Confronting data sparsity to identify potential sources of Zika virus spillover infection among primates

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ABSTRACT
The recent Zika virus (ZIKV) epidemic in the Americas ranks among the largest outbreaks in modern times. Like other mosquito-borne flaviviruses, ZIKV circulates in sylvatic cycles among primates that can serve as reservoirs of spillover infection to humans. Identifying sylvatic reservoirs is critical to mitigating spillover risk, but relevant surveillance and biological data remain limited for this and most other zoonoses. We confronted this data sparsity by combining a machine learning method, Bayesian multi-label learning, with a multiple imputation method on primate traits. The resulting models distinguished flavivirus-positive primates with 82% accuracy and suggest that species posing the greatest spillover risk are also among the best adapted to human habitations. Given pervasive data sparsity describing animal hosts, and the virtual guarantee of data sparsity in scenarios involving novel or emerging zoonoses, we show that computational methods can be useful in extracting actionable inference from available data to support improved epidemiological response and prevention.

1. Introduction
In one of the largest zoonotic disease outbreaks in modern times, the American Zika virus epidemic spread from Brazil to more than 30 surrounding countries in South and Central America (hereafter, the Americas). Zika virus is one of several flaviviruses transmitted to humans by mosquito vectors, which cause several zoonotic diseases (yellow fever, Dengue, St. Louis encephalitis, Japanese encephalitis, and West Nile). The species in which these viruses are maintained in the wild (sylvatic reservoirs) are thought to be distinct from species that maintain flaviviruses transmitted primarily by tick vectors (e.g., leading to Kyasanur Forest disease, Powassan, and Omsk hemorrhagic fever among other zoonoses). Compared to the other mosquito-borne flaviviruses, American Zika virus was relatively understudied, and is thought to have infected over half a million people in the latest outbreak, causing neurologic disorders in over 3600 infants to date (Mitchell, 2016). While this Zika virus epidemic was de-categorized as a public health emergency of international concern in November 2016, the long-term public health and societal consequences of endemic Zika virus infection in the Americas could be substantial. In addition to teratogenic effects presenting as microcephaly and other serious brain anomalies, congenital Zika syndrome comprises a broad suite of abnormalities of vision, hearing, muscle tone, and joint movement (Baud et al., 2017). The immediate costs of outbreak response, via increased vector control and screening pregnant women, will be further extended by costs accumulating over the long-term to support a generation of...
children with lifelong neurologic and developmental disorders, musculoskeletal deformities, and associated disabilities including blindness. These disorders are likely to strain a limited health care system, especially in countries where resources for the disabled are already limited.

Zika virus (ZIKV) was first discovered in a sentinel rhesus macaque (Macaca mulatta) in Uganda. Like other mosquito-borne flaviviruses (e.g., yellow fever virus, West Nile virus), ZIKV originated (and persists today) in a paleotropical sylvatic (wild) cycle involving non-human primate species (hereafter, *primates*) and forest-living *Aedes* mosquitoes (Bueno et al., 2016). These ancestral sylvatic strains spilled over into a transmission cycle maintained in humans and anthropophilic mosquitoes (e.g., dengue virus), thereby moving into global circulation. Primates acting as virus reservoirs or amplifying hosts can transmit Zika virus to human populations via competent mosquito vectors that feed on both human and non-human hosts (Fig. 1) (Althouse et al., 2018; Evans et al., 2017; Kuno et al., 2017). In addition to proximity with hosts of the sylvatic cycle, flavivirus spillover events are likely to be influenced by changing ecological patterns (e.g., climate warming) that support increasing vector population abundance, or increasing proximity of humans to sylvatic hosts (Kilpatrick and Randolph, 2012).

Mosquito-borne zoonoses repeated spillover to humans (e.g., West Nile and yellow fever) are best managed via multi-faceted control efforts that simultaneously address human susceptibility, vector abundance, and sylvatic sources of infection (Kilpatrick and Randolph, 2012). For example, vaccine therapy has proven remarkably effective for yellow fever, achieving close to 100% efficacy with a single vaccination that may confer lifelong immunity (Gotuzzo et al., 2013). Yet, outbreaks of yellow fever occur with regularity due to incomplete vaccine coverage in humans and repeated spillover infection from multiple sylvatic sources of infection, including non-human primates (Hanley et al., 2013). Thus, even if vaccine coverage and vector control were highly efficient, the successful mitigation of ZIKV and other mosquito-borne flaviviruses may still depend on effectively managing viral spillover from persistent sylvatic species that transmit infection to humans (Althouse et al., 2016; Bueno et al., 2016). Recent theoretical work exploring ZIKV risk in the Americas suggests a high probability of ZIKV being maintained by relatively small populations of susceptible primates – with as few as 6000 individuals and 10,000 mosquitoes, a sylvatic cycle would maintain a steady pool of infected hosts to facilitate repeated spillover transmission to humans (Althouse et al., 2016).

