OCCASIONAL PAPERS

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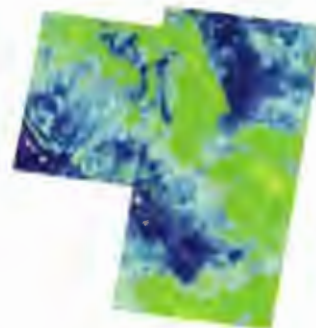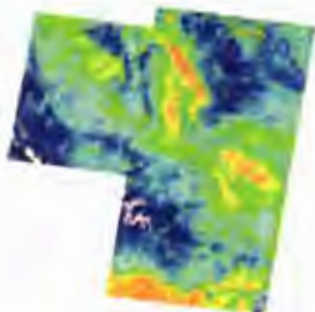
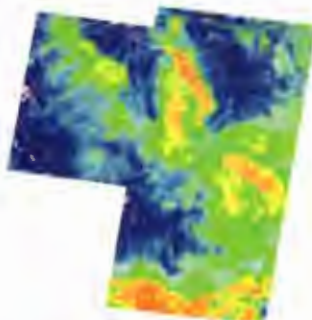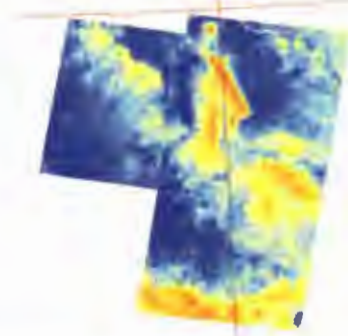1992 image/1993 risk
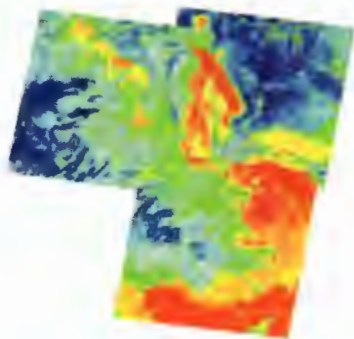
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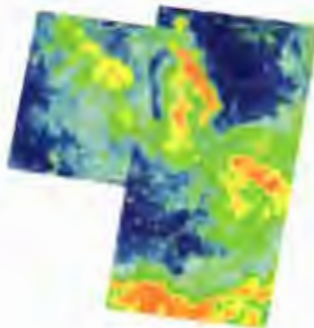
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PREDICTED HANTAVIRUS RISK IN 2006 FOR THE SOUTHWESTERN U.S.

Editorial Comment: *Occasional Paper* Number 255 by Gregory Glass and his colleagues represents a significant departure from the usual—routine—museum publication. In this paper the authors marshal data and analyses to estimate risk of outbreak of an emergent zoonotic disease associated with deer mice in the southwestern United States. To our knowledge, the paper by Glass and colleagues represents the first time in which remote sensing, ongoing mammalogical fieldwork, ecological assessment, and museum-based historical datasets have been combined to estimate outbreak potential. Scientifically, this publication lays out a testable hypothesis that could lead to important breakthroughs in understanding and responding to emergent disease.

The original hantavirus outbreak in the southwestern United States in 1993 triggered comprehensive new research in medical and biological science. This research included diagnostics and treatment of hantavirus pulmonary syndrome (HPS) in human beings, epidemiology of the disease, basic virology and genetic variation among strains of the infectious agent, and traditional mammalogy. It resulted in new collaborations between university scientists and their counterparts in federal agencies, joint programs between the NIH and NSF, and prompted Congress to allocate substantial financial resources to the subject.

In retrospect, the original hantavirus outbreak was a reminder of how little was known about the potential for zoonoses in the United States. Now, thirteen years after the fact, the scientific community has used its multidisciplinary skills to significantly advance our understanding of North American hantaviruses and to respond to other diseases such as arenavirus-associated illnesses and Lyme disease. But at the same time, we now think of hantaviruses in a totally new context—category A infectious agents, disease surveillance, biosecurity, bioterrorism, confinement laboratory facilities, and nonproliferation of expertise and weapons technologies are all part of the new post-9/11 mix.

Emergent diseases are a global problem. Climate change, habitat destruction, land use, and human population densities are factors in outbreaks. And such outbreaks have economic, social, and political consequences. Not surprisingly, the factors and challenges of emergent disease on a global scale are complex enough to affect United States foreign policy. Moreover, given the realities of state-sponsored biological weapons research and development, and potential for transnational terrorists to acquire and use biological agents, data about zoonotic diseases and their pathogens, reservoirs, and vectors have made their way into strategy sessions at Homeland Security and the National Security Council. So, a lot has happened since the Four Corners outbreak and identification of deer mice as the reservoir of Sin Nombre virus. Nevertheless, in the end it is scientific research that will provide policy makers and strategic planners with the information and understanding needed to counteract the natural and human-initiated threats posed by emergent disease agents. Papers such as this one by Glass and colleagues have great potential to that end.

Museum-based research collections of mammals and birds, catalogued tissue specimens, geographic data documenting capture sites and conditions, and the field notes of biologists are essential ingredients in the study of emergent disease. Avian influenza, Ebola, Nipah, and SARS are four specific examples of where museum voucher specimens, basic biological science, molecular systematics, population genetics, application of the genetic species concept, and appreciation of the zoogeographic history of reservoir species combine to provide information that is critical to preparation and response to outbreaks. Coupled with prediction through remote sensing and modeling there is an unparalleled opportunity for common good.

Guest Editor
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Front cover: Interannual variation in Hantavirus Pulmonary Syndrome risk based on satellite imagery.

Predicted Hantavirus Risk in 2006 for the Southwestern U. S.

