

Pandemic Human Viruses Cause Decline of Endangered Great Apes

Sophie Köndgen,^{1,2,9} Hjalmar Kühl,^{2,9} Paul K. N'Goran,^{2,3,9} Peter D. Walsh,² Svenja Schenk,^{2,4} Nancy Ernst,^{1,2} Roman Biek,⁵ Pierre Formenty,⁶ Kerstin Mätz-Rensing,⁷ Brunhilde Schweiger,¹ Sandra Junglen,^{1,2} Heinz Ellerbrok,¹ Andreas Nitsche,¹ Thomas Briese,⁸ W. Ian Lipkin,⁸ Georg Pauli,¹ Christophe Boesch,² and Fabian H. Leendertz^{1,2,*}

¹Robert Koch-Institut

Nordufer 20
D-13353 Berlin
Germany

²Department of Primatology
Max Planck Institute for Evolutionary Anthropology
Deutscher Platz 6
D-04103 Leipzig
Germany

³Centre Suisse des Recherches Scientifiques en Côte d'Ivoire
Abidjan 01 BP 2494
Côte d'Ivoire

⁴Berlin Veterinary Faculty
Institute of Immunology and Molecular Biology
Philippstr. 13
10115 Berlin
Germany

⁵Division of Environmental and Evolutionary Biology
University of Glasgow
Graham Kerr Building, Room 401
Glasgow G12 8QQ
United Kingdom

⁶Ebola Taï Forest Project
World Health Organization (WHO)
WHO Office in Abidjan
Abidjan 01
Côte d'Ivoire

⁷German Primate Center
Kellnerweg 4
D-37077 Göttingen
Germany

⁸Centre for Infection and Immunity
Mailman School of Public Health
Columbia University
New York, New York 10032

Summary

Commercial hunting and habitat loss are major drivers of the rapid decline of great apes [1]. Ecotourism and research have been widely promoted as a means of providing alternative value for apes and their habitats [2]. However, close contact between humans and habituated apes during ape tourism and research has raised concerns that disease transmission risks might outweigh benefits [3–7]. To date only bacterial and parasitic infections of typically low

virulence have been shown to move from humans to wild apes [8, 9]. Here, we present the first direct evidence of virus transmission from humans to wild apes. Tissue samples from habituated chimpanzees that died during three respiratory-disease outbreaks at our research site, Côte d'Ivoire, contained two common human paramyxoviruses. Viral strains sampled from chimpanzees were closely related to strains circulating in contemporaneous, worldwide human epidemics. Twenty-four years of mortality data from observed chimpanzees reveal that such respiratory outbreaks could have a long history. In contrast, survey data show that research presence has had a strong positive effect in suppressing poaching around the research site. These observations illustrate the challenge of maximizing the benefit of research and tourism to great apes while minimizing the negative side effects.

Results and Discussion

When five distinct respiratory outbreaks hit three communities of habituated chimpanzees at the Taï chimpanzee research project in 1999 (north group), 2004 (twice in south group), 2005 (south group), and 2006 (south group and east group), we made systematic clinical observations. Morbidity was high in the outbreaks (Table 1), with an average of 92.2% of individuals showing clinical symptoms, including elevated breathing rate, conspicuous breathing sounds, breathing with mouth open, sneezing, and either dry or humid cough. Heavily affected animals showed a decrease in daily-food intake and signs of weakness such as increased resting time and decreased ability to keep up with other animals or to sustain physical activity. Recovery without medical intervention was not observed in such advanced cases. Time from first visible symptoms to death ranged from 1 day for infants to 11 days for adults.

Three of the outbreaks resulted in mortalities, killing at least 6 of 32 (19%) individuals in the north group and 8 of 44 (18%) individuals in 2004 and 1 of 34 (3%) in 2006 in the south group. Mortality was age specific, with mainly juveniles and infants dying during the 2004 outbreak in south group and a higher proportion of adults dying during the 1999 outbreak in the north group (Table 1). We were able to perform necropsy and pathological and histological analyses on seven of these victims found shortly after death. The main pathologic and histopathologic changes were observed in lung tissue, with severe purulent multifocal bronchopneumonia, lung edema in all lobes, and involvement of the upper respiratory tract.