A critical question is whether and in which species ZIKV will establish a sylvatic cycle in its new range in the Americas. Identifying which species are most likely to serve as reservoirs is paramount for targeting surveillance, especially in regions where biodiversity is exceptionally high. Fundamentally, the ability for primate hosts to support and sustain a sylvatic virus cycle is at least partially dependent on biologically encoded interactions between hosts and pathogens. In hosts, intrinsic traits - for example, basal metabolic rates, traits indicating a ‘slow’ vs. ‘fast’ pace of life (e.g., litter sizes, reproductive rates), behavior, and biogeography – are readily observable features that distinguish one host species from another, but also recapitulate an unobservable evolutionary history underlying the capacity of certain species to perpetuate zoonotic pathogens (Han et al., 2016a). This general pattern, that organismal traits can serve as useful indicators of zoonotic capacity, has been supported by various studies; For example, Cable et al. linked host metabolic rates to rates of pathogenesis across multiple hosts and multiple zoonoses (Cable et al., 2007); Han et al. (a) showed that traits associated with a fast life history strategy were more common in rodents known to be reservoirs of zoonotic disease (Han et al., 2015); and (b) utilized organismal trait information to predict novel bat hosts of filoviruses like Ebola (Han et al., 2016b), predictions which were subsequently validated by independent field surveillance (Goldstein et al., 2018; Yang et al., 2017).

Like many zoonotic disease systems, the Zika virus system suffers from data sparsity. Among global primates, only two species have been confirmed positive for Zika virus, and an incomplete understanding of primate biology and ecology, even for relatively common species, limits our ability to make data-driven decisions about surveillance and spillover prevention. Here, we leverage intrinsic biological features of the world’s primates together with data on which primates have tested positive for six mosquito-borne flaviviruses. To overcome data sparsity in both primate traits and ZIKV positivity, we apply a multiple imputation approach and a Bayesian multi-label machine learning approach. Applied in tandem, these methods preserve biological dependency patterns among species traits and leverage information on primate hosts known to be positive for mosquito-borne flaviviruses to identify particular species whose intrinsic trait profiles suggest a high probability of serving as hosts for ZIKV and other mosquito-borne flaviviruses.

### 2. Methods

We compiled data on intrinsic traits (a.k.a. features) describing all primate species (sample size *n* = 376) from PanTHERIA, of which 18 species were confirmed (in peer-reviewed publications available at the time this study was undertaken) as reservoirs of one or more of six mosquito-borne flaviviruses (FLAV) with non-human mammalian reservoirs according to the GIDEON database (Berger, 2005; Jones et al., 2009). FLAV-positivity for all positive primate species is summarized in Table 1. At the time of analysis, mosquito-borne flaviviruses include the...
The datasets generated during and/or analysed during the current study are available in the Figshare repository, https://doi.org/10.6084/m9.figshare.5459176.v1. Code to reproduce these analyses are available at https://github.com/shubhobm/Predict-zika-res.

### Table 1

<table>
<thead>
<tr>
<th>Species</th>
<th>FLAV positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alouatta caraya</td>
<td>SLEV, YFV</td>
</tr>
<tr>
<td>Alouatta seniculus</td>
<td>YFV</td>
</tr>
<tr>
<td>Callithrix jacchus</td>
<td>ZIKV</td>
</tr>
<tr>
<td>Cebus apella</td>
<td>YFV</td>
</tr>
<tr>
<td>Cebus libidinoussl</td>
<td>ZIKV</td>
</tr>
<tr>
<td>Cercocebus ays</td>
<td>WNV</td>
</tr>
<tr>
<td>Chlorocebus aethiops</td>
<td>ZIKV</td>
</tr>
<tr>
<td>Erythrocebus patas</td>
<td>ZIKV</td>
</tr>
<tr>
<td>Lemur catta</td>
<td>YFV</td>
</tr>
<tr>
<td>Macaca fascicularis</td>
<td>DENV, JEV</td>
</tr>
<tr>
<td>Macaca fuscata</td>
<td>JEV</td>
</tr>
<tr>
<td>Macaca leonina</td>
<td>DENV, JEV</td>
</tr>
<tr>
<td>Macaca mulatta</td>
<td>WNV</td>
</tr>
<tr>
<td>Macaca nemestrina</td>
<td>DENV, JEV, WNV</td>
</tr>
<tr>
<td>Macaca sinica</td>
<td>DENV</td>
</tr>
<tr>
<td>Macaca sylvius</td>
<td>WNV</td>
</tr>
<tr>
<td>Mandrillus sphinx</td>
<td>WNV, YFV</td>
</tr>
<tr>
<td>Pithecus pithicus</td>
<td>YFV</td>
</tr>
<tr>
<td>Saginus midas</td>
<td>YFV</td>
</tr>
<tr>
<td>Trachypithecus cristatus</td>
<td>DENV</td>
</tr>
</tbody>
</table>