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James N. Mills, James Cheek, Joseph Cook, and Terry L. Yates

Abstract

Landsat Thematic Mapper (TM) imagery taken in the year before the outbreak of hantavirus pulmonary syndrome (HPS) was previously related to the location of human cases of disease. In this paper we show that the logistic regression approach developed from that analysis was consistent for subsequent years during the 1990s. During the past six years a drought has affected the southwestern U.S. and the numbers of HPS cases diminished, but with the interruption of the drought in 2004, there was concern that HPS would re-emerge. Analyses of TM images for 2004 indicated a generally low level of risk in the study area – a prediction substantiated by the occurrence of four cases in the lone high risk area. Examination of TM images for portions of southern Colorado and north-central New Mexico also indicated relatively low risk for 2005 and these results were confirmed. Risk analysis for 2006 predicts that HPS cases in the Four Corners area will be similar in frequency and distribution to those seen in 1998 and 1999. However, areas of southern Colorado and north-central New Mexico show a marked increase in the level and geographic extent of predicted risk. Survey samples of *Peromyscus maniculatus* at two sites in north-central New Mexico show crude prevalence rates of 23-34% to Sin Nombre virus.

Key words: disease forecasting, Hantavirus Pulmonary Syndrome, Landsat TM imagery, *Peromyscus maniculatus*, remote sensing, Sin Nombre virus

Introduction

The apparently sudden appearance of hantavirus pulmonary syndrome (HPS; also known as hantavirus cardiopulmonary syndrome or HCPS) in the southwestern United States in 1993 (Nichol et al. 1993) was a major factor in reawakening research interest in the ecology of infectious diseases and the role that climate variability plays in changing levels of risk (Mills 2005). HPS is a disease in humans caused by infection with a variety of hantaviruses (Family Bunyaviridae). Most hantaviruses infect rodent species within the family Muridae, and general patterns of clinical disease have been linked to phylogenetic patterns of the rodent-virus co-evolution (Yates et al. 2002), with the disease caused by hantaviruses associated with New World sigmodontine rodents predominantly causing a pulmonary presentation and high case fatality.

Systematics collections play important roles in the study of zoonotic agents, generally, and

hantaviruses, in particular (Ruedas et al. 2000; Yates et al. 2002). They serve as important sources of materials, allowing the rapid identification of agents and providing a historical context for the identification of 'emerging' diseases. They also are critical in allowing the accurate identification of environmental and biological sources of infectious agents. The correct identification of animal reservoirs is critically important to establishing the potential extent of human and domestic animal risk. For example, most sigmodontine reservoirs of hantaviruses are not associated with high density, urban environments. This implies a substantial reduction in risk for large portions of the human population in the Americas – and probably accounts for the relatively small number of cases reported annually. This is in contrast to Asia, where large rural populations are exposed and the annual numbers of human cases of hantaviral disease range from 50,000 to 500,000. Even within the geographic range of se-

lected reservoir species, a relatively small portion of HPS cases are associated with recreational activities; rather, most cases have been linked to significant occupational and home exposures while cleaning rodent droppings. This suggests an intensive exposure to aerosolized virus is the major route of infection.

Retrospective studies in the southwestern U.S showed that environmental conditions as monitored by satellite imagery prior to summer monsoons of one year were associated with the geographic extent and numbers of HPS cases the following year (Glass et al. 2000). The ecological basis for this relationship is thought to be due to the direct and indirect impacts that increased net primary productivity has on the rodent-virus system (Yates et al. 2002). This led to the proposal that analysis of the imagery could serve as an early warning system of increasing levels of HPS risk and that long-term monitoring of imagery could improve our understanding of climate-ecosystem-human health interactions (Ostfeld et al. 2005). During the past half dozen years this region has experienced significant drought conditions with attendant decrease in local HPS cases. However, environmental condi-

tions ameliorated with near-record precipitation levels in 2004-2005 (http://www.srh.noaa.gov/abq/climate /Monthlyreports/Annual/2004/ 2004weatherhighlights. htm) and raised concerns that an increase in HPS cases might be expected.

As a result, we extended our earlier analyses of the 1993 HPS outbreak and the later lull in HPS cases during a La Niña in 1995-96 to evaluate whether the risk algorithm performed consistently, in this region, across time. During the initial development of the algorithm we defined the expected proportion of cases that should occur in low, moderate, and high risk areas (Glass et al. 2000). To evaluate the consistency of our algorithm, we compared these predictions to the observed numbers of cases in 1994, 1998, and 1999. Subsequently, we generated risk maps for 2005 and 2006. For the past two years we have extended our analyses to regions in Colorado and New Mexico, east of the historical focus of study in the region of western New Mexico and the Four Corners area. Our model indicates increased risk to humans for HPS, compared to the past few years, during 2006 especially in northern New Mexico and southern Colorado.

METHODS

Locations of likely sites of exposure for human HPS cases were obtained as part of the original outbreak investigation in 1993 and, at the same time, community-based human controls representing individuals who had used the same health care clinics were obtained by the appropriate authorities (Childs et al. 1995; Glass et al. 2000). These locations were co-registered to Landsat Thematic Mapper 5 (TM) satellite imagery and a digital elevation model (DEM) for the region. The TM imagery was used as a surrogate of environmental conditions in the vicinity of case and control sites. In the original analyses, logistic regression was used to model the log-odds that a site would be a case location based on the local environmental conditions, as measured by TM imagery (Collett 1994). The final model was examined for spatial structure by K-function analysis (Bailey and Gatrell 1995) but there was no indication of residual spatial structure, so the logistic model was considered appropriately specified.

The predicted risk for each site was estimated from the logistic regression model and stratified by case or control status. This information was used to generate a Receiver Operator Characteristic (ROC) function (Fletcher et al. 1982) for the analysis. The ROC was used to categorize the continuous predicted values from the logistic model into thresholds of low, moderate, and high risk. The ROC was generated by comparing the a priori case and control status with the predicted risk from the logistic regression model and identifying thresholds that would correctly classify the greatest proportion of cases while minimizing the misclassification of controls.

