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COMMENTARY

Pathogen Flow: What We Need to Know

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We are in the midst of a global health crisis involving the spread of drug-resistant strains of a wide range of microorganisms [Levy & Marshall, 2004]. The evolution of resistance is driven by inappropriate prescription of antimicrobial drugs, the widespread use of antibiotics in agriculture, and failure by patients to complete courses of prescribed antibiotics. One recent study, for example, estimated that 94,360 cases of invasive methicillin-resistant *Staphylococcus aureus* occurred in the United States in 2005, resulting in 18,650 deaths [Klevens et al., 2007]. Additional research has uncovered a resistance "hotspot" for the protozoa that cause malaria along the border of Thailand and Cambodia, with artemisinin-based treatments the latest set of drugs to fail in this region [Dondorp et al., 2009; Enserink, 2008]. Similarly, viruses—such as the influenza virus—evolve resistance to antiviral drugs [de Jong et al., 2005]. Even vaccines can favor pathogen evolution, including successful evasion of the immune response [Read & Mackinnon, 2007].

Simultaneous with anthropogenic impacts on the evolution of these microorganisms, humans continue to make inroads to wildlife habitats and have greater contact with wildlife through the bushmeat trade, clearing of forest, and expanding human populations along forest edges [Eves et al., 2008]. In response to these threats to biodiversity, a large number of ape sanctuaries have been created to care for injured and orphaned animals [Andre et al., 2008; Beck, 2010; Faust et al., 2011]. The close contact between animals and humans in sanctuaries further increases interspecies contact, especially when the animals interact closely with humans in an effort to provide an appropriate developmental context [Cox & Institute, 2005; Farmer & Courage, 2008; Wobber & Hare, 2011].

The article by Schaumburg et al. [2012] in this issue links these two anthropogenic effects by finding that sanctuary-housed chimpanzees show evidence of colonization by drug-resistant strains of *S. aureus* found in human populations, including among veterinarians working in the sanctuaries. The results have implications for managing primates, and the authors place their findings in the context of reintroduction efforts. Specifically, the study shows that human pathogens can be introduced to apes destined for release, and thus potentially into wildlife populations. Viewing these organisms as markers for other infectious agents, their presence raises the prospect of substantial pathogen flow from humans to the sanctuary apes, and possibly transmission from ape-to-ape, including wild apes.

These results are provocative and worthy of further consideration and investigation. In this commentary, we call attention to several questions in the context of these findings, in some cases amplifying points already raised by Schaumburg et al. [2012]. By raising these questions explicitly, we aim to build a clearer picture through synthesis of existing knowledge and identification of new research directions. As a way to frame some of our points, we remind readers of the formula for the basic reproductive number, R_0, for directly transmitted microorganisms, such as the bacteria in the Schaumburg et al. [2012] article:

$$R_o = \frac{\beta S}{\alpha + b + \gamma}$$

Values of R_0 should be greater than 1 for the maintenance of an infectious organism in a susceptible population, and R_0 is increased by higher population density (S), higher transmission rate (β), lower

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disease-related mortality rate (α), lower background mortality rate (b), and lower rate of clearing infections (γ). In other words, increases in variables on the top of the equation (numerator) increase parasite success, while increases in variables in the bottom of the equation (denominator) decrease parasite success. Focusing on the release implications of the article, parasite success refers to ape-to-ape transmission in wild populations.

Do the antibiotic-resistant strains of bacteria actually cause higher morbidity and mortality in primates? Evidence of the bacteria was made through swabs of the nose and mouth, but it remains unknown if these bacteria cause actual infections that impact animal health. Typically, these organisms cause problems in humans only after opportunistic infections, such as skin trauma that provides an entry point for bacteria. Thus, we need to know the extent to which these bacteria—and others that are commonly found on the skin of humans and other animals—represent a significant selective force on individuals through disease-related mortality, α. A lower α may be desirable in terms of fewer animals lost to disease, but would also favor the spread of the organisms into wild populations through greater post-introduction survival of infected individuals.

How effectively do these (and similar) infectious organisms spread from ape-to-ape? One factor that would affect transmission is the abundance of the organism on areas of the body in which contact among individuals might occur. While we have evidence for the occurrence of these bacteria, it would be desirable to have more information on their abundance. Perhaps the antibiotic-resistant organisms compete less successfully with other microorganisms on a chimpanzee's skin, which would result in low abundance and low β. We might further be interested in whether the degree of contact between humans and apes increases the risk of transmission, and whether transmission chains can be detected, either with genetic data [De Gruijter et al. 2004, 2005] or with temporal information on infection dynamics [Franz & Nunn, 2009]. If individual apes are effectively "dead-end hosts" (i.e. $\beta = 0$), then there is no risk of transmission in wild ape populations. Conversely, if individual chimpanzees are effective at transmitting the organisms ($\beta > 0$), the risks may be significant, especially given that some individuals may serve as uninfected carriers.

Which individuals are most likely to carry human pathogens into wild populations? Sanctuary animals—especially young animals—have extensive close contact with humans, with the youngest animals often in skin-to-skin contact with their human caretakers. Thus, it is unsurprising that bacteria on the surface of human skin are transferred from humans to apes, and from the skin into oral and nasal passages. In fact, we might expect that many components of the human skin microbiota are also found on sanctuary apes—both beneficial and harmful organisms—and that the composition of their microbiota will change as conditions change, including upon release into natural habitats. It would therefore be interesting to know whether the degree of contact with humans predicts the type and abundance of microorganisms on the chimpanzees. We predict, for example, that a higher abundance of antibiotic-resistant *S. aureus* will be found on the youngest animals, and on others that are more commonly in contact with humans. It is important to develop these predictions for variation in human-acquired *S. aureus* further, and to test them in different ape sanctuaries.