dengue viruses (all serotypes; DENV), yellow fever virus (YFV), St. Louis encephalitis (SLEV), Japanese encephalitis (JEV), and West Nile virus (WNV). In this database, a reservoir is defined as a species for which there is public health consensus that some populations maintain continuous infection and may therefore serve as the source of spillover infection to human populations. This definition excludes species that suffer acute disease-induced mortality, sentinel species, and laboratory-infected animals that are not known to be infected in the wild (Holzmann et al., 2010). However, species that have been converted and those testing positive for antibodies against mosquito-borne flaviviruses are included, as are species that are sampled from captive colonies or species that are most likely only incidentally infected (e.g., WNV). We label all such species as positive for mosquito-borne flaviviruses (“FLAV +”, or “flavivirus positivity”) in this analysis, though clearly the wide variation in definitions means that our label combines species that are susceptible or competent for infection together with species that are true reservoirs. Among these 6 mosquito-borne viruses, only three are currently recognized as having primate reservoirs contributing to a sylvatic transmission cycle (YFV, DENV, ZIKV). We expanded this to the more conservative list of six flaviviruses to borrow information across diseases, thus augmenting the otherwise very sparsely labeled dataset of FLAV + primates available for applying our machine learning algorithm. Moreover, the public health consequences of this approach, namely, labeling a FLAV- species as FLAV+ (type I error), was preferred to the alternative (inflating type II error, i.e., failing to predict FLAV + primate species). Among the 18 primate species that were FLAV + in this dataset, two species are confirmed reservoirs of ZIKV (Chlorocebus aethiops and Erythrocebus patas). Both of these species are Old World (paleotropical) primates found in the Sahel and Sudan-Guinea grassland biomes across northern Africa.

Our initial data set on primate characteristics contained 50 features for 376 species. These features describe various aspects of host species including their ecology (e.g., social group size, terrestriality, age to sexual maturity), physiology (e.g., metabolic rate, neonate size), biogeography (e.g., geographic range area, home range size), etc (Supplementary Tables S1 for variable names and definitions). However, not all features were known for all species, even though primate are among the best-studied mammal groups. Upon filtering this dataset to remove sparse features (variables with data missing for more than 80% of species), as well as extremely understudied species (data present for fewer than two features) and Homo sapiens, our final dataset contained 33 features for 364 primate species. In this matrix, approximately one third of species (34.9%) was missing data for one or more features. We imputed these missing trait data using the Multiply Imputed Chained Equations (MICE) method (Penone et al., 2014; Raghunathan et al., 2001). This method retains biological relationships while reducing bias compared to the common practice of dropping those species that are missing data from the analysis, even when there is underlying structure in missing data (i.e., data are not missing completely at random) (Penone et al., 2014). Given a set of initial values for a given species, the MICE method predicts missing entries of a particular feature by iteratively leveraging the information available across the other variables, thus preserving biological dependency patterns among features. This process is repeated until the entries across a number of imputed datasets reach a stable distribution, indicated by the value of the Gelman-Rubin R statistic being less than 1.1 (Gelman and Rubin, 1992).

We obtained ten such imputed datasets from the original data matrix and applied a recently developed supervised learning method, Bayesian Multi-label Learning via Positive Labels (BMLPL), to build predictive models (Rai et al., 2015). This method achieves superior performance in settings where the goal is to assign a subset of labels to samples in a highly sparse matrix with correlated labels. In our study, seropositivity of primate species to any of 6 mosquito-borne flaviviruses comprises species-level vectors of binary labels that are highly correlated (phylogenetically), where the labels (seropositive status) are highly sparse, especially for Zika virus. Using BMLPL, we leveraged correlations between labels by simultaneously modeling as binary responses the host status for all 6 major mosquito-borne flaviviruses across all primate species, and considering species-level features as predictors.

