RESEARCH ARTICLE

Risk Assessment: A Model for Predicting Cross-Species Transmission of Simian Foamy Virus From Macaques (*M. fascicularis*) to Humans at a Monkey Temple in Bali, Indonesia

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Contact between humans and nonhuman primates (NHPs) frequently occurs at monkey temples (religious sites that have become associated with free-ranging populations of NHPs) in Asia, creating the potential for NHP–human disease transmission. In March 2003 a multidisciplinary panel of experts participated in a workshop designed to model the risk of NHP–human pathogen transmission. The panel developed a risk assessment model to describe the likelihood of cross-species transmission of simian foamy virus (SFV) from temple macaques (*Macaca fascicularis*) to visitors at monkey temples. SFV is an enzootic simian retrovirus that has been shown to be transmitted from NHPs to humans. In operationalizing the model field data, laboratory data and expert opinions were used to estimate the likelihood of SFV transmission within this context. This model sets the stage for a discussion about modeling as a risk assessment tool and the kinds of data that are required to accurately predict transmission. Am. J. Primatol. 68:934–948, 2006. © 2006 Wiley-Liss, Inc.

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INTRODUCTION

Over the past few decades research on NHP-borne zoonoses has focused on individual pathogens and their molecular biology, and documenting NHP–human transmission [Brooks et al., 2002; Callahan et al., 1999; Centers for Disease Control and Prevention, 1992, 1996; Hayami et al., 1994; Khabbaz et al., 1994; Freifeld et al., 1995; Lerche et al., 2001; Peters et al., 2002; Sandstrom et al., 2000]. As a result, researchers have learned much about the structure and evolution of the HIV virus, which has led to important advances in the treatment of HIV/AIDS. The focus on HIV is appropriate given the impact of the HIV/AIDS pandemic. However, the scientific community has been slow to address the broader, underlying threat to which HIV points: the danger that other NHP borne pathogens pose to human populations [Murphy, 2002]. Few studies have investigated the possible contexts of transmission, that is, how pathogens are transmitted in the ''real world.'' For example, aside from a few articles on enzootic simian pathogens and their relationship to bushmeat hunting and pet ownership, virtually no published research has addressed other potential contexts for cross-species transmission [Chen et al., 1996, 1997; Goepfert et al., 1996; Ostrowski et al., 1998; Peters et al., 2002; Wolfe et al., 2004]. Furthermore, since HIV/SIV has yet to be detected in NHPs outside of Africa, the issue of cross-species transmission in Asia and South America has been largely ignored. If we hope to learn about the conditions under which future NHP-borne zoonoses are likely to emerge, and to take action to prevent their spread in human populations, it is critical to investigate not only which infectious agents pose a threat, but also which NHP populations constitute their reservoirs, and the conditions and contexts in which they are transmitted to humans. This kind of research requires the acquisition and integration of data from different disciplines. Serologic and molecular data are needed to determine the prevalence of pathogens in both human and NHP populations. Data on NHP behavior and human–NHP interactions are needed to describe the contexts in which human–NHP contact occurs. Epidemiologic and epizootiologic analyses are required to integrate the two types of data, and provide a population-based perspective on cross-species transmission as well as a basis for describing the conditions under which cross-species disease transmission is likely to occur.

Approach to Studying the Transmission of NHP-Borne Zoonoses to Humans

One approach to studying cross-species infectious agent transmission is to develop risk-analysis models that break the ''process'' of disease transmission into component parts (a detailed discussion of this process is presented by Travis and colleagues at the beginning of this issue). Processes and interactions that could lead to cross-species disease transmission are explicitly described as a hypothetical infection chain. Data from laboratory and field experiments are used to estimate the probability of each component, expected natural variation, and margins of error. When data are unavailable, expert opinion provides a guideline for probability estimates. Further, identification of areas for which insufficient information exists highlights gaps that can be addressed in future research or by reexaminations of existing data. The output of such models includes the probability that an infection event will take place under different scenarios, the margin of error, and the extent to which various components influence risk.

