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Drought and immunity determine the intensity of West Nile virus epidemics and climate change impacts

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The effect of global climate change on infectious disease remains hotly debated because multiple extrinsic and intrinsic drivers interact to influence transmission dynamics in nonlinear ways. The dominant drivers of widespread pathogens, like West Nile virus, can be challenging to identify due to regional variability in vector and host ecology, with past studies producing disparate findings. Here, we used analyses at national and state scales to examine a suite of climatic and intrinsic drivers of continental-scale West Nile virus epidemics, including an empirically derived mechanistic relationship between temperature and transmission potential that accounts for this spatial variability in vectors. We found that drought was the primary climatic driver of increased West Nile virus epidemics, rather than within-season or winter temperatures, or precipitation independently. Local-scale data from one region suggested this effect was due to changes in mosquito infection prevalence rather than mosquito abundance. In addition, human acquired immunity following regional epidemics limited subsequent transmission in many states. We show that over the next 30 years, increased drought severity from climate change could triple West Nile virus cases, but only in regions with low human immunity. These results illustrate how changes in drought severity can alter the transmission dynamics of vector-borne diseases.

1. Background

Climate change and emerging infectious diseases are predicted to have substantial impacts on human health [1,2]. However, predictions about how these threats will interact, and where disease risk will be greatest, have been the subject of substantial controversy [2–5]. Warming is most likely to increase disease risk in places where transmission is primarily limited by low temperatures [3–5]. However, public health efforts may limit the effects of climate on disease risk [6]. Similarly, precipitation and drought can have contrasting effects on vector population and host–vector dynamics [7], further complicating prediction efforts.

Although climate change impacts on disease have drawn substantial attention, acquired immunity also plays a large role in disease dynamics [8,9]. Even when herd immunity has traditionally been considered less important for disease transmission (e.g. in cases when seroprevalence is low, or for zoonotic pathogens for which humans are incidental hosts), host heterogeneity in risk of exposure to vectors can increase the effective immunity far above-measured levels [10]. The interaction of intrinsic and extrinsic factors makes it difficult to examine immunity or climate alone [11].

