the depressed genes, with the fourth presumably responding to depleted TFs not tested, by this model. In

contrast, among the five genes that were unchanged in mutant RNA-expressing cells, none (0/5) was stimulated by TF overexpression.

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Multiple Ebola Virus Transmission Events and Rapid Decline of Central African Wildlife

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Several human and animal Ebola outbreaks have occurred over the past 4 years in Gabon and the Republic of Congo. The human outbreaks consisted of multiple simultaneous epidemics caused by different viral strains, and each epidemic resulted from the handling of a distinct gorilla, chimpanzee, or duiker carcass. These animal populations declined markedly during human Ebola outbreaks, apparently as a result of Ebola infection. Recovered carcasses were infected by a variety of Ebola strains, suggesting that Ebola outbreaks in great apes result from multiple virus introductions from the natural host. Surveillance of animal mortality may help to predict and prevent human Ebola outbreaks.

Human Ebola virus (EBOV) infection causes hemorrhagic fever and death within a few days (1). The most lethal strains, causing up to 88% mortality, occur in Gabon, the Republic of Congo (RC), and the Democratic Republic of Congo (DRC) in central Africa, and belong to the Zaire subtype, which is one of four known EBOV subtypes. Together with Marburg virus, EBOV forms the *Filoviridae* family, a group of enveloped, nonsegmented, negative-strand RNA viruses (2). The genome is ~19,000 nucleotides long and bears

linearly arranged genes that encode seven structural proteins and one nonstructural protein (3). Human Ebola outbreaks usually occur abruptly from an unidentified source, with subsequent spread from person to person (4). The first three known outbreaks of Ebola occurred between 1976 and 1979 in Zaire (now DRC) and Sudan, with 318 (5), 284 (6) and 34 (7) cases, respectively. No further cases were recognized in Africa until late 1994. Since then, EBOV has appeared in human beings eight times, in several sub-

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Saharan African countries, including Côte d'Ivoire (8), DRC (1), Uganda (9), RC, and Gabon (10). Epidemiologic observations showed that chimpanzees were the source of one human case in Côte d'Ivoire in late 1994 (8) and of an outbreak in Gabon in 1996 (4). The recent high frequency of EBOV outbreaks in central Africa, associated with high

lethality and serious social consequences, has made Ebola a major public health priority. Given the very rapid spread of the disease and the lack of a vaccine or effective therapy, the cornerstone of management remains the prevention and rapid control of outbreaks.

In the past two years, five human Ebola virus outbreaks of the Zaire subtype have occurred in western central Africa (Gabon and RC), with a total of 313 cases and 264 deaths (11). Epidemiologic investigations show that these outbreaks resulted from multiple introductions of the virus from different infected animal sources (Fig. 1A). The index cases (mainly hunters) were all infected when handling dead animals (gorilla, chimpanzee, or duiker), and subsequent transmission occurred by direct person-to-person contact, especially within families. We use the term "epidemic chain" to designate all cases of infection arising from a given index case and thus from a given animal carcass. At least ten epidemic chains were identified between October 2001 and May 2003 (Fig. 1A).

To determine whether these outbreaks resulted from multiple introductions of a single

viral strain or from separate introductions of several different viral strains, we sequenced the entire open reading frame of the EBOV glycoprotein (GP) gene in all available infected human samples. Nucleotide sequence variations were found among the viruses responsible for the different epidemic chains (Table 1) but not between samples from patients involved in a given epidemic chain. On the basis of genetic analysis, we identified eight viral strains, indicating that the five human outbreaks involved distinct animal sources and viral strains.