Monkey Temples of Asia: Context for Zoonotic Transmission

NHPs and humans come into contact in a variety of contexts in Asia, including NHP pet ownership, performance monkeys, ecotourism, NHP bushmeat hunting, and monkey temples [Aggimarangsee, 1992; Fuentes & Gamerl, 2005; Jones-Engel et al., 2001, 2003, 2005a,b; Schillaci et al., 2005]. However, worldwide, monkey temples may account for more human–NHP contact than any other context. Asia's monkey temples (religious sites that over time have become associated with populations of free-ranging macaques) play an important role in many South and Southeast Asian cultures in general, and particularly in the communities in which they are located. People who live or work in or around monkey temples, such as workers employed to maintain the temples; nuns, monks, and others who live on or around the temple grounds; merchants who sell a variety of goods to tourists; and neighboring farmers whose fields are raided by NHPs are among those who spend the most time around temple macaques. Others may come into contact with temple macaques when they visit for purposes of worship, recreation, or tourism. Monkey temples may be particularly important because every year they bring millions of people, including hundreds of thousands of tourists, from around the world into close proximity with free-ranging NHPs [Engel et al., 2002; Fuentes & Gamerl, 2005; Wheatley, 1998; Jones-Engel et al., 2005b, 2006; Fuentes et al., 2005]. In short, large numbers of people and NHPs come together at monkey temples, which makes these temples an important context in which to investigate cross-species transmission of infectious agents.

Simian Foamy Virus (SFV)

SFV is a retrovirus that is enzootic to both New and Old World NHPs [Meiering & Linial, 2001]. Though the virus has been shown to kill cells in vitro, research to date has yet to link SFV infection to disease in animals or humans [Meiering & Linial, 2001; Switzer et al., 2004]. Among NHPs, SFV is probably transmitted through contact with saliva [Falcone et al., 1999]. SFV infection of humans exposed to NHPs has been shown in several settings, including laboratory and zoo workers, bushmeat hunters in Africa, and, most recently, a monkey-temple worker in Indonesia [Brooks et al., 2002; Jones-Engel et al., 2005b; Sandstrom et al., 2000; Switzer et al., 2004; Wolfe et al., 2004]. Human–human transmission of SFV has not been documented [Meiering & Linial, 2001; Switzer et al., 2004].

SFV was deemed a logical virus with which to model NHP–human disease transmission among visitors to monkey temples. Prior work in this field has examined SFV transmission from NHPs to other human populations, providing a ready comparison for model predictions. SFV has not been found to occur naturally in human populations, so infection in humans constitutes strong evidence of NHP–human transmission and thus may be regarded as a marker for the possibility of cross-species transmission of other NHP-borne infectious agents. The lack of disease-related morbidity, mortality, or treatment makes prevalence estimates more representative of actual transmission rates for SFV than would be expected for some other agents.

MATERIALS AND METHODS

In March 2003 the Lincoln Park Zoo sponsored a workshop on human–NHP cross-species disease transmission. Experts from a variety of fields attended the

workshop, including physicians, veterinarians, anthropologists, primatologists, virologists, epidemiologists, infectious disease specialists, and experts versed in the creation and implementation of mathematical models. The goal of the workshop was to develop a model to estimate the risk of cross-species transmission of pathogens between humans and NHPs, evaluate potentially efficient intervention points, and identify critical information gaps.

What is the Risk of a Visitor to a Monkey Temple Becoming Infected With SFV?

The panel approached the model-building process by focusing on a specific question: What is the likelihood that a visitor to a monkey temple will become infected with SFV from a macaque (*Macaca* spp.)? This specific question was chosen for several reasons. First, it is a question that is not easily addressed by a field study. It is logistically difficult to measure infection rates among visitors to monkey temples because serologic or molecular evidence of infection usually takes weeks to appear, so one would need to track visitors down several weeks after their visit to a monkey temple–a difficult task, given their diverse geographic origins. Second, the number of people who are potentially affected is significant. Third, though rates of NHP–human transmission of SFV were previously measured in other human populations in contact with NHPs, these data are not applicable to monkey-temple visitors because monkey temples differ in important ways from previously studied contexts. Finally, previous field and laboratory studies have yielded data germane to cross-species transmission of SFV that can be used to inform the model. Specifically, we drew upon 5 years of data on human–macaque interactions at monkey temples in Bali, including data that specifically describe aggressive interactions and macaque bites. Other available data included the 1) data on the seroprevalence of SFV among macaques at Balinese monkey temples, 2) the wound-care practices of the workers at monkey temples, 3) demographic data on NHP and human populations, and 4) extensive data on behaviors in both populations that relate to infectious transmission. For the purposes of developing and evaluating an initial model, the panel focused only on the likelihood of SFV transmission through bite wounds.

The panel agreed that the risk of macaque–human transmission of SFV could be conceptualized as depending on five main variables that capture the most critical aspects of release assessment (RA), exposure assessment (EA), and consequence assessment (CA):

1. Likelihood that the biting macaque is seropositive for SFV (RA).
2. Likelihood that the biting macaque was shedding SFV when it bit the human (RA).
3. Likelihood that a visitor to a monkey temple is bitten by a macaque at the temple (EA).
4. Likelihood that the bite transmits the virus (CA).
5. Likelihood that the human washed the wound effectively after the bite (CA).