What other infectious organisms might we expect to spread into wild populations through contact with humans in sanctuaries? In considering this question, it is useful to think in terms of transmission modes [Beck, 2007; Nunn & Altizer, 2006]. In addition to close physical contact, the proximity of apes and humans in sanctuaries might lead to the transfer of respiratory pathogens. Many of these organisms have a "hit-and-run" strategy, resulting in rapid clearance by the host immune system (i.e. high γ) and thus reduced R_0. This also allows for relatively easy disease control by shortening the quarantine time prior to release. Furthermore, such pathogens often result in lasting host immunity, reducing the concern of reinfection. Organisms with a longer infectious period (i.e. lower rates of clearance), such as tuberculosis, are expected to have a higher R_0 and are known to spread from humans to nonhuman primates, and thus pose a greater risk. Finally, gastrointestinal parasites and pathogens may be acquired by sanctuary apes and potentially carried to wildlife through release. In this case, however, we expect issues in sanctuaries mainly with directly transmitted organisms (i.e. those without intermediate hosts) that also lack a critical developmental stage in soil or water. In sum, we can prioritize the list of risky organisms by paying attention to R_0 and transmission mode, and we can improve efforts to prevent human-to-wildlife disease transmission by focusing on screening sanctuary animals for the most high-risk organisms prior to release.

What are the threats to wild apes from human contact, including through research? Wild apes are also exposed to human pathogens through crop raiding, research activity, tourism, and extraction of forest resources [Eves et al., 2008; Goldberg et al., 2007; Litchfield, 2008], and this exposure has resulted in many examples of population declines [Kaur et al., 2008; Koendgen et al., 2008; Nunn & Altizer, 2006]. Primatologists in particular have diverse experiences with many different species of primates and their pathogens, and could thus serve as a "mixing vessel" for the creation of new infectious agents [Engel & Jones-Engel, 2011]. The marker organism approach that the authors used has been helpful in

understanding pathogen flow in wild systems (e.g. Goldberg et al., 2008]. One recent study (by some of the same authors) used similar markers to assess sharing of *S. aureus* among wild primates, including chimpanzees [Schaumburg et al., 2012]. While they found that humans and some primates appear to share *S. aureus* of recent common origin, evidence for genes conferring antibiotic resistance was limited to a single gene in one sample (obtained from chimpanzees, and possibly related to previous treatment with penicillin). With such limited study, however, more research is needed to assess the links between human scientific field studies and the wild animals under investigation, especially with regard to transmission involving fecal–oral or respiratory pathogens. While such sampling of wild chimpanzees and humans is more challenging to achieve noninvasively in the case of respiratory pathogens, it is feasible for fecally transmitted organisms (and even many other nonfecally transmitted organisms can be detected in feces, as demonstrated through research on Simian Immunodeficiency Virus (SIV) and *Plasmodium* [Keele et al., 2009; Liu et al., 2010]).

Are the human-derived microorganisms successful in competition with native microorganisms? Throughout, it is worth keeping in mind that resistance is not a new phenomenon that has evolved only in the postantibiotic period. Genes encoding resistance have been found, for example, in soil and permafrost microbial communities from 30,000 years ago [D'Costa et al., 2011]. Importantly, we might expect that many of the resistant bacteria on chimpanzees are not competitive relative to other bacteria when selective pressures favoring their evolution are absent. Hence, many of these organisms may be lost upon dissemination into the wild—another topic for further research if we are to truly understand the implications of these findings.

In conclusion, Schaumberg et al. [2012] demonstrate the risk of pathogen transmission from humans to apes in captive settings. This type of research is essential to inform the release of sanctuary apes to mitigate risks of disease introduction. Between 2000 and 2006, the chimpanzee population living in Pan African Sanctuary Alliance (PASA) sanctuaries grew at an astonishing 15% per year, driven by the adoption of an average of 56 new orphans from the bushmeat trade per year [Faust et al., 2011]. Captive managers are increasingly considering the feasibility of release as a potential mechanism to manage these populations over time [Faust et al., 2011], and disease transmission has long been recognized as a key concern in preparing animals for release [Britt et al., 2004; Seddon et al., 2007]. Recognizing this potential, PASA recommends close adherence to the IUCN release guidelines [Baker, 2002; Beck et al., 2007]. Guidelines include prerelease screening for behavioral, genetic, demographic, and health problems; recommendations for the release location; educational outreach in the release area; and postrelease monitoring of released populations. As a result, release programs for African apes in the past decade included prerelease health checks and quarantine periods [Andre et al., 2008; Farmer & Courage, 2008; Goossens et al., 2005; Humle et al., 2011; Moscovice et al., 2010].

The findings reported by Schaumberg et al. [2012] will spark additional research and lead to the next generation of recommendations to aid both captive and wild apes. Indeed, release remains an art form where researcher input is desperately needed. Scientists should work to help captive ape managers balance the demands of the real world—that is, political, time, demographic, and financial pressures—with techniques designed to aid in mitigating risk to the individuals and species being released when reintroduction is deemed appropriate [Seddon et al., 2007]. We hope the framework provided here gives some traction on these practical scientific questions, which are essential to evaluating the practicality of ongoing and future release programs.

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