We and local villagers noted a high number of animal carcasses in forested areas just before and during the 2001 human Ebola outbreaks in Gabon (Fig. 1B; table S1). Discovery of dead animals in the forest is normally rare, owing to rapid decomposition and the low number of nonpredatory deaths. Over a period of 8 months, we found or were informed by local villagers of at least 64 animal carcasses (gorillas, chimpanzees, and duikers) in the outbreak area of the Zadio region in Gabon (3000 km²), with a peak in November and De-

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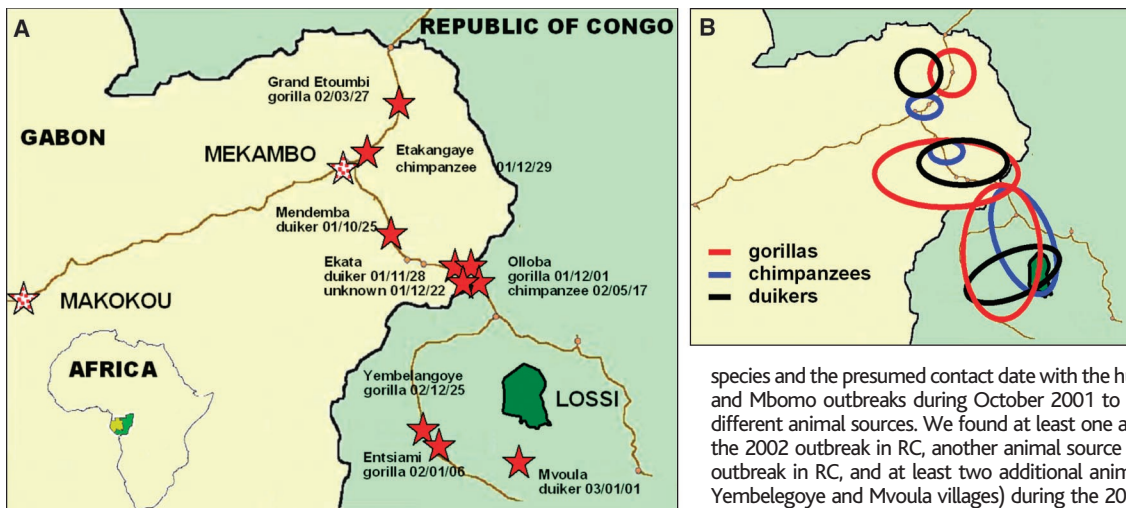


Fig. 1. (A) Location of sources of Ebola outbreaks in Gabon and the Republic of Congo between October 2001 and May 2003. Stars indicate the location of the first human case, each infected by an animal source. Red stars indicate identified or suspected animal sources. Red and white stars indicate unknown sources. The figure also indicates the incriminated animal species and the presumed contact date with the human index case. The Mekambo and Mbomo outbreaks during October 2001 to May 2002 involved at least six different animal sources. We found at least one animal source in Entsiami during the 2002 outbreak in RC, another animal source in Olloba during the May 2002 outbreak in RC, and at least two additional animal sources in the Kelle area (in Yembelengoye and Mvoula villages) during the 2003 outbreak in RC. (B) Location of animal carcasses in Gabon during the 2001 to 2002 outbreak and in RC during

the 2002 to 2003 outbreak. Animal carcasses were precisely located by us or local villagers by using global positioning satellite technology.

Table 1. Nucleotide differences between sequences of the EBOV GP gene identified during Ebola outbreaks in Gabon and the Republic of Congo between October 2001 and May 2003. The table gives the names of identified epidemic chains and reports the number of viral sequences obtained in each chain. See (12).

Epidemic chain	Nucleotide position															
	247	543	795	1147	1201	1239	1240	1271	1476	1500	1540	1578	1584	1610	1684	2135
Mendemba A (Oct 01) 7 available sequences	G	C	A	A	A	C	T	T	G	T	T	T	G	A	A	T
Mendemba B (Oct 01) 10 available sequences	G	C	A	A	A	C	T	T	G	T	T	T	G	G	A	T
Ekata (Nov 01)																
Olloba (Dec 01) 1 available sequence	G	C	A	A	A	C	T	T	G	T	T	T	A	A	A	C
Ekata (Dec 01)																
Etakangaye (Dec 01) 1 available sequence	G	T	G	G	A	C	T	T	G	T	T	T	G	G	A	T
Makokou (Dec 01) 2 available sequences	G	C	A	A	A	C	C	T	G	T	T	T	G	G	A	T
Entsiami (Jan 02) 1 available sequence	G	C	A	A	G	C	T	T	A	T	T	T	A	A	A	T
Olloba (May 02)																
Yembelengoye (Dec 02) 8 available sequences								C	G	C	C	C	A	A	A	
Mvoula (Jan 03) 1 available sequence	A	C	A	G	A	T	T	C	G	T	T	T	A	A	G	

ember 2001; most were gorillas (36; table S1). Considering that we have observed that a gorilla carcass decomposes completely within one month in the tropical forest and that the carcasses were found in the vicinity of villages (within 2 hours walking distance), hundreds or even thousands of animals may have died in the thinly populated 3000 km² of this forest region.