In the original analyses, the digital numbers from the TM imagery that had been radiometrically and geometrically corrected were used as possible predictor variables (Glass et al. 2000). However, for the current multi-year analysis, the effects of variation in

atmospheric conditions among years for the TM imagery also were adjusted using a regression intersection method (Crippen 1987). TM 5 images from mid-June for the years 1993, 1997, and 1998 were added to the previously examined TM 5 data from 1992 and 1995.

We evaluated the interannual consistency of the logistic regression approach by using the case and control sites from the original study (Glass et al. 2000) to extract environmental conditions at those locations in 1993, 1995, 1997, and 1998 from the TM imagery for those years. The logistic regression algorithm was applied using those locations and the expected risk for each pixel in the entire study area was generated from the model for each year. According to the original interpretation, analyses of images from these years should predict the location and geographic extent of HPS risk in the subsequent years; 1994, 1996, 1998, and 1999, respectively. To test this hypothesis, we examined the numbers of HPS cases in those years, determined their most likely exposure site by history and residence, located their position on the risk map for the appropriate year, and determined the proportion of HPS cases for those years in low, moderate, and high risk areas. If the logistic model was generally applicable in this region across years, then the numbers of cases should be proportional to the extent of low, moderate, and high risk areas, and the proportion of cases falling in each category of risk should follow the ROC function.

For 2005 and 2006, TM 5 images from mid-June 2004 and 2005 were acquired and processed, as described above. Additionally, imagery for two scenes extending north and east of the Four Corners region were included. These scenes included regions where studies of Sin Nombre virus (SNV) transmission in

deer mice (*Peromyscus maniculatus*) were being conducted (Abramson et al. 2003). The same logistic regression model was applied to these TM images as a predicted measure of risk.

Sampled deer mice were collected as an independent measure of SNV activity. This was done both to help validate the utility of the logistic regression analysis in areas outside of the Four Corners region and to reduce reporting bias that might accompany unreported cases of HPS in humans. Mice were trapped along short-term line transects set with Sherman live traps. Approximately 40 traps were set per transect and geographic coordinates of the trap lines were recorded using Global Positioning System receivers. Traps were run for four consecutive nights. Trapped animals were processed using standard protocols (Mills et al. 1998) and blood samples collected and stored in liquid nitrogen until testing for antibodies to SNV. Antibody testing was performed by one of two methods; either an enzyme-linked immunosorbent assay (ELISA) was used, or a modified slot-blot assay was applied. The ELISA was performed by the U. S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, and followed their established protocols (Feldmann et al. 1993). The strip immunoassay followed procedures outlined in Yee et al. (2003) and used antigens to SNV nucleocapsid protein immobilized on a membrane as a target for circulating antibodies in a test sample. Goat anti-*Peromyscus* antibodies also were fixed to the strip as positive controls for the detection of deer mouse antibodies, generally. Negative and positive control test samples to SNV also were included during each assay. Specimens and data were archived at the Museum of Southwestern Biology (MSB), Albuquerque, New Mexico.

RESULTS

Regression analysis, using environmental conditions extracted from the TM images near the original case and control sites, showed substantial interannual variation in the extent and severity of predicted HPS risk in the region (Figure 1). As previously described (Glass et al. 2000), the risk in 1992 was widespread and high throughout much of the higher elevations (> 2094 m) in the region, with low risk areas confined

to the lower elevations. The largest number of sites with human HPS cases in the region was reported in 1993. In contrast, in 1995, environmental signatures indicated that risk was generally low, and moderately high levels of risk were geographically restricted to the highest elevations (Figure 1). Only a single case of HPS was reported in 1996.
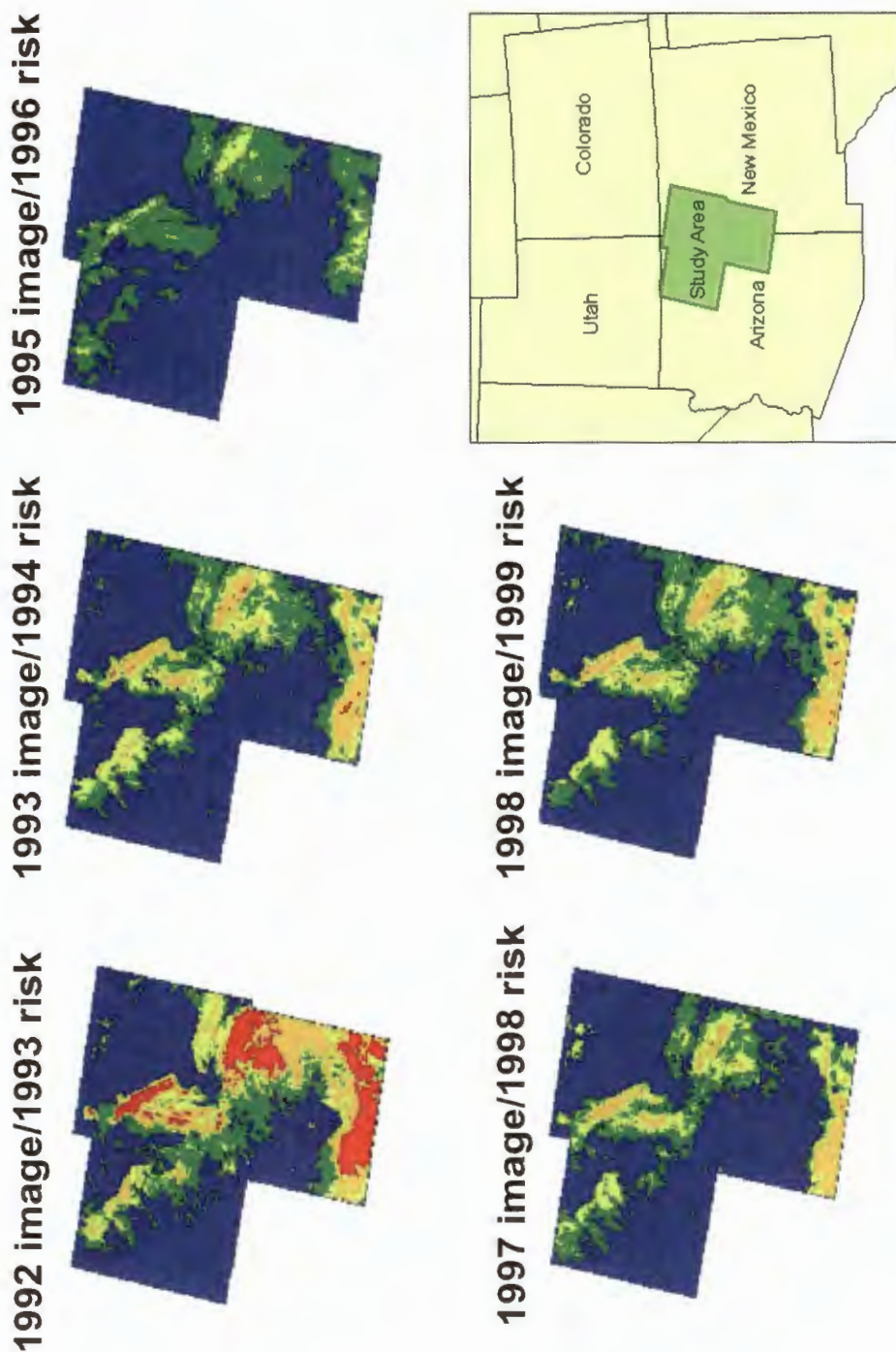
Figure 1. Modeled HPS risk in Four Corners region (locator map, lower right) based on Landsat Thematic Mapper (TM) imagery and elevation at case and control locations in the study area. Risk was estimated from logistic regression modeling of Landsat TM imagery comparing environmental signatures at sites with previous HPS cases compared to other residential locations. Imagery from one year is used to estimate risk the following year. For example, 1992 imagery was used to model risk in 1993 (upper left). Imagery from 1993 (upper center) and 1995 (upper right) show the broad range of year-to-year variation. Imagery for 1997 and 1998 (bottom left, center) show predicted HPS risk during the last El Niño. The color scale was generated in arbitrary units from low (blue) to high (red) and does not estimate absolute risk. Locator map (bottom right) shows the study area.