Basic Structure of Risk Assessment Model

The model was developed as a flow diagram that details in a stepwise fashion the major factors that can increase or decrease the likelihood that a person will become infected with SFV while visiting a monkey temple (Table I). These were divided into three categories: release assessment (RA), exposure assessment (EA),

TABLE I. Factors Included in a Risk Assessment for Transmission of Simian Foamy Virus from Macaques to Humans in Indonesia

Release assessment	Exposure assessment	Consequence assessment
1) Prevalence of infectious animals	4) Contact rate between monkeys and humans	7) Dose received/where bitten
2) Probability of actively shedding sufficient pathogens	5) Likelihood of a person being bitten during contact	8) Person's immune status effects
3) Likely routes of transmission	6) Type of bite (shallow/deep, minor/severe)	9) First aid efficacy
		10) Likelihood that infection becomes established in new host

and consequence assessment (CA) (Travis et al., this issue). For each component of the model, existing data were analyzed and probability ranges were estimated based on the best available information. For some components (for example, seroprevalence of SFV among monkey populations), data based on scientific studies were available. For parts of the model for which little or no data were available, data from other contexts were used to arrive at estimates with extrapolations based on discussions among the convened experts at the workshop. Variability was incorporated by using distributions to reflect ranges of values from multiple sites or studies. Uncertainty about estimates used in the model was evaluated by first specifying the lowest, highest, and most likely values, and then analyzing the sensitivity of model predictions to changes in these values. The flow diagram was translated into a spreadsheet format (Table II) that allowed the incorporation of distributions and analysis of different scenarios using a Monte Carlo simulation (@Risk; Palisade Corporation, Newfield, NY).

Estimating the Seroprevalence of SFV in Monkey Temple Macaques

The estimated prevalence of antibodies to SFV p74 and p70 antigens using Western blotting (see Jones-Engel et al. [2005] for serology methodology) was drawn from 5 years of serological survey data on free-ranging macaques (*Macaca* spp.) in Indonesia, Thailand, Nepal, and Singapore [Engel et al., 2002; Jones-Engel et al., 2005, 2006; Jones-Engel and Engel, unpublished data]. The sensitivity and specificity of the test used were both 100% [Allan et al., 1999; Blewett et al., 2000]. Seroprevalence among macaque populations ranged from 67% to 97%. The combined seroprevalence for more than 300 macaques, 83%, was used as the most likely value. These values were combined using a triangular distribution based on the minimum, maximum, and most likely values [Evans et al., 2000].

Estimating the Likelihood That a Biting Macaque Is Shedding Virus

There are no available data that measure rates of SFV shedding among free-ranging macaques. Analogous data derived from studies on laboratory baboons (*Papio* spp.) revealed that approximately 13% of healthy adult animals and 35% of adults treated with immunosuppressive research protocols shed the virus at any given time [Blewett et al., 2000]. The seroprevalence of antibodies to SFV among these laboratory baboons ranged from approximately 85% to 95%. To link prevalence of shedding to seroprevalence in monkeys, we divided the percentage

TABLE II. Risk Assessment Model for Transmission of Simian Foamy Virus From Macaques to Visitors to a Monkey Temple in Indonesia

Variable	Value[a]	Assumptions[b]
RELEASE ASSESSMENT		
Infectious macaque at the monkey temple		
1 Prevalence of infection (determines probability that an individual monkey is infected)	0.825	Minimum = 66.7%; most likely = 83.8%; maximum = 97%
2a Probability that seropositive monkey is shedding	0.26	Minimum = 15%; maximum = 37%; equal likelihoods
2b Probability that saliva has $\geq$ID100	1	Assume all shedding is $\geq$ID100
3 Is human contact possible (1 = yes, 0 = no)	1	Use a 0 if no human exposure is possible
EXPOSURE ASSESSMENT		
Macaque bites a human		
4 Probability that a monkey has contact with a visitor (single visit)	0.51	Minimum = 30%; most likely = 50%; maximum = 73%
5 Probability that a monkey bites following contact with a visitor	0.19	Minimum = 6%; most likely = 11.4%; maximum = 40%
6 Probability of bite severe enough for inoculation	0.95	95% of bites transmit SFV, or 50% of bites
CONSEQUENCE ASSESSMENT		
Human victim characteristics		
7 Increase/decrease risk due to tissue site of bite	1	Currently no change in risk due to tissue site
8a Probability that visitor is not already immune to SFV	1	Assumes visitors not previously infected with SFV
8b Probability of infection following inoculation in nonimmune person	1	Assumes no additional moderating factors
Human response to bite		
9a Probability that washing doses not take place	0.31	Minimum = 7%; maximum = 55%; equal likelihoods
9b Probability that washing takes place	0.69	Minimum = 45%; maximum = 93%; linked to 9a
9c Remaining risk following washing[c]	0.05	0.05 = 95% effective; 0.5 = 50% effective
10 Total probability of infection of visitor	0.0069	Probability for a single visit and bite