Necropsy samples were screened for respiratory pathogens by using different PCR methods. As for most human respiratory cases, a mix of bacterial and viral respiratory pathogens was found in the lungs. The most common bacterium was *Streptococcus pneumoniae*, which was found in all respiratory outbreaks. In addition, *Pasteurella multocida* played a role in the 2004 outbreak [10]. All available samples tested positive for one of two paramyxoviruses: human respiratory syncytial virus (HRSV) was diagnosed in two individuals that died in the 1999 north group outbreak and in one adult female (east group) and one infant (south group) who died in the 2006 outbreak, which

*Correspondence: leendertzf@rki.de

⁹These authors contributed equally to this work.

Table 1. Characteristics of Three Respiratory Epidemics Observed in the Tai Chimpanzees

Group	May 1999	March 2004	February 2006	
	North	South	South	East
Pathogens identified	HRSV, <i>S. pneumoniae</i> strain 2308	HMPV, <i>S. pneumoniae</i> strain 2309, <i>P. multocida</i>	HRSV, <i>S. pneumoniae</i> strain 2309	HRSV, <i>S. pneumoniae</i> strain 2308
Morbidity ^a	100%	100%	92%	ND ^b
Mortality ^d	6 ^c /32	8/44	1/34	2
Adult/adolescent ^e	5/15	0/22	0/19	2
juvenile ^e	1/7	3/10	0/5	0
infant ^e	0/10	5/12	1/10	0

^a Morbidity rates refer to the total number of weaned individuals observed with respiratory symptoms during an epidemic.

^b ND, not determined because this group is not fully habituated and the number of individuals unknown.

^c After this outbreak three infants died of starvation after their mothers died of disease.

^d Mortality refers to total group size and the number of cases of death due to respiratory disease excluding indirect cases (*).

^e Age classes for Tai chimpanzees: infant, 0–5 years; juvenile, 5–10 years; adolescent, 10–15 years; adult, >15 years.

occurred simultaneously in both groups. The second virus identified was human metapneumovirus (HMPV), detected in three animals that died in the 2004 south group outbreak (Table 1).

HRSV and HMPV are common causes of respiratory disease in humans and are the leading causes of lower respiratory disease in children and, in developing countries, a major source of infant mortality [11, 12]. In adults, HRSV and HMPV usually cause mild upper-respiratory-tract infection but can lead to pneumonia and bronchiolitis. Both viruses are shed in respiratory secretions but also have been detected in feces or sweat [13]. Transmission of HRSV occurs through droplets of respiratory secretions or through direct contact with contaminated surfaces: HRSV in fresh secretions survives 20 min on hands and up to 7 hr on plain surfaces [14]. HRSV and HMPV also are known to cause mild respiratory symptoms in captive chimpanzees [15, 16]. Although paramyxoviruses can cause severe respiratory symptoms in their own right, they also predispose captive chimpanzees to secondary bacterial infection [17]. Thus, though the Tai chimpanzee outbreaks may have been initially triggered by HRSV and HMPV, secondary infection with *S. pneumoniae* or *P. multocida* may have been the proximate cause of death [10].

To establish the origin of the chimpanzee outbreaks, we conducted phylogenetic analyses on those pathogens that potentially transmit from humans to chimpanzees (HRSV, HMPV, and *S. pneumoniae*). Two new strains of *S. pneumoniae* were identified, one detected in the south group (2004 and 2006 outbreaks) and the second in the north (1999 outbreak) and east (2006 outbreak) groups. These two strains were evolutionarily closer to known human strain of *S. pneumoniae* than to each other [10]. However, they did not provide conclusive evidence of recent introduction from humans. In contrast, both HMPV and two strains of HRSV clustered firmly within known human clades (Figures 1A and 1B). HRSV strains are known to circulate globally and tend to form temporal, rather than regional, clusters [18]. This is also evident from the HRSV tree (Figure 1A), where closely related strains were often distributed worldwide. Intriguingly, the 1999 chimpanzee HRSV contained a specific insert of 60 base pairs that were first found in human respiratory outbreaks in Buenos Aires in 1999 [19]. The HRSV strain found in the chimpanzees in 2006 grouped most closely with a strain reported recently from Asia. For HMPV, fewer sequences were available, but the chimpanzee's strains were closely related to strains circulating in North America and Asia from 1997 to 2000 (Figure 1B).