Analyses of TM imagery for 1993, 1997, and 1998 indicated that HPS risk in 1994, 1998, and 1999 were similar, and the numbers of HPS cases should have fallen at intermediate levels between observations in 1993 and 1996 (Figure 1). Highest risk areas were not as evident as those observed in 1992 but tended to occur in core areas of the Chuska, Zuni, and Mangas mountains. As predicted, the numbers of HPS cases reported from the region in 1994, 1998, and 1999 fell between the 28 reported HPS cases in 1993 and the one case in 1996, totaling 22 cases for the three years with a near equal distribution among years. There were seven cases reported in 1994, six cases in 1998, and eight cases in 1999.

The ROC function from the 1993 case-control data was designed so that low, moderate, and high risk thresholds would have 10% of cases in low risk areas, 25% in moderate risk areas, and 65% in high risk areas. The distribution of observed cases among the predicted risk categories for 1994-1999 was consistent with this distribution (Figure 2). The observed distribution of HPS cases among the three classes differed from the expected distribution by only a single individual, leading us to conclude that the logistic regression approach to risk analysis in this region produced a consistent classification throughout the 1990s.

In early 2005, TM 5 imagery was obtained for June 2004 from the Four Corners area and the logistic regression algorithm was applied (Figure 3A). Results for this region indicated that there would be a relatively low level of risk anticipated for the 2005 season, with the exception of a region in northeastern Arizona focusing in northern Navajo and Apache counties. This region had generally been at low risk throughout the years examined in the 1990s (Figure 1). However, in 2005, a cluster of four cases was reported in this area.
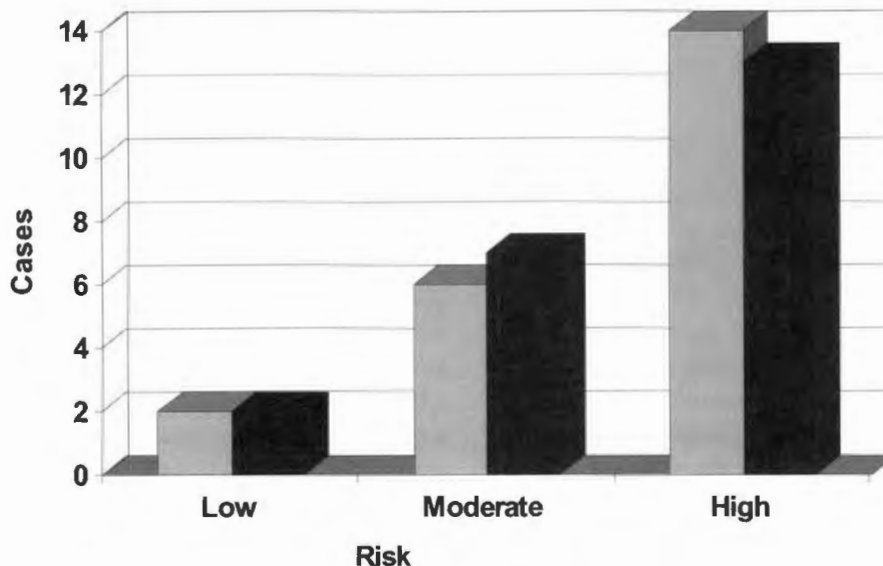