[a]Value represents single value or median value of specified distribution.
[b]See text for description and references for assumptions.
[c]Probability that washing does not take place + Probability that washing takes place $\times$ Remaining risk following washing.

shedding by the percentage that were seropositive, yielding estimates of 15% (13%/85%) and 37% (35%/95%). As a result, 15% was used as the minimum value for the probability of a macaque shedding SFV, and 37% was used as the maximum value. We used a uniform distribution [Evans et al., 2000] between these two-point estimates in our model, which allowed all values within this interval to have an equal likelihood of being used in calculations during the analysis.

Our model assumes that all biting macaques have an equal probability of being infected with SFV. Our data show that only macaques over the age of about 1 year tend to bite humans. By this age, most of the macaques showed serologic evidence of SFV infection. We have no data comparing viral shedding in macaques of different ages or sexes.

Estimating the Likelihood That a Visitor to a Monkey Temple Is Bitten

We subdivided this variable into two probabilities: 1) the probability that a monkey would interact with a visitor to a monkey temple, and 2) the probability that during the interaction the visitor would be bitten. We used two studies to obtain estimates for these probabilities. Data collected as part of a 5-year observational study of human–macaque interactions at the Padangtegal monkey temple in central Bali were available for inclusion in the model [Fuentes & Gamerl, 2005; Fuentes et al., 2005]. The main focus of this study was behavioral interactions, rather than bite risk among visitors. Although the likelihood that a monkey would interact with a visitor varied with the demographic characteristics of both monkeys and humans, an encounter was estimated to occur for 30–73% of visitors, with the most likely prediction being 50%. Among these contacts, the proportion that led to a visitor receiving a bite was quite low, with a minimum value estimated from these data of 6% and a most likely value of 11.4%. A maximum estimate of 40% for the likelihood of a visitor being bitten at a Balinese monkey temple was based on a study that reported that 40% of visitors were bitten by macaques at the Sangeh monkey temple [Wheatley, 1998]. The overall likelihood of a bite was calculated as the probability of contact with a monkey, drawn from a triangular distribution using the minimum, maximum, and most likely values [Evans et al., 2000], multiplied by the probability that a bite occurred during this contact, which was drawn from a separate triangular distribution.

These calculations examined only the risk of SFV transmitted through macaque bites. While bites represent a likely route of SFV transmission, data from previous serostudies of NHP-exposed human populations suggest that other modes of transmission, particularly mucosal contact with macaque body fluids, have the capacity to transmit SFV [Falcone et al., 1999; Heberling & Kalter, 1975; Lerche et al., 1986]. In the context of monkey temples, where macaques often climb about the head and shoulders of visitors, it is possible that SFV shed in urine, feces, and/or saliva will contact the conjunctival, nasal, or oral mucosae of visitors, providing additional opportunities for cross-species transmission. However, since much less is known about the frequency and dynamics of such contact, we chose to simplify the model by focusing only on bites. This is a knowledge gap that has been identified for quantification in future behavioral observations. If these additional potential exposures are important, our model would be expected to underestimate the risk of SFV infection among visitors, but given the present lack of data it is difficult to speculate by how much.

Estimating the Likelihood That a Bite by a Shedding Macaque Will Transmit SFV Infection

Several factors are likely to influence the potential for transmission by a bite, including the size of the inoculum (number of infectious viral particles, related to volume of saliva inoculated and the concentration of virus in saliva), severity of the bite (in terms of tissue injury), location and vascularity of the injured area, and immune status of the victim. Because there is a high degree of uncertainty regarding these variables, and a large range of possible values, we ran the model separately to compare estimates of 50% and 95% transmission. Varying a single transmission coefficient assumes that a bite from an adult, for example, is as likely to result in human infection as a bite from a juvenile. The reality is probably far more complex, but would affect transmission rates only if population demographics were very fluid among these NHPs.

In addition, whether or not a human becomes infected may depend in part on his/her sex, age, or other factors, such as immune function. Since few data on these variables are available, we elected to generalize them in the present model. As more is learned, the inclusion of these variables in the model may improve its predictive accuracy.