Although HRSV and HMPV sequences from humans in West or Central Africa were not available for outbreak years, our analysis indicates that in all three cases viruses amplified

from chimpanzees and humans shared a common ancestor within 3–6 years (HRSV) and 8 years (HMPV). As humans are the only known reservoir host for both viruses, these results strongly suggest that humans introduced the two viruses directly and repeatedly into wild chimpanzee populations in the recent past. The study groups do not range outside the park, and there are currently no villages or plantations inside the park. Therefore, either research personnel or poachers are the most plausible sources of infection. However, potential transmission foci, such as poaching camps, have been detected in the study-group territories on only a few occasions over the last 24 years, and poachers only occasionally enter the study-group core areas where most chimpanzee activity is concentrated. In contrast, an average of about one research personnel spends 8 hr a day within 15 m of chimpanzee parties typically containing 5–10 individuals. Transmission through bridge hosts such as monkeys cannot be excluded. However, contact with respiratory pathogens deposited by humans on the forest floor is much less likely for monkeys, which are largely arboreal, than it is for chimpanzees, which are regularly terrestrial.

These were not the only multiple mortality events in Tai chimpanzees. In the last 24 years, the north and south groups experienced 13 events in which a cumulative total of four or more deaths were recorded in 1–3 consecutive months (Figures 2A and 2B). In four of these events, we could identify the cause of death, including Ebola [20], anthrax [21], and two poaching incidents. Eight of the remaining nine multiple death events showed a subadult-biased mortality pattern typical of human respiratory outbreaks [22] (Figure 2C). In contrast the Ebola, anthrax, and poaching events all showed adult-biased mortality. Furthermore, both the frequency of multiple mortality events (Figures 2A and 2B) and the per capita rate of subadult mortality (multiple and nonmultiple events pooled) decreased strongly with decreasing community size (H.K., unpublished data): Such density dependence is typical of respiratory disease, but not of accidental death or vector-borne disease [23]. Subadult mortality rates also increased sharply a few years into the habituation of both the north and south groups when researcher effort increased and approach distances decreased. This researcher-exposure effect was a much stronger predictor of subadult mortality rate than was local human-population size or deforestation rate (H.K., unpublished data), again implicating research personnel rather than local villagers as the source of infection.

In addition, multiple mortality events did not occur at an elevated rate in the season of low food availability, as might be