We applied BMLPL to each of the ten imputed data matrices, and calculated probability of each primate species being a reservoir of ZIKV by taking the mean of predicted probabilities across these ten models.
classification task was therefore to identify those species with and without an intrinsic capacity to carry ZIKV infection based on trait similarities. An AUC = 1.0 for any classification model indicates that the model is able to distinguish perfectly between classes across all samples. Our model achieved an AUC of 0.96 when trained on the full data for all 364 primates included in our study (Fig. 2, top left). The cross-validation process gives a better idea about how the model performs when predicting the risk of an undetected primate being a ZIKV reservoir. To do this, the BMLPL method was tasked with predicting reservoir probabilities for primates that are in one of the 10 cross-validation folds using a model trained on the other nine folds. This was repeated for samples in all folds, and then averaged over the 10 imputed datasets, achieving prediction accuracy (measured by AUC) of 0.82 (Fig. 2, top right).

For each primate species, we report a ZIKV reservoir risk score (i.e., the probability of testing positive for ZIKV (ZIKV+)) and the corresponding percentile of this risk compared to all other primates (Table 2, Supplementary Table S2). The model assigned high risk scores to the majority (13 of 18) of primate species that are known reservoirs of other mosquito-borne flaviviruses (Fig. 2, bottom panel). However, for five of these 18 species (Fig. 2, bottom panel, red points), the cross-validated risk scores were low, indicating that in the absence of a priori confirmations as flavivirus-positives, deficiencies in basic biological data about these species would have precluded our capacity to identify them as posing a risk of carrying mosquito-borne flaviviruses.

In the Americas, we identify six species that were at or above the 90th percentile probability of being ZIKV+ (Table 2, Supplementary Table S2). None of these species have yet tested positive for ZIKV. Moreover, three species have yet to test positively for any mosquito-borne flavivirus (Cebus albifrons, the white-fronted capuchin; Saimiri boliviensis, the black-capped squirrel monkey; Cebus capucinus, the white-faced capuchin). The model identified 29 species spanning sub-Saharan Africa, India, and Southeast Asia that were at or above the 90th percentile probability of ZIKV positivity (Fig. 3). While we discuss species comprising the 90th percentile probability in more detail below, this probability cutoff was chosen arbitrarily and additional species fall just below this cutoff (e.g., six neotropical species within the 85th percentile (mean score > 0.228): Cebus olivaceus, Alouatta seniculus, Cebus apella, Saimiri boliviensis, Ateles paniscus, and Chiropotes albinasus). The full list of primate species and their associated scores for FLAV positivity can be found in Table S2. In addition, the geographic ranges of all confirmed and predicted Zika-positive primate species are plotted in Fig. 3, which is also available as an interactive map at

Table 2

<table>
<thead>
<tr>
<th>Species</th>
<th>Status</th>
<th>Percentile risk ZIKV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cebus apella</td>
<td>YFV+</td>
<td>94.7</td>
</tr>
<tr>
<td>Cebus albifrons</td>
<td>Undetected</td>
<td>97.3</td>
</tr>
<tr>
<td>Alouatta seniculus</td>
<td>YFV+</td>
<td>95.9</td>
</tr>
<tr>
<td>Alouatta caraya</td>
<td>YFV+, SLEV+</td>
<td>94.2</td>
</tr>
<tr>
<td>Saimiri boliviensis</td>
<td>Undetected</td>
<td>92.9</td>
</tr>
<tr>
<td>Cebus capucinus</td>
<td>Undetected</td>
<td>90.7</td>
</tr>
</tbody>
</table>
The five most influential features for predicting ZIKV positivity (in descending order of relative importance) are maximum latitude, body mass, interbirth interval, age at first birth, and maximum longitude. Relative importance for all the features can be found in Fig. 7 (c) of the Supplementary Methods S3.

5. Discussion

In the Americas, Zika virus efforts have shifted from a state of emergency response to a longer-term goal of ZIKV control and eradication. The likelihood of achieving these goals depends fundamentally on whether ZIKV has spilled back from the predominantly human-centered transmission cycle to establish a persistent sylvatic cycle (Althouse et al., 2016). Our model leveraged information describing biological, ecological, and life history characteristics of primates to predict the zoonotic capacity in some species to serve as suitable reservoirs for ZIKV. On the basis of high-level features alone, our model was able to distinguish primate species that were positive for mosquito-borne flaviviruses with 82% accuracy and identified particular species with high risk of ZIKV positivity. While there are relatively few species that have been found FLAV+, and even fewer species that
have been found ZIKV+, these species are broadly distributed geo-
graphically and overlap in some places with dense human population
centers.