Figure 2. Comparison of total number of predicted (light bars) and observed (dark bars) HPS cases from 1994, 1996, 1998, and 1999 (combined) in study area. The expected numbers of cases was established from the Receiver Operator Characteristic (ROC) function from analysis of the 1992 imagery. The ROC function established thresholds of the logistic regression function so that low risk areas should account for 10% of all cases, moderate risk areas should account for 25% of all cases, and high risk areas should account for 65% of all cases. The similarity between observed and expected case distribution indicates the logistic model was well specified throughout the 1990s.
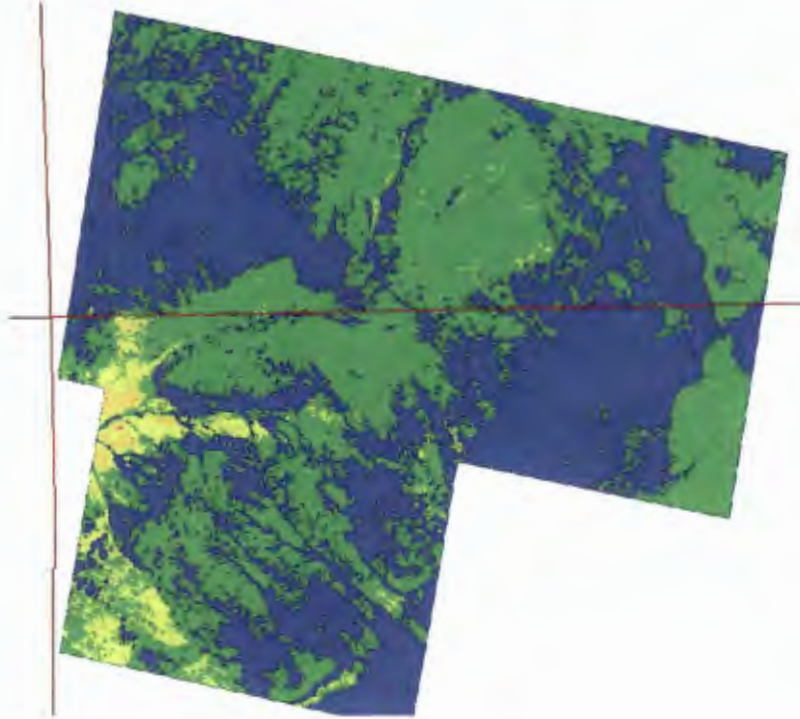
Figure 3B.

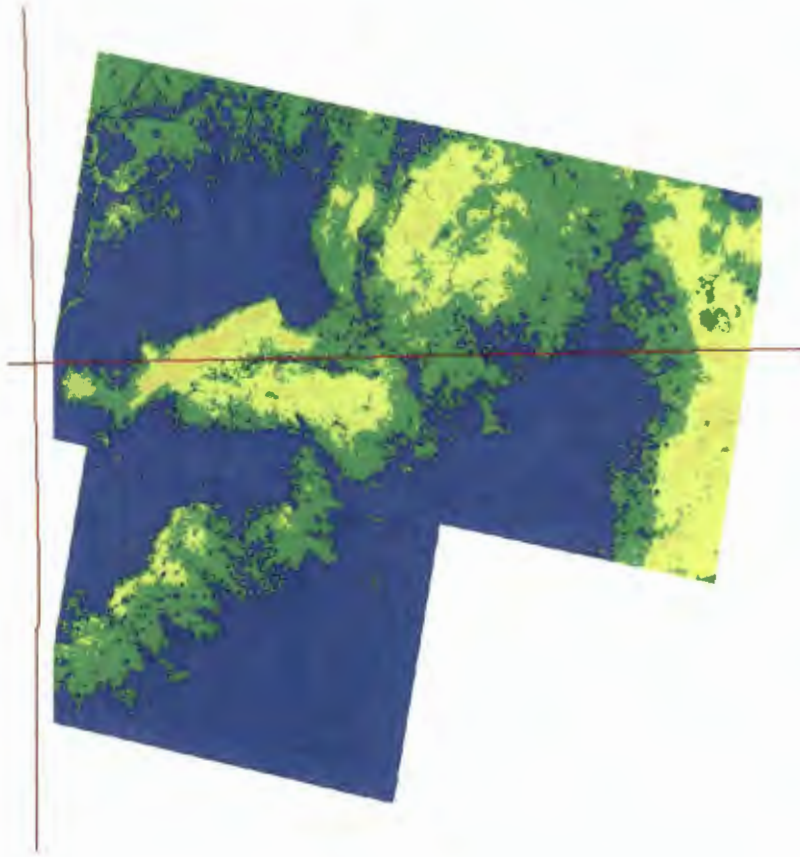## 2005 image/2006 risk

Figure 3A.

2004 image/2005 risk

Figure 3. Logistic regression model of HPS risk in the study area shown in Figure 1 in 2005 (A) and 2006 (B), using Landsat TM imagery from 2004 and 2005, respectively. Risk in 2005 (A) was generally low, except for a focus in northeastern Arizona in a region that had experienced relatively few cases in the 1990s (Figure 1). In 2006 (B), HPS risk appears similar in extent and severity to that seen for 1994, 1998, and 1999 (Figure 1). The color scale is as shown for Figure 1.

For comparison, the region east and north of the Four Corners study area in southern Colorado and northern New Mexico was examined (Figure 4A) during the same time period. Analyses indicated there would be a generally low risk for HPS in the area during 2005, although there were a few areas of moderate to high risk observed adjacent to some small population centers. Four cases in this region of southern Colorado were reported in 2005 – each associated with the small foci of predicted high risk areas.

Satellite imagery obtained in June 2005 predicted that for 2006, the Four Corners area had a similar geographic extent and level of HPS risk as seen for 1994, 1998, and 1999 (Figures 1 and 3B). The area of highest risk for 2006 was somewhat more restricted than seen in the previous years but was more extensive than for 1996. Thus, we anticipate 4-8 cases of HPS for this area during the 2006 season. In contrast, the predicted area of high risk in southern Colorado and northern New Mexico was greatly extended and intensified for 2006 (Figure 4B). Many of the moderately high risk areas in 2005 show a marked increase in risk for 2006, and relatively lower risk areas in 2005 show an increase to moderate-high risk category.