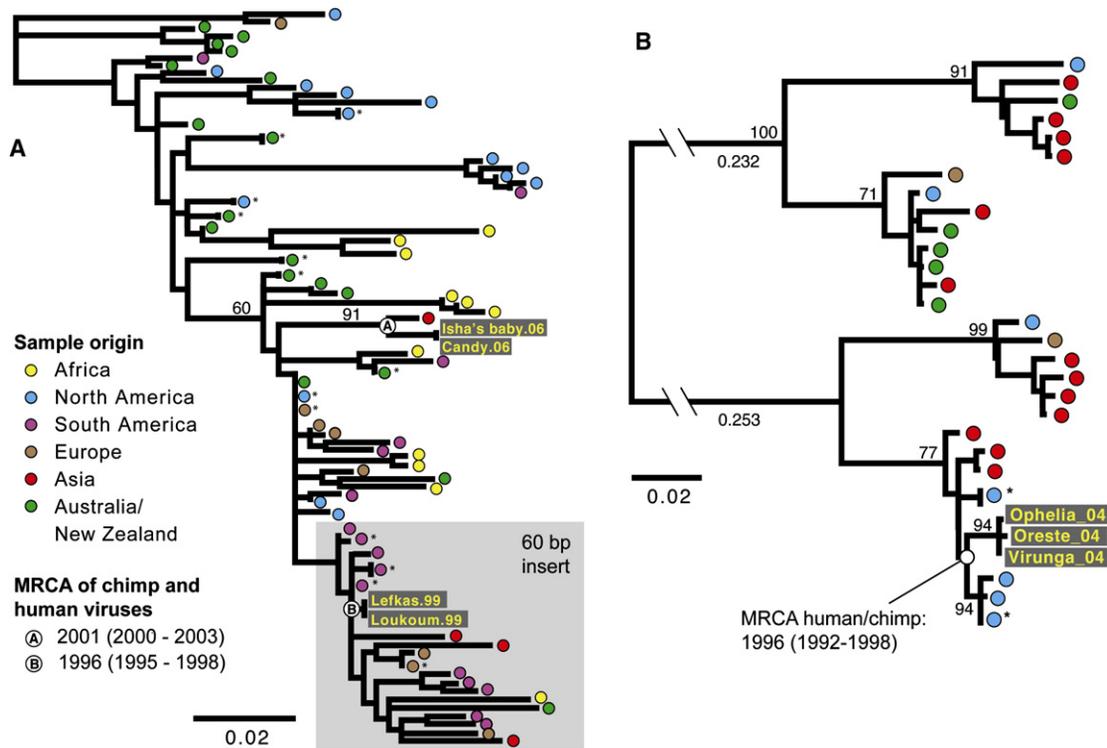


Figure 1. Phylogenetic Position of HRSV and HMPV Amplified from Chimpanzees Relative to Human Viruses Sampled Worldwide

Shown are the phylogenetic trees of HRSV (A) and HMPV (B). Trees were generated under the maximum likelihood criterion [34]. Percent bootstrap support for the relevant internal nodes is shown above branches. Names of infected chimpanzees are boxed. Asterisks next to taxa symbols indicate multiple identical sequences from the same locality. Dates associated with the most recent common ancestors (MRCA) of chimpanzee and human viruses were estimated with a Bayesian molecular clock technique [35]. Dates next to ancestral nodes are the estimated year and the 95% posterior density interval. The grey box in (A) signifies sequences that share a 60 base pair (bp) insert [19]. Branches in the most basal position in (B) are not drawn to scale; actual branch lengths are shown below branches. Rooting of the tree was accomplished for HRSV by using the two oldest sequences (1960 and 1962) as outgroups and for HMPV by the midpoint method.

expected if food stress was a driver; rather, they occurred more often in the season of high food availability. Furthermore, adult social-connectivity and high infant-play rates were better predictors of multiple mortality events than was rainfall (H.K., unpublished data), a factor often correlated with human respiratory-disease outbreaks in the tropics [12]. The implication of social connectivity is also consistent with communicable disease as the cause of death. These observations suggest that the majority of the nine remaining multiple mortality events we observed in the last 24 years were respiratory-disease outbreaks. Respiratory mortality also can lead to isolated mortality events, as seen during the confirmed outbreaks of 2005 and 2006 in the south group. This might have been the case for some of the 45% of deaths over the last 24 years that did not occur in multiple events.

It has long been recognized that respiratory disease is the most important cause of morbidity and mortality among wild great apes habituated to human presence for research or tourism [4, 24–27]. However, the etiological agents of such disease have not been documented. Possibly as a consequence of respiratory disease, about half of the long-term chimpanzee research populations have shown major declines [4, 28]. Our results suggest that the close approach of humans to apes, which is central to both research and tourism programs, represents a serious threat to wild apes. This represents a dilemma because both activities have clear benefits for ape conservation. For instance, ape tourism constitutes an important source of income in some countries [2]. Likewise, the presence