In the Americas, there were five species with risk scores in the 90th
percentile. The proximity of these species to human settlements and
opportunities for human contacts at high frequencies suggests prior-
itzing them for ZIKV surveillance in the Americas. The tufted capuchin
(Cebus apella), the Venezuelan red howler (Alouatta seniculus), and the
white faced capuchin (Cebus capucinus) are exceptionally well-adapted
to co-existing in dense human settlements, with some populations of the
white faced capuchin considered to be commensal with humans
(McKinney, 2011). In the neotropics, the Venezuelan red howler
monkey (Alouatta seniculus) and the spider monkey (Saimiri boliviensis)
are hunted for bushmeat in parts of their range, while the tufted capu-
chín and the white fronted capuchin (Cebus albifrons) are commonly
kept as pets and are hunted for live trade export (Peres, 2000; Peres and
Dolman, 2000). Although the hunting pressure on black howlers
(Alouatta caraya) is somewhat lower compared to the capuchins, this
species has frequent contact with livestock arising from a combination
of diminishing natural habitat and the encroachment of agricultural
land into patchily deforested areas (Crockett, 1998).

Neotropical primates with the highest ZIKV + risk scores are all
relatively common species that are predominantly arboreal. This hab-
itat stratification between humans (terrestrial) and non-human pri-
mates (arboreal) may suggest that spatial segregation will reduce spil-
lower risk to humans. However, ZIKV was first isolated from a forest-
dwelling mosquito vector (Aedes africanus) caught in the forest canopy
as well as on the ground (Haddow et al., 1964). Moreover, Evans et al.
assigned high likelihoods of ZIKV competence to a number of forest-
dwelling primatophilic mosquito based on shared traits with known
flavivirus vectors (Evans et al., 2017). ZIKV was recently isolated from
one of these species, Culex quinquefasciatus, which easily adapts to both
forested and human altered landscapes (Song et al., 2017). Thus, in
addition to controlling Aedes aegypti vectors that are predominantly
responsible for human-to-human transmission, surveillance should ex-
pand to consider other possible vector species that may perpetuate a
sylvatic cycle and play a role in spillover transmission in the long-term
(Evans et al., 2017).

We observed patterns of geographic overlap between predicted
ZIKV + primates and human cases in Central and South America that
suggest particular species that may be further prioritized for ZIKV
surveillance to assess possible spill-back from humans (Fig. 3; https://
smajumdar.shinyapps.io/Zika_risk_map/) (Messina et al., 2016). The
geographic ranges of two monkey species (Alouatta palliata, ZIKV + risk
score = 86.8; Ateles geoffroyi, ZIKV + risk score = 71.3) overlap with all
recorded human ZIKV cases (as of January 2016) in Mexico, Guatemala,
El Salvador, Honduras, Nicaragua, and Panama (Messina et al., 2016).

Similar geographic overlaps are apparent in the paleotropics. For ex-
ample, in addition to one known ZIKV reservoir (Erythrocephus patas) in
Uganda, there are four primate species with high ZIKV + risk scores
whose ranges overlap with human cases of ZIKV (Papio anubis, risk
score = 97.4; Colobus guereza, risk score = 94.8; Chlorocebus pygery-
thrus, risk score = 92.4; Galago senegalensis, risk score = 83) (Supple-
mentary Table S2; ZIKV + NHPs in https://smajumdar.shinyapps.io/
Zika_risk_map/). Surveillance efforts could additionally be prioritized by
species’ proximity to centers of human population density, or to
zones of high activity/traffic (border crossings, where there can be
high, but transient, human density). In light of ongoing transmission in
southeast Asia, the current outbreak of Zika virus in India (“WHO | Zika
virus infection: India,” 2018), and recent evidence that the American
strain of Zika virus is more efficiently transmitted by Aedes aegypti than
the Asian strain (Pompon et al., 2017), species-specific predictions of
primate reservoirs for Zika virus may also aid in prioritizing ongoing
ZIKV surveillance in Asia for both old and new virus strains. Similarly,
improving ZIKV surveillance within its native range (Africa) will vali-
date and improve model predictions for ZIKV as well as the other
mosquito-borne flaviviruses. Multiple data streams that include, for
example, locations of known and potential human cases, and data-
driven predictions of both mosquito vectors and ZIKV + primates may
combine to offer more immediately actionable insight to ZIKV man-
agement, which may be especially important given the long periods of
latent ZIKV infection observed in primate hosts (Hirsch et al., 2017)
and the potential for underreported latency in humans (Cardona-Ospina
et al., 2018).