Sampling of *P. maniculatus* at two high risk locations in northern New Mexico (approximately 2,000 trap nights) located near Los Alamos and Taos showed a high prevalence of antibody positive mice during the past two years. Typical reports of the crude prevalence (numbers with detectable antibody/numbers of animals tested) in both short-term surveys and longitudinal studies ranges from 0-25% (Calisher et al. 2005; Mills et al. 1998). At the Los Alamos site, 271 *P. maniculatus* were tested for SNV antibodies during two time periods. Crude prevalences were 24% ($n = 60/249$) in mice tested by ELISA and 23% ($n = 5/22$) in another sample tested by immunoblotting. Sampling near the Taos location during spring 2006 indicated an even higher prevalence of 34.3% ($n = 12/35$) in mice tested by immunoblotting (MSB 145830-145850, 145852-145858, 145862-145868). A single *Peromyscus truei* (MSB 145851) was collected and also had antibodies cross-reactive with SNV. Anecdotal reports of large numbers of deer mice entering rural residences north of Albuquerque, New Mexico also have been obtained (Yates, pers. obs.; C. Hice, pers. comm.).

DISCUSSION

Results of the current study support the perspective that satellite imagery as a monitor of leading environmental conditions can be used to identify the location and extent of permissive sites for zoonotic pathogen transmission (Glass et al. 2000; Glass 2001; Ostfeld et al. 2005). The utility of satellite imagery in characterizing extensive portions of the landscape makes it feasible to examine large swaths of the environment and, consequently, widespread human populations. This capability is critical for many infectious diseases transmitted to humans from wildlife reservoirs or vectors because the numbers of human cases in any one location are often small and are subject to numerous social and behavioral activities that can modify risk, as well as broader-based environmental factors. For example, Reiter postulated that the use of air conditioning and the preference for indoor activities by people during prime mosquito activity periods modulated dengue virus transmission by mosquitoes in Laredo, Texas

compared to virus transmission in Nuevo Laredo, Tamaulipas (Reiter et al. 2003). Monitoring substantial portions of the human population is key to generating sufficient analytical power to identify environmental factors that increase disease risk, as well as having a meaningful public health impact. An additional benefit of satellite remote sensing is that the repeated monitoring of the environment allows for the (relatively) straightforward characterization of environmental changes that may drive changing patterns of disease risk (Ostfeld et al. 2005). If the environmental changes lead disease outbreaks by a sufficient time period, then their detection can be used to forecast times and places of increasing risk. By combining an accurate forecast of disease risk with information dissemination and communication to the at-risk population and state and local health authorities, disease acquisition may be interrupted and early recognition and diagnosis of disease may be enhanced.
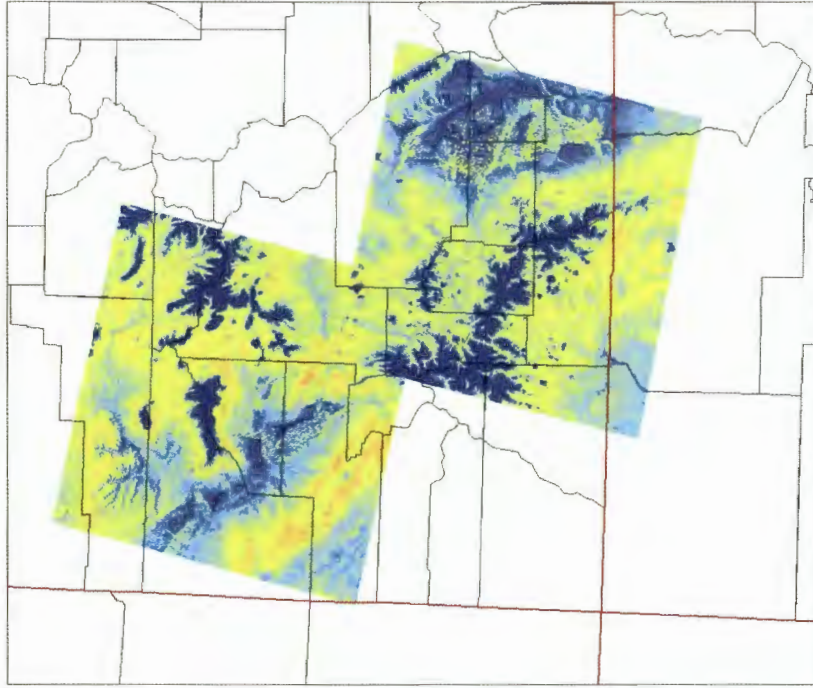
Figure 4B