of both research and tourism projects in Tai National Park has suppressed poaching, resulting in a strong positive correlation between proximity to chimpanzee habituation sites and the density of chimpanzees (Figures 3A–3D). In this case, the ape conservation benefits of research and tourism seem to have outweighed the costs. In order to reduce the negative effects of research and tourism, strict hygiene protocols, including vaccination requirements for tourists, tourism personnel, park staff, and research personnel against all potentially dangerous diseases for which vaccines are available (e.g., measles, mumps, and rubella), should be implemented [5, 6, 29, 30]. Only nonsymptomatic visitors and staff should have access to habituated apes. Feces, vomit, and other human debris or wastes should be removed from areas where chimpanzees may come in contact with it or buried at a depth where other animals will not uncover it [29]. Because carriers of human respiratory pathogens are often nonsymptomatic, wearing of masks (e.g., N95 masks as recommended for avian flu) [31] should be mandatory. Human populations living around the parks and reserves should be vaccinated, thereby decreasing the chances of human-pathogen introduction into chimpanzee populations. As in the Tai project, demographic, clinical, and diagnostic monitoring systems should be implemented to objectively document the negative effects of research or tourism. Furthermore, we urge an intensification of research on ways to prevent disease transmission, as well as the development of new methods for vaccine and treatment delivery, to wild apes (e.g., oral baiting).

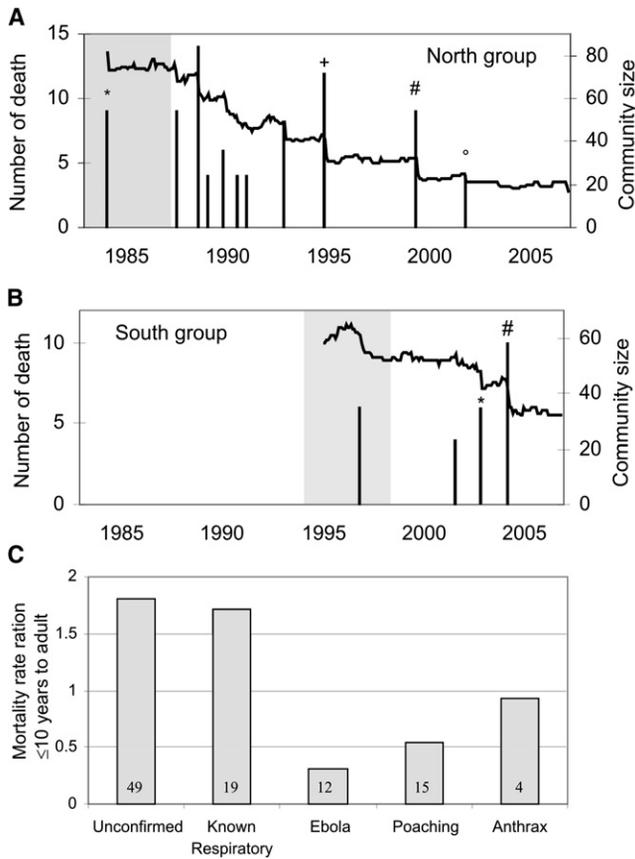


Figure 2. Mortality Time Series

Multiple mortality events (consecutive months with a cumulative total of at least four deaths) in the north group (A) and south group (B). Confirmed causes of death are marked as follows: asterisk (*), poaching; plus symbol (+), Ebola virus infection; number symbol (#), respiratory infection; degree symbol (°), Anthrax infection. Gray shaded areas indicate the first 4 years after habituation in which chimpanzees allow increasingly closer approach by researchers. (C) shows the ratio of subadult (≤ 10 years) to adult mortality rate during multiple mortality events. Mortality rates are deaths per individual alive at the start of each event. Numbers at the base of each bar indicate the number of deaths. Data are pooled for north and south groups.

Experimental Procedures

Pathology

Necropsies on chimpanzees were conducted under high safety standards and precautions such as protection suits, gloves, and face masks were used to avoid contamination of samples with human pathogens. Tissue samples were preserved in liquid nitrogen, RNAlater (QIAGEN) and 10% buffered Formalin [29]. Pathological and histological examinations were performed on all organs.

Molecular Analyses

DNA and RNA were extracted from frozen lung tissue by using DNAeasy and RNAeasy tissue kits (QIAGEN). cDNA was synthesized with the Superscript Kit (Invitrogen) and random hexamer primers (TIB Molbiol). Various PCR-based approaches were applied in order to identify relevant pathogens (details in online methods). PCR for HRSV [32] and HMPV [33] were positive. PCR products were sequenced and the obtained sequences were compared to human sequences from the GenBank database. Phylogenetic trees were constructed by using maximum likelihood in the program TreeFinder [34]. All sequences for which the year of sampling was known were used to estimate divergence times by using the program Beast [35].