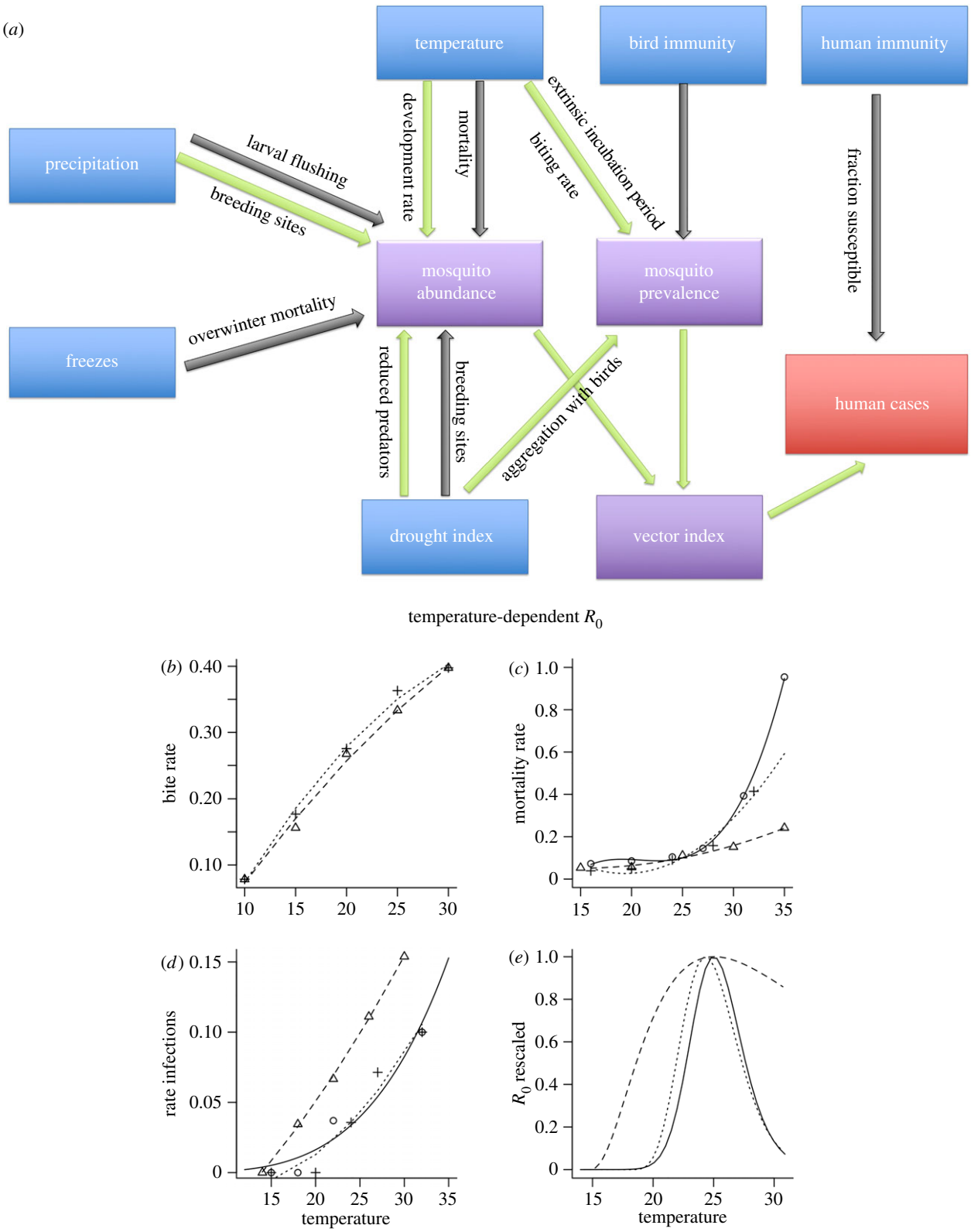

Figure 1. Mechanisms influencing WNV transmission. (*a*) Variables (blue/white) that influence human WNND cases (red/dark grey) either positively (green/white arrows) or negatively (black arrows), either directly, or via effects on mosquito populations (purple/light grey). Note that it is the product of mosquito abundance and prevalence that determine risk to humans. The fitted relationships for the temperature-dependent: (*b*) biting rate [15], (*c*) mortality rate [16,17], (*d*) and the inverse of the extrinsic incubation period [18,19] (L.D. Kramer and A.M.K., unpublished data) were used to generate (*e*) the resulting estimated relationships between temperature and partial-R_0 for West Nile virus for *C. tarsalis* (triangles, dashed lines), *C. pipiens* (circles, solid lines) and *C. quinquefasciatus* (cross-hatches, dotted lines; see Material and methods). (Online version in colour.) Q2

Predicting yearly epidemics of West Nile virus (WNV) is emblematic of these challenges. Since the introduction of WNV to the USA in 1999, there has been, on average, 50-fold interannual variation in the number of cases in each state where WNV occurs [12,13]. This enormous variability makes public health allocation decisions difficult, and highlights the utility of accurate predictions of future case burdens [14].

Transmission of vector-borne pathogens like WNV is influenced by multiple climatic drivers (figure 1*a*). Temperature is hypothesized to have unimodal effects on transmission,

because increases in replication rates of pathogens and vectors are eventually overwhelmed by accelerating decreases in vector survival at high temperatures [5,20] (figure 1*b–e*). Similarly, increased precipitation could either increase or reduce mosquito abundance by creating breeding sites or flushing container-breeding mosquitoes, depending upon the intensity [21,22]. Additionally, mosquito populations could either decline during droughts due to reduced breeding habitat, or increase in abundance due to increased habitat quality or reduced predators [23]. Furthermore, drought—which is influenced by both precipitation and temperature—could increase WNV prevalence in mosquitoes via higher contact rates (because of host aggregation [24]), or higher vector-to-host ratios (due to drought-induced reductions in juvenile birds [25,26]).

Our analyses build upon previous studies of climate-WNV associations that were conducted over smaller state or county-level areas [7,27–31], for shorter periods of time [22,32,33], or that analysed dichotomized values of WNV [34,35]. We have added key mechanistic drivers including human population immunity and a temperature-dependent R_0, and we project WNV incidence, rather than changes in the distribution or probability of above-average years [32,35,36], or changes in vector populations [37] under future climate change. We analysed the intrinsic (immune) and extrinsic (climate) factors driving interannual variation in West Nile neuroinvasive disease (WNND) incidence across the continental USA since WNV introduction (1999–2013), and explored potential mechanisms by analysing vector transmission data from a WNV hotspot. State-level analyses allowed us to examine regional variation in WNV drivers that arise from varying host and vector ecologies and infection histories in different parts of the country. Specifically, we hypothesized that temperature would be most important at the colder edges of the vector distributions, and that immunity would be most important in states that had previously had large epidemics.

2. Material and methods

(a) Models

We fit annual numbers of human WNND cases, N, to the following model:

$$\mathrm{Ln}(N) = \mathrm{Ln}(N_0) + \lambda I + \alpha T + \omega P + \delta D + \gamma F, \tag{2.1}$$

where I is cumulative incidence (see the electronic supplementary material, figure S1), T is the value of the mosquito species-specific temperature-driven relative R_0 value (using mean May through August temperatures; see the electronic supplementary material), P is total May through August precipitation, D is average May through August values of the Palmer Drought Severity Index [38] and F is winter severity (freezes: the number of weeks in the previous winter with average temperature below 0°C). The parameters λ, α, ω, δ and γ are the fitted coefficients for these predictors.