2005 image/2006 risk
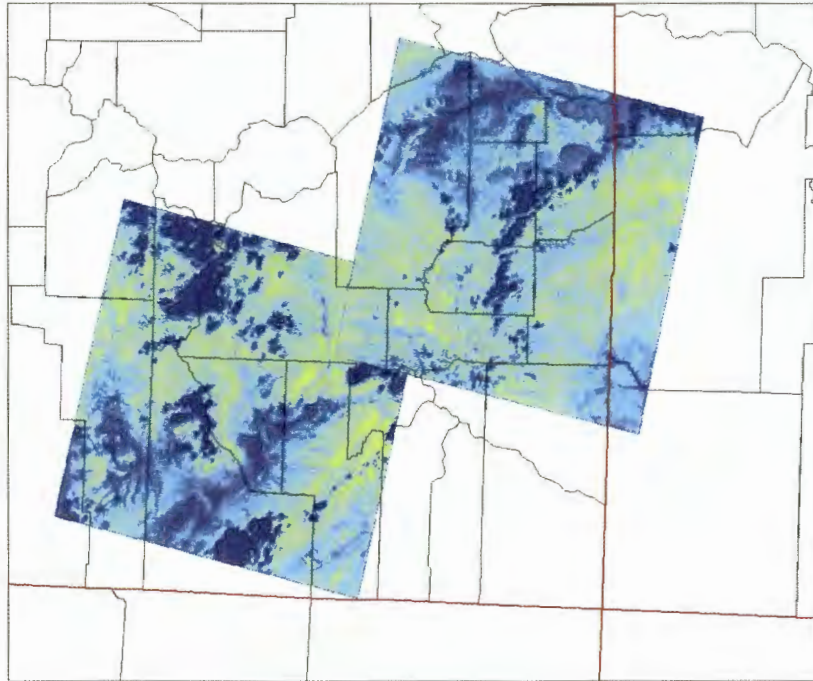
Figure 4A

2004 image/2005 risk

Figure 4. Logistic regression model of HPS risk in southern Colorado and north-central New Mexico. State boundaries (red lines) and county boundaries (black lines) are indicated for relationship to the study area shown in Figure 1. Risk is shown in 2005 (A) and 2006 (B), using Landsat TM imagery from 2004 and 2005, respectively. Risk in 2005 (A) was generally low, except for several diffuse areas of moderate–high risk in Colorado. In 2006 (B), HPS risk appears to be markedly increased in extent and intensity throughout much of the region. The color scale is as shown for Figure 1.

Analyses of satellite data in the years following the original detection of HPS in the southwestern U.S. identified two factors that supported the use of TM imagery for outbreak forecasting. First, the geographic extents of moderate and high risk areas, as identified on the risk maps generated from the logistic regression algorithm of the imagery, corresponded with the numbers of HPS cases seen in the following years (Figure 1). Second, throughout the 1990s, the cases occurred in the proportions expected in low, moderate, and high risk areas set by the ROC during the original analyses (Figure 2). Thus, the geographic extent of higher risk areas was related to the total numbers of HPS cases expected the following year and the cases were distributed among low, moderate, and high risk areas in the proportion expected by the ROC. This indicates the model was robust across multiple years, spanning much of that decade.

When the multi-year regional drought was interrupted in 2004-05, there was marked concern that HPS cases would increase, associated with the amelioration of environmental stressors that would cause a trophic cascade (Yates et al. 2002). To evaluate this possibility, longitudinal sampling of small mammals was continued in a limited number of locations (Yates et al. 2002). This approach was limited both by the number of locations that could be monitored by field crews, as well as the short lead-time for warning caused by the need to process animals in the field and test collected specimens for evidence of SNV infection in near-real time. However, satellite imagery indicated that, with the exception of a region in northeastern Arizona, much of the Four Corners area remained at low risk for HPS. The occurrence of a geographic cluster of four HPS cases only in the single, discrete high risk region of northeastern Arizona during 2005 and no cases in the historically high risk areas of the region (Figure 3A) indicated that the satellite imagery analyses provided a substantial benefit to supplement traditional surveillance methods. Similarly, analyses of the imagery indicated that much of southern Colorado and north-central New Mexico should be at low risk in 2005, and indeed, the only four reported cases were located in focal high risk sites in southern Colorado (Figure 4A).

Risk assessment for zoonotic diseases with satellite imagery is not a replacement for careful documentation and characterization of materials obtained in ecological and survey field studies. Field work is critical for defining the key populations and species involved in pathogen transmission cycles, as well as the kinetics of pathogen transmission. At a minimum, biological materials are needed to establish the identity and prevalence of pathogens. Although in recent years many papers have addressed the importance of ecological interactions in disease systems (e.g., Ostfeld et al. 2005), almost none have dealt with the very important role that systematics collections play as sources of material and expertise for rapidly identifying the host species and determining the geographic and temporal ranges of emerging pathogens, as well as repositories where specimens can be maintained to confirm key portions of our understanding of transmission processes. For example, museum specimens that had been archived well in advance to the discovery of any hantavirus (much less SNV) allowed researchers to document that SNV was an unrecognized circulating virus in *P. maniculatus* for many years before HPS was identified, and therefore SNV was a newly recognized rather than newly developed pathogen (Yates et al. 2002). Similarly, museum specimens were instrumental in showing that *Borrelia burgdorferi*, a bacterium responsible for some Lyme disease, was an enzootic agent in North America for nearly a century before the disease was recognized (Marshall et al. 1994). Thus, systematics collections serve an important role in providing a historical context for the patterns of disease emergence.

Systematics collections also play a key role by maintaining voucher materials that can be used to re-examine interpretations of the data as our knowledge evolves. Archiving of small mammal specimens collected during the original HPS outbreak investigation in 1993 made it possible to confirm that *P. maniculatus* was the reservoir species for SNV and that infection (as determined by the amplification of SNV nucleic acids from stored tissues) in other species was rare – most likely resulting from spillover from the primary host. These, and similar data, have led to the perspective of a coevolutionary relationship between hantaviruses and their rodent hosts (Yates et al. 2002). Similarly, the retention of voucher specimens has allowed us to demonstrate that sibling species of *Calomys* account for the distribution of Machupo virus in South America (Ruedas et al. 2000). The failure of surveillance studies to obtain and properly maintain speci-

mens and ancillary data in appropriate facilities limits the utility of the data and calls into question the interpretation of results that are difficult to re-evaluate.

Interpretation of environmental conditions with satellite imagery allows us to extrapolate our knowledge of disease systems based on in-depth local studies by identifying where and when environmental conditions similar to the local studies occur. In this paper, our analyses indicate that landscape level surveillance with satellite imagery, coupled with epidemiologic analyses, generate a robust result that characterize the suitability of the environment for HPS cases nearly a year in advance of the transmission season. The current imagery indicates that 2006 should experience a return to the numbers of HPS cases that have not been observed since the late 1990s in the Four Corners area (Figure 1 and Figure 3B). However, we do not anticipate numbers of HPS cases approaching those seen in 1993, when the disease was first recognized. More significantly, imagery for southern Colorado and north-central New Mexico indicate a substantial increase in the geographic extent and level of risk for this area compared to 2005 (Figure 4).