Gorilla (*Gorilla gorilla*) population censuses before and after the Kelle outbreak in 2003 in RC showed marked declines after the outbreak (Table 2). Indices of the presence of gorilla and duiker (*Cephalophus* spp.)—sighting, hearing, and smelling the animals by trained trackers, and seeing dung, trails, or nests—fell by 50% between 2002 and 2003 in the 320-km² Lossi sanctuary (Table 2). Similarly, chimpanzee (*Pan troglodytes*) indices declined by 88%. Although a decline in indices does not indicate a similar decline in population densities, it is a robust indicator of a corresponding population decline (12). Corroborating this observation, eight groups of gorillas, 143 individuals in all, that had been monitored almost daily for 10 years in a 35-km² region of the Lossi sanctuary, disappeared between October 2002 and January 2003. These animals have not been seen since, neither within the sanctuary nor elsewhere. Together, these data indicate temporal and spatial overlaps between human Ebola outbreaks and increased mortality among large wild mammals (Fig. 1, A and B). Our

data also confirm that Ebola outbreaks occur abruptly, exterminating exposed animal populations very rapidly and very locally (groups living in other parts of the sanctuary were barely affected). The duiker populations in the areas covered by our study may recover rapidly after an outbreak, owing to this species' rapid reproductive cycle. In contrast, the slow reproductive cycle of the great apes, together with hunting and poaching, may lead to their extinction in western central Africa. This last observation is supported by recent data indicating that ape populations in Gabon declined by more than half between 1983 and 2000 (13). These findings are also consistent with those of a study conducted in the Taï Forest of Côte d'Ivoire, in which 11 of 43 members of a wild chimpanzee group disappeared in November 1994. One chimpanzee was positive by EBOV-specific immunohistochemical staining (14).

Using a combination of antigen detection, serology, DNA amplification, sequencing, immunohistochemical staining, and virus isolation, we confirmed that the gorillas, chimpanzees, and duiker carcasses were indeed infected by EBOV (Table 3; Fig. 2). In total, ten gorillas, three chimpanzees, and one duiker tested positive. Of interest, all muscle tissues were negative for EBOV-specific immunoglobulin G (IgG), indicating that the animals had died without developing specific IgG responses, similar to the situation in human infections in which a fatal outcome is

characterized by impaired humoral responses and a failure to generate specific IgG (15).

Deaths in wildlife tended to precede and to be linked to human infections. For example, we detected EBOV in gorilla and chimpanzee carcasses in early December 2002 at the Lossi sanctuary, and the first human cases in the associated outbreak (Yembelengoye and Mvoula, 2003) appeared at the end of that month. In addition, serum from the index case (a survivor) in the last human epidemic in Mekambo (Grand Etoumbi, March 2002) (Fig. 1) was positive for EBOV-specific IgG, and EBOV virus sequences from the L gene were detected in bone-marrow samples of the gorilla identified as the source of this outbreak, conclusively linking the two cases.

Nucleotide sequence variations of the GP gene, distinct from those observed previously in humans, were also found in infected tissues from dead animals. We identified 11 different EBOV strains from human and animal samples between October 2001 and May 2003 in northern Gabon and in the region bordering RC. Molecular analyses based on estimated nucleotide substitution rates indicate that the four known EBOV subtypes diverged thousands of years ago and do not spread rapidly from one region to another of the central African forest block (16). A previous study focusing on the most divergent region of the GP gene shows that the EBOV isolates obtained from fatalities and survivors during the Kikwit outbreak in 1995 are genetically stable (17). Similarly, there were no nucleotide sequence variations in the GP and nucleoprotein genes among isolates from fatalities, survivors, and asymptotically infected individuals during the 7-month Gabon outbreak in 1996–1997 (18). The same study shows that the Boué sequence diverges from that of other Zaire subtype strains by only 1 to 2% (36 substitutions of a 2174-nucleotide fragment), despite the 20-year interval and 3000-km distance between the Boué 1996 and Zaire 1976/1995 outbreaks. The very high genetic stability of EBOV, and our findings of many different EBOV sequences that

Table 2. Gorilla, chimpanzee, and duiker population indices, used to estimate population densities, were compared before (2000) and after (2003) the Ebola outbreak in the 320-km² Lossi sanctuary area in the Republic of Congo. See (12).