Estimating the Likelihood That a Bite Victim Will Perform Wound Care

Visitors to monkey temples come from diverse geographic locations and may have a wide variety of beliefs regarding interactions with NHPs and disease transmission. The visitor populations differ substantially among monkey temples, with some temples drawing mainly local visitors and others predominantly international tourists [Fuentes & Gamerl, 2005; Fuentes et al., 2005]. However, no data are available that describe the wound-care practices of visitors (local or nonlocal). Data from two studies of wound care by workers at monkey temples in Bali, based on a questionnaire, revealed that 45% of workers at the Sangeh monkey temple and 93% of workers at the Alas Kedaton monkey temple recalled washing their wounds [Engel et al., 2002] (Jones-Engel and Engel, unpublished data). Workers at these two monkey temples are quite different demographically (the majority of workers at Sangeh are men, while most workers at Alas Kedaton are women). Since we were interested in the impact that this variable would have on the predicted outcome of infection, we used these numbers to estimate a range of 7–55% of those bitten who did not wash, with an equal probability for all values in between.

Data describing other significant variables, including the time elapsed before wound care and the thoroughness of wound care, are not available. In the initial model, we assumed that all washing would be quite effective and prevent 95% of SFV infections that would have occurred after bites without washing. We also ran the model using a lower effectiveness of washing, estimated as 50%.

Estimating the Overall Likelihood That a Visitor Will Become Infected With SFV Due to a Bite From a Macaque During a Visit to a Monkey Temple

The probabilities and distributions for each variable in the risk assessment were entered into the spreadsheet. Latin Hypercube sampling was used to derive input values from distributions. We calculated the overall probability of SFV infection from the derived inputs by multiplying all of the probabilities in a chain, except for those related to washing. We included the effects of washing by

multiplying the chain of all other probabilities by (probability that washing does not take place) plus (probability that washing takes place) times (remaining risk following washing).

The mean, median, and 5th–95th percentiles in the predicted probability of a visitor becoming infected with SFV were determined by 1,000 iterations. Distributions of probabilities were graphed to assess symmetry and kurtosis. Sensitivity analyses were conducted by determining the median probability of human SFV infection for a range of fixed values of one input, when other inputs were allowed to vary across their predefined distributions. The probability of infection following a bite, and the assumed effectiveness of wound care were both held constant at the 95% level while other variables were evaluated. Then the effects of varying bite infectiousness and wound care efficacy were evaluated over a range of values with other inputs drawn from their defined distributions. Each input was assessed for probabilities ranging from 0% to 100%, and then as it varied from the minimum to the maximum of its defined distribution. The results were graphed to show the relationship between the median probability of human SFV infection among visitors, and 1) all mathematically possible values (0–100%) and 2) the range of data-supported values for inputs. Normalized least-squares regression coefficients were also calculated between variable inputs (those sampled from distributions) and the range of resulting infection probabilities, and plotted on a bar graph from the most to the least influential (largest to smallest absolute value) to create a ''tornado'' influence graph.

RESULTS

Based on this simple model, the median probability that a visitor would become infected with SFV due to a bite during a visit to a monkey temple was 0.0056 or 0.56% (5th percentile: 0.0018; 95th percentile: 0.0160). This translates to 5.6 of every 1,000 people visiting a monkey temple becoming infected. Figure 1 shows the variability observed in 1,000 runs, using the input ranges that we defined. The output predictions include a range of values that capture what we specified as natural variability between populations and conditions.
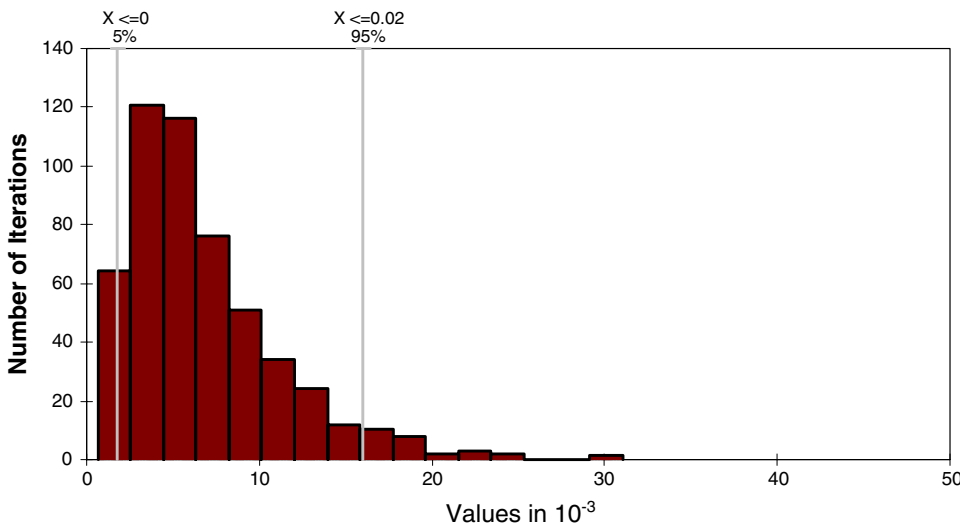