The increased risk level predicted by this study is notable in that it occurs to the east of the region traditionally considered as the major epicenter of HPS in the southwestern U.S. The analyses indicate that large portions of the environment in this area have a signature similar to those differentiating HPS locations from sites where people did not acquire HPS. The short-term survey sampling of reservoir populations in north-central New Mexico also indicates there is a general agreement between the application of the risk algorithm to this area and the presence of a high proportion of SNV infected *P. maniculatus* – much as was observed in the Four Corners area (Glass et al. 2002). This suggests that as a characterization of environmental permissiveness, our analyses may be generalized outside of the Four Corners area.

Extending a forecast east of the Four Corners region is more or less problematic depending on the detail of the forecast that is required. An estimate of the absolute numbers of HPS cases expected for the region is unlikely to be successful at this time because of a lack of knowledge about historical case distributions in this area. If the numbers and locations of cases during previous years were available and were coupled with TM imagery from past years, we could bracket the expected numbers of cases as we have done for the Four Corners area where substantially more epidemiologic data have been available. However, such data were not available for the current analysis.

We believe the current strategy remains useful for the Four Corners region because it has not experienced major demographic changes that substantially altered human population abundance or spatial distribution since the original case-control study was undertaken. The use of the control population in the study design helps identify the differences in environmental signatures between sites where people became infected and where they did not, at least for the population monitored by the health clinics during the outbreak. The biological interpretation of these differences is discussed elsewhere. The clinics used for the control population had seen HPS patients and primarily drew patients from rural backgrounds. As such, the controls may not be characteristic of the population as a whole, making estimates of the incidence rate for the entire population impossible to estimate. However, our goal is not to estimate absolute incidence but rather to estimate the change in the odds of HPS for individuals living within the region and who experienced particular environments (as measured by TM 5 imagery the previous year). As such, the controls did correspond to the population that was observed to be at highest risk at the time of the original outbreak (Childs et al. 1995). To the extent that most attempts to prevent rodent ingress into rural housing are unsuccessful (Hjelle and Glass 2000), additional social/ethnic aspects of the bias in the original sampling may not be too great if rural populations, generally, are the primary populations that are likely to be exposed to SNV (Childs et al. 1995). Additionally, concerns of design bias in sampling the human population are mitigated by previous studies (Glass et al. 2002) that showed the high risk areas identified using the risk algorithm with the Landsat TM imagery also identified areas with large numbers of SNV-infected *P. maniculatus*, especially if these high risk areas persisted for at least two consecutive years. Ongoing, more extensive studies confirm this relationship in the Four Corners area (Hice et al. 2005).

As we extend the geographic region surveyed by this imagery, estimating human risk becomes more challenging for several reasons. The total rural population abundance and its geographic distribution in southern Colorado and northern New Mexico are difficult to assess. Thus, the population at risk is unknown. One approach for estimating the human population at risk would be to use high spatial-resolution imagery (< 4 m) to locate and enumerate rural housing in this area and then estimate the expected numbers of individuals per unit, but this was considered impractical given the time constraints of the study.

The effect of the size of the at-risk population on the numbers of expected cases is straightforward. For example, elevation above 2094 m is a risk factor for HPS (Glass et al. 2000), and other authors (Douglas et al. 2005) have demonstrated that for HPS, as with all other diseases, defining the population at risk affects the estimates of incidence and prevalence of disease. Incidence and prevalence differ from the absolute numbers of cases by taking into account the possible numbers of individuals at risk (Mausner and Kramer 1985). If all of the high risk areas in 2006 occur at higher elevations (Figure 4B), and only a few individuals reside there, then few cases, in absolute numbers, would be found even if a high proportion of that population (high prevalence/incidence) were affected. Thus, two areas could have a similar number of cases of disease (the desired prediction), but differ in their incidences by having differences in the sizes of their at risk populations. This outcome was observed during a study of Lyme disease in Baltimore County, Maryland (Glass et al. 1992). The numbers of cases were less common in the northern portion of the county than in the southern portion, but the incidence of disease was substantially elevated in the northern portion. This result was attributable to the lower human population size in the northern portion of the county, which offset the increased per capita risk for the area. In this situation, a case-control study design also was used to successfully identify a suite of environmental risk factors for that disease and to generate a risk map. In the following year, individuals were more than 16 times as likely to acquire Lyme disease

in predicted high risk areas, even though, again, the absolute numbers of cases were smaller (Glass et al. 1995).

Thus, the analysis of TM imagery for SNV identifies locations that have environmental signatures that are suitable for infected *P. maniculatus*, but the size of the at-risk human population will be important in determining the numbers of HPS cases that occur. Other social and behavioral factors are considered less important in this system because current strategies to reduce or eliminate exposures in high risk areas appear to be unsuccessful (Hjelle and Glass 2000). Thus, to a first approximation, the numbers of cases will be a reflection of the *P. maniculatus*-human transmission and the human population in the stratified low, moderate, and high risk areas (Childs 2004; Ostfeld et al. 2005).

A more general interpretation of the 2006 risk map for southern Colorado and north-central New Mexico is that the suitability of environmental conditions for HPS in the region has strengthened for the upcoming season compared to the previous year. The areas that were at moderate-high risk in 2005 (Figure 4A) remain at the same or higher levels in 2006 (Figure 4B). Areas that were low-moderate risk in 2005 have environmental characteristics increasingly associated with HPS. Even in the absence of a widespread HPS outbreak throughout the region, the areas that experienced HPS cases in 2005 also will be susceptible in 2006, with a higher likelihood of transmission. Additional areas in the western and southern portions of the region that were at moderate risk in 2005 also appear to be suitable for HPS cases this year even though no cases were reported in 2005.

The analysis suggests that current guidelines for the public to help reduce risk and minimize contact, as well as reminders for health care providers to consider HPS in a differential diagnosis (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5109a1.htm), should receive attention after a period of relatively low transmission of SNV in this region.

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