Unsurprisingly, the variables that were most important for model
accuracy included those delimiting known geographic range limits of
primate species, with ZIKV + probability increasing for species with
ranges limits in the paleotropics (i.e., Africa, where ZIKV + primate
species occur) (partial dependence plots in Supplementary Fig. S4).
Primates who are ZIKV + tend to have a slightly larger body size as
adults compared to ZIKV- species. We also find that ZIKV + species
tend to give birth earlier in life, with shorter intervals between births,
compared to ZIKV- primate species. There are many reasons these traits
may be related to ZIKV positivity. For example, small species may have
greater ZIKV competence (viral amplification leading to higher titers of
circulating virus) due to a relative lack of adaptive immunity, which is
expensive to maintain and therefore represents an energetic trade-off
with reproductive investments. On the other hand, larger species may
invest more heavily in adaptive immune responses, leading to greater
tolerance to flavivirus infections (persistent infections without detri-
mental effects), a strategy that may also be advantageous for con-
tending with a greater diversity of parasites encountered over longer
lifespans. Tests of such hypotheses require more specific data collec-
tion, for example, on comparative immunology in ZIKV + species that
differ in size and rate of fitness output and species’ investments that
affect near vs. long-term fitness (Zuk and Stoehr, 2002; Lochmiller and
Derenberg, 2006).

While our modeling approaches successfully assigned high risk
scores to most of the species for which there was prior evidence of FLAV
positivity (Fig. 2), they could not compensate for extreme data-defi-
ciency. For instance, when we employed the ten-fold cross-validation
process by re-labeling FLAV + species in each holdout fold as FLAV-

 observes model-assigned risk scores, we found that some confirmed
FLAV + species were still assigned relatively low risk scores (Fig. 2,
bottom two panels), likely due to the large percentage of trait data that
were imputed for very common species such as Lemur catta (ring-
tailed lemur), Sanguinus midas (golden-handed tamarin), and Alouatta
caraya (black howler monkey) (Fig. 2, red dots). Likewise, with FLAV
positivity, predictions from the BMLPL model depend on a number of
latent variables that are fixed in the beginning of the modeling process,
and we found little variation in predictions across models that varied in
the number of latent variables (considering from one to six latent
variables). This suggests that the primate species identified by our Zika-
specific model should also be considered as having a high probability of
being positive for one or more of the other five mosquito-borne flavi-
viruses included in our analysis. The sparsity of positive labels meant
that a true external validation, where the model is built on a (larger)
subset of the samples and then validated on the remaining samples,
would not be very informative. In such scenarios, 10-fold cross vali-
dation provides a more accurate estimate of out-of-sample predictive
capability of BMLPL compared to in-sample validation. While this va-
lidation approach is more appropriate for dealing with label sparsity,
when comparing predictive accuracy across models it is important to
note that models validated using in-sample cross-validation will gen-
erate higher AUCs compared to those validated using typical out-of-
sample procedures.

The limits imposed by a pervasive lack of basic biological in-
formation, even for very common species that frequently co-occur with
humans, underlie the predictive capability of more complex phenomena,
such as disease competence and spillover risk to humans (Han and
Drake, 2016). Here, we show that even in the presence of limited and
irregular species-level data, methodological and computational
advances can be leveraged to build predictive models that capitalize on existing species-level data while simultaneously supporting research to improve empirical baselines about sylvatic cycles of ZIKV and other zoonoses. Iterative feedbacks between modeling and empirical data collection will lead to long-term efficiency gains in the mitigation and prevention of zoonotic spillover infection to humans.

Author contributions

Generated idea (BH, KV, AM), designed the study (BH, KV, AM), collated data (BH), developed analytical methods (SM, FC, DW, KV), validated results (BH, FC, BG, AP, DW, KV), visualized data and results (SM, BG, AP), wrote the manuscript (BH, SM, KV), coordinated research activities (DW, KV, AM), and acquired funding (KV, AM, BH). All authors were involved in improving study design following interpretation of analyses, and in reviewing the final manuscript.

Competing interests

The authors declare no competing interests.

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Appendix S. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.epidem.2019.01.005.

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