Fig. 1. Output distribution of the probability of infection with SFV during a visit to a monkey temple based on @Risk Model (Table II) with default input values.

Using the same model, but with 50% (rather than 95%) of bites presumed to be able to transmit SFV, the median probability that a visitor would become infected with SFV due to a bite during a visit to a monkey temple was 0.0030 or 0.3% (5th percentile: 0.0009; 95th percentile: 0.0084). This translates to three of every 1,000 people visiting a monkey temple becoming infected.

When the effectiveness of wound washing in preventing SFV transmission was decreased from 95% to 50%, the median number of people predicted to be infected increased to 1.15% or 11.5 per 1,000 (5th percentile: 0.0048; 95th percentile: 0.0267). With both the lower estimate of SFV transmission (50%) and washing effectiveness (50%), the median number of people predicted to be infected was 0.61% or 6.1 per 1,000 (5th percentile: 0.0025; 95th percentile: 0.0141).

When input probabilities were varied from 0% to 100%, all inputs were positively correlated with transmission risk, and the most influential variables were those that related to biting and SFV shedding by the monkeys, and prevalence and effectiveness of washing by the humans (Fig. 2). When input variations were limited to value ranges supported by data and literature (Figs. 3 and 4), these same four inputs were the most important (i.e., led to the highest potential transmission rates), while probability of a monkey biting a visitor and the probability of the visitor not washing the wound were the most influential (i.e., with the greatest slope across the input range). Variables can have an impact because they are pivotal or because they can vary across an extremely wide range of values, leading to many changes in the model.

DISCUSSION

Risk Assessment–An Important Aspect of Risk Analysis

The operationalization of risk assessment described above illustrates how field data, experimental data, and expert opinion can inform a mathematical model to estimate the risk of an event—in this case, the likelihood that a visitor to a monkey temple will be infected with SFV as a result of being bitten by a macaque. The model predicts that for every 1,000 visitors to monkey temples,
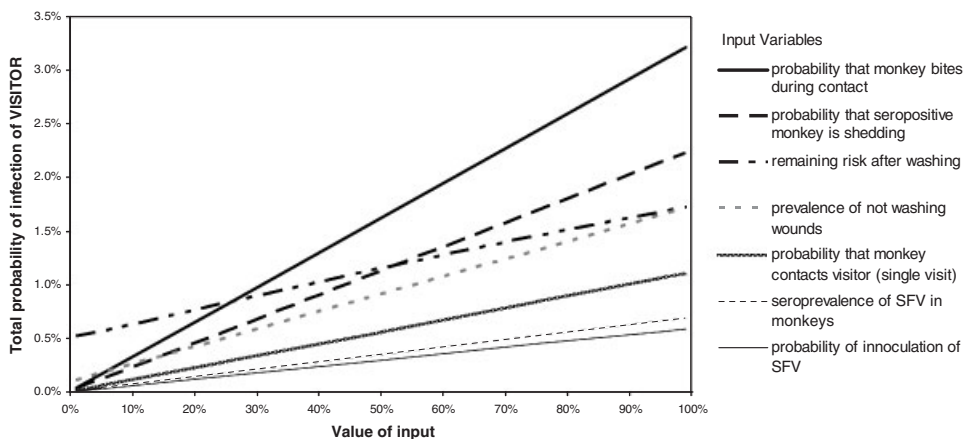