Animals	Indices/km in 2000	Indices/km in 2003	Reduction rate (%)
Gorillas	1.69	0.74	56
Chimpanzees	0.28	0.03	89
Duikers	4.72	2.22	53

Table 3. Analysis of animal carcasses. Reverse transcription polymerase chain reaction (PCR), antigen capture (Ag), immunohistochemical (IHC) staining, and Ebola-specific IgG assays were performed as previously described (20–22).

Animals	Location	Date	Tissue	PCR	Ag	IHC
Gorilla	Gabon	Nov 2001	Muscle	+	+	+
	Gabon	Feb 2002	Bone marrow	+		
	Gabon	Feb 2002	Bone	+		
	Gabon	Feb 2002	Bone	+		
	Lossi	Dec 2002	Muscle	+	+	+
	Lossi	Dec 2002	Muscle	+	+	+
	Lossi	Dec 2002	Bone	+		
	Lossi	Dec 2002	Bone	+		
	Lossi	Feb 2003	Muscle	–	+	
	Mbanza	June 2003	Muscle	+	+	
Chimpanzee	Lossi	Dec 2002	Muscle	–	+	+
	Lossi	Dec 2002	Muscle	–	+	–
	Lossi	Feb 2003	Muscle	+	+	
Duiker	Lossi	Dec 2002	Bone	+		
	Lossi	Dec 2002	Bone	–		
	Lossi	June 2003	Skin			

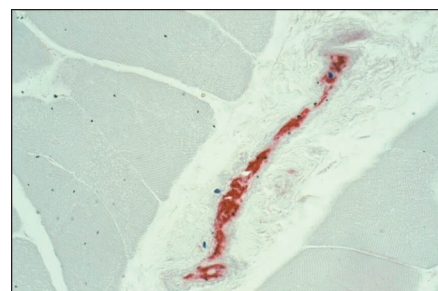


Fig. 2. Immunohistochemical staining of Ebola viral antigen in muscle of a dead gorilla. Viral antigens are seen in endothelial cells lining blood vessels. Naphthol fast red substrate with hematoxylin counterstain. Original magnification ×63.

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do not vary during transmission along a given human epidemic chain indicate that multiple independent introductions of the virus from its natural host to great apes had occurred.

Humans and duikers scavenging for meat probably become infected by contact with dead apes. However, we found that animal carcasses left in the forest are not infectious after 3 to 4 days (19). Therefore, virus transmission between different groups of apes is unlikely, because infectivity is short-lived and physical contact between individuals from different groups is rare. Different strains of EBOV may be widespread throughout the forests of central Africa, with simultaneous infection of great apes occurring from still unknown natural hosts under particular but unknown environmental conditions. Ebola outbreaks in great apes have always been reported at the beginning of the dry seasons (December 1995 in Mayibout, July 1996 in Booué, July 2001 in Mekambo, December 2001 in Kelle, and December 2002 in the second Kelle outbreak). Thus, Ebola outbreaks probably do not occur as a single outbreak spreading throughout the Congo basin as others have proposed (13), but are due to multiple episodic infection of great apes from the reservoir.

The simultaneous occurrence of multiple epidemic chains in animals complicates the work of outbreak-response teams, because new cases may appear in unmonitored popu-

lations. Almost all human Ebola outbreaks in Gabon and RC have been linked to the handling of dead animals by villagers or hunters, and increased animal mortality always preceded the first human cases. A monitoring network for large-animal mortality rates is needed for rapid implementation of EBOV prevention measures when increased deaths are observed among wild animals living near human communities.

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Table S1

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