Demography

A total of 266 different chimpanzees were identified in north and south groups, including 132 individuals first observed as newborns and 11

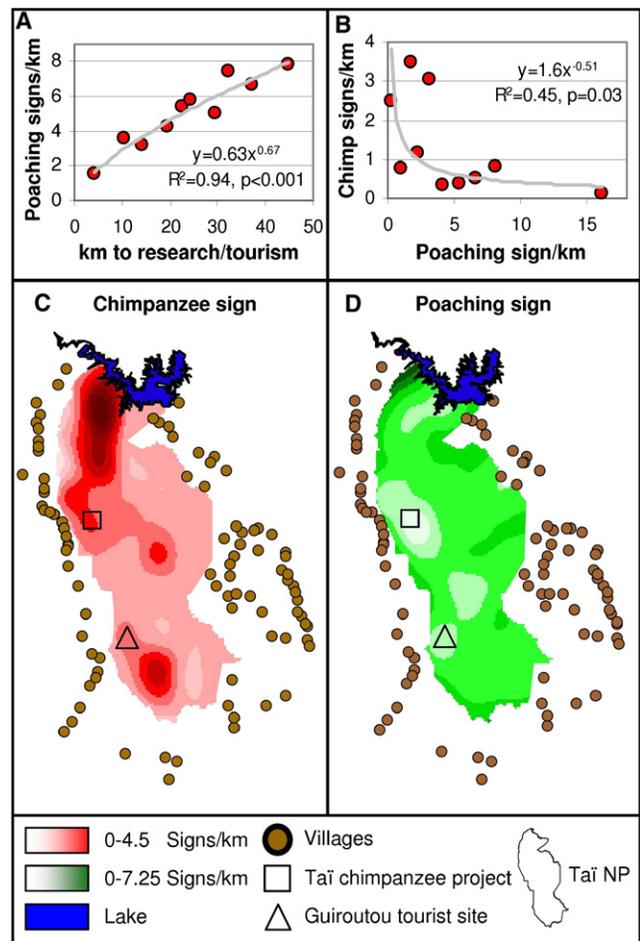


Figure 3. Protective Effect of Research and Tourism

Chimpanzee and poaching distributions in Taï National Park, Côte d'Ivoire, were sampled by using 368 km of line transects.

(A) Poaching intensity (poaching signs/transect, km) was a major predictor of chimpanzee density (signs of chimpanzee presence/transect, km).

(B) Poaching-sign encounter rates increased strongly with increasing distance from two chimpanzee habituation sites.

(C) Encounter rates for signs of chimpanzee presence reached a peak in the remote core of the park. Surfaces are for natural log-transformed encounter rates interpolated by using spline function in ArcView 3.2 (neighborhood size = 12, weight = 0.1). Exceptions to the accessibility gradient were seen at sites of the Taï chimpanzee research project and the Guiroutou chimpanzee tourism project, both of which were situated in accessible areas near villages but showed low poaching intensity and relatively high chimpanzee density.

(D) Poaching showed the classic accessibility gradient, decreasing in intensity with increasing distance from villages on the periphery of the park. For details on survey methods and results of generalized linear modeling analyses see the Supplemental Data available online.

adolescent female immigrants. Deaths were assigned to the month in which fresh carcasses were found or, in most cases, the last month in which an individual was seen alive. High chimpanzee gregariousness meant that most individuals rarely went more than one month without being sighted by observers. Deaths during observer absences (e.g., during civil war) were assigned to the midpoint of the month of observer absence.

Accession Numbers

Sequences data on the HRSV and HMPV strains are available in Genbank under the accession number EU240450-240456.

Supplemental Data

Supplemental Experimental Procedures, one figure, and four tables are available at <http://www.current-biology.com/cgi/content/full/18/4/260/DC1/>.

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