Fig. 2. Spider sensitivity analysis graph showing median values for the output, probability of SFV infection, as each input was varied from 0% to 100%, with other variables sampled randomly from their defined distributions. The probability of infection following a bite and the effectiveness of wound care were 95% when other inputs were assessed.
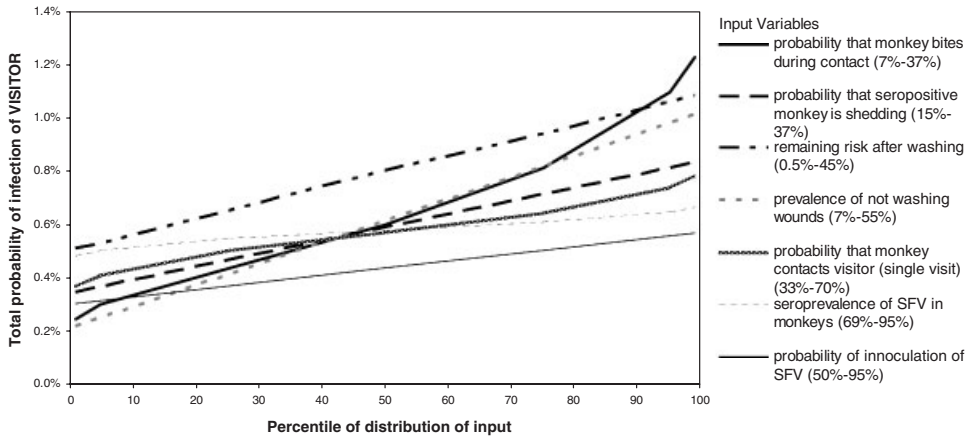
Fig. 3. Spider sensitivity analysis graph showing median values for the output, probability of SFV infection, as each input was varied over the range of possible values defined for input variables, with other variables sampled randomly from their defined distributions. The probability of infection following a bite and the effectiveness of wound care were 95% when other inputs were assessed.
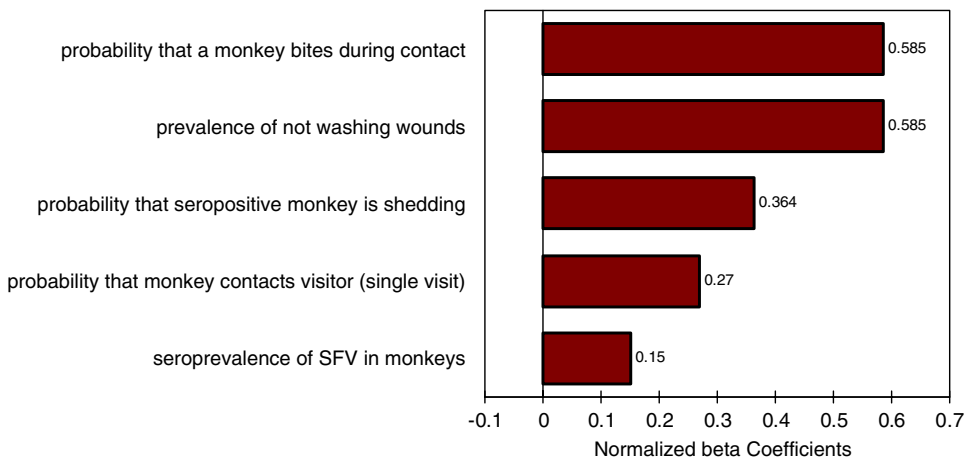

Fig. 4. Tornado influence graph ranking input variables in the model (Table II) from the most to the least influential. Some inputs were individually assessed at set values across their defined distributions, while other inputs were sampled randomly from their distributions. The probability of infection following a bite and the effectiveness of wound care were 95% in these simulations.

approximately six persons will be infected with SFV. This estimate should be placed in the context of previous research measuring the rate of SFV infection in human populations that have contact with NHPs. SFV prevalence has been measured in zoo workers (6.98%) and bushmeat hunters in Cameroon (1.0%) [Switzer et al., 2004; Wolfe et al., 2004]. Studies of primate-laboratory workers found SFV prevalences of 2.93% [Switzer et al., 2004] and 4.3% [Brooks et al., 2002]. In addition, one of 82 (1.2%) workers at a monkey temple in Bali was found to be infected with SFV [Jones-Engel et al., 2005b].

Visitors to monkey temples constitute a unique demographic group whose risk of acquiring NHP-borne infections may differ from that observed in other NHP-exposed populations, such as laboratory and zoo workers and bushmeat hunters [Sotir et al., 1997]. Visitors typically spend only an hour or two [Fuentes & Gamerl, 2005] at a monkey temple, in contrast to the everyday exposure over years for zoo and laboratory workers or bushmeat hunters. Most visitors have little or no experience in interacting with free-ranging NHPs and may unwittingly provoke aggression and, as a result, high-risk contact. Many visitors, particularly Westerners, wear short pants and short-sleeved shirts, since monkey temples are typically located in tropical or subtropical areas. Few visitors are aware of the possibility of NHP–human transmission of disease and thus do not use protective eyewear or gloves, or practice wound care to reduce the likelihood of transmission of infection. As a result, extrapolating the risk of infection to visitors from seroprevalence measured in other NHP-exposed populations is unlikely to provide an accurate estimate of risk for visitors to monkey temples.

The significance of the model lies not so much in the output, but in the process involved. The modeling process—bringing together the best available data to describe how infectious agents can be transmitted from NHPs to humans–shows with greater clarity how far we are from being able to accurately predict the likelihood of cross-species disease transmission. The model is especially useful for elucidating areas where data are the most lacking, and in suggesting both where further research is needed and how to acquire the data. For example, there was a six-fold increase in median risk for SFV transmission (0.0025–0.0123) if the probability of a monkey biting following contact was assumed to be 37% rather than 7%. Similarly, if the estimate of SFV transmission through a bite was lowered even further to 5%, the median proportion of people predicted to be infected was 0.03% (3/10,000 visitors; 5th percentile: 0.0001; 95th percentile: 0.0008) if wound-washing was 95% effective, and 0.06% (6/10,000 visitors; 5th percentile: 0.0003; 95th percentile: 0.0014) if wound-washing was only 50% effective.

Despite the significant amount of data available describing human–macaque interactions at monkey temples, the model points out that data specifically measuring the likelihood that a visitor to a monkey temple will be bitten are not currently available. The data referenced in this report were gathered through behavioral observations that measured bites as a percentage of observed human–macaque interactions. To improve the model's accuracy, it is important to gather data in the future that specifically measure the rate at which *all* visitors are bitten, not just those who interact with macaques. This is one illustration of how the process of developing the model can guide future data acquisition. In addition, collecting data on bite rates from different nationalities and demographic groups visiting the monkey temples may help to identify groups that are at particularly high risk for receiving bite injuries. The present model relies on data acquired at monkey temples in Bali, Indonesia, and may not be representative of monkey temples in other countries or other species of macaques. It will be important to expand the number of monkey temples where such data are acquired to increase the generalizability of the model.

Operationalizing the model made it clear that there is a great deal of uncertainty surrounding estimation of the likelihood that, once bitten, a person will become infected with SFV. This uncertainty is based on a lack of data describing 1) the severity of the bite wound, 2) the amount of infectious virus introduced by bites, 3) the effect of the victim's immune status on viral replication, and 4) the likelihood of infection from bites in different anatomical

locations. These gaps in available data point the way to future research that can greatly improve the predictive value of the model. Data on the severity and anatomic locations of bites can be collected in the field. Laboratory data could improve an estimation of the likelihood of transmission given different bite and wound dynamics and the possible role that immunologic status may play in modifying the risk of infection.

Our assumption in the above operationalization of the model was that any kind of wound washing would prevent transmission of SFV. However, this is likely an inaccurate assumption. There are no data on time intervals between bite and wound care, the thoroughness of wound care at monkey temples, or on how the timing and techniques of wound care (e.g., irrigation, debridement, and antisepsis) impact the likelihood of SFV infection in bite victims. As a result, though the two data sets available describing wound-care practices by monkey temple workers indicate that 45–93% of bite victims do engage in some kind of wound care, these numbers probably overestimate the protective effect of wound care. In order to estimate with greater reliability the effect that wound care may have on the risk of SFV infection, field data should include details on the prevalence, timing, and type of wound care. Laboratory data on the effect of wound-care timing and the efficacy of wound care could also improve the model's accuracy. Furthermore, it is likely that wound-care practices differ among the different demographic groups that visit monkey temples. This is another area in which acquiring these kinds of data could improve the model.

Data on the seroprevalence of SFV infection among macaques was based on a large number of free-ranging macaques sampled in several countries in Asia. As a result, our confidence in this number is high. However, it should be noted that there are millions of macaques in Asia, and it is possible that in some populations there is a variation in the seroprevalence of SFV. For this model, the available data on shedding rates were derived from laboratory colonies of baboons. Again, specific data regarding shedding in *free-ranging macaque* populations would improve the model's accuracy. Specifically, field protocols should be expanded to include the acquisition of oral, genital, and rectal mucosal swabs to test for the presence of SFV.

CONCLUSIONS

It is evident from the above risk-assessment model that much remains to be learned before this particular model can make accurate predictions about the risk of cross-species infectious-agent transmission. However, this model does predict that the risk of being infected with SFV among visitors to a monkey temple is not negligible. This model is conceived as the first step in a process whereby NHP–human cross-species disease transmission can be examined. As such, it is hoped that this report will stimulate debate and discussion, as well as further laboratory and field research in this area. In addition, we believe that the above risk-assessment approach can help researchers think about cross-species transmission in other contexts of human–NHP contact.

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