We chose these weather factors because they were biologically relevant to vector and host species involved in WNV transmission, and they were correlated with WNV risk in previous local-scale studies [27,28,39]. There was relatively low correlation among these predictors; the maximum variance inflation factor was 2.17, below a suggested cut-off of 3 [40]. We used county-level values of these weather variables to create state-wide weighted averages, with counties weighted by the relative number of WNND recorded in each county between 1999 and 2009 (county-level WNND data after 2009 were not available from the CDC). We used precipitation and temperature data from May through August, because these are the months when the majority of WNV infective mosquitoes become infected [41].

We estimated three temperature-dependent R_0 relationships, one for each of the three dominant WNV mosquito vector species, using the fitted relationships for temperature-dependent biting rates, mortality rates and inverse of the extrinsic incubation period for *Culex tarsalis*, *C. quinquefasciatus* and *C. pipiens* (electronic supplementary material). To calculate the vector-specific temperature-R_0 curve shown in figure 1*e*, we derived the equation for effective reproductive ratio in a partially susceptible host population. We inserted the fitted relationships with temperature into the equation to estimate values of relative R_0 at a given temperature for each mosquito species, which we used in place of raw temperature values (electronic supplementary material).

We constrained the parameters for the slope of the relationship between log cases and both cumulative incidence (λ), and number of freezes (γ) to be negative and temperature-driven R_0 (α) to be positive to reflect the biological mechanisms these parameters represent. To fit this model at the national level, we used a generalized linear mixed effects model by penalized quasi-likelihood with a negative binomial distribution and log link, allowing the slope of the immunity term to vary as a random effect of state using function glmmPQL in the MASS package in R, v. 3.0.2. At the state level, we fit the same model (without the state random effects) using glm.nb in the MASS package. There was no evidence of significant temporal autocorrelation in the residuals of the fitted models. We excluded initial years in which human WNND was found in less than 30% of counties making up the final distribution in a state to ensure we analysed trends only after full establishment. We also excluded states with less than 10 total cases or less than 6 years of data. We performed analyses at the state level because this is the highest spatial resolution for which the CDC provides access to ArboNET data differentiated by case definition (e.g. fever, encephalitis, etc.). We calculated the relative importance of predictor variables based on the magnitude of coefficients of standardized (Z-transformed) predictor variables. We performed cross-validation of the fitted models by re-fitting the final models while excluding each year of data sequentially, and using the new fitted model to predict the excluded datapoints. We then generated a prediction accuracy value for each state (electronic supplementary material, table S2) as follows: Q1

$$P_{\mathrm{mod}} = 1 - \frac{\sum_{t=2}^{t} (P_t - C_t)^2}{\sum_{t=2}^{t} (C_{t-1} - C_t)^2}, \tag{2.2}$$

where t is the year, P is the predicted value and C is the number of cases.

(b) Historical meteorological and future climate data sources

To build our predictive models, we used bias-corrected daily minimum and maximum temperature and precipitation data from 1999 to 2013 in the National Centers for Environmental Prediction North American Regional Reanalysis (NARR) data [42]. Owing to biases in the NARR data that can affect the frequency of occurrence of critical biological thresholds [43], we bias-corrected temperature and precipitation variables at the monthly scale using Oregon State University's monthly PRISM climate data as our observational standard [44] (see the electronic supplementary material). To project the influence of future climate change on the prevalence of WNND cases, we used bias-corrected data from an ensemble of 10 realizations of the International Center for Theoretical Physics regional climate model ('RegCM4') [45] using the RCP8.5 scenario, which is the IPCC scenario that is most consistent with the recent trajectory of historical emissions ([46], electronic supplementary material). Bias correction with historically

observed standards assumes that the structure of biases in the historical period will remain similar in future projections [47].

(c) Future case projections

We generated projections for current and future numbers of WNND cases using fitted models that included only the significant predictors. We estimated mean current (MC) and extreme current (EC) cases by taking the mean (MC) and 95th percentile (EC) of projections for each year using the 1999–2013 bias-corrected NARR climate. For future projections, we estimated cases using climate data from the years 2036–2049 for each of the 10 climate model realizations in each year. We then averaged across years within each of the model realizations to get 10 projected values (one for each model realization), and calculated the mean (MF) and 95th percentile (EF) of those values. Error bars include both the standard error of the mean and the standard deviation of the residuals between current projected and actual numbers of cases nationally from 2003 to 2013 (after WNV had spread across the USA). Extreme outliers (e.g. values for Michigan and one model realization in Maryland) were excluded from the national case totals because they resulted from a non-asymptotic relationship between R_0 and incidence (see the electronic supplementary material).

(d) Local mosquito data

Mosquitoes were collected from 15 counties in Colorado between 2003 and 2008 using CDC light and hay-infusion baited gravid traps that were run one night per week from June to September. *Culex* mosquitoes were pooled by species and tested for WNV using reverse transcriptase polymerase chain reaction in pools of up to 50 [48]. To determine whether there were more human infections at a given level of entomological risk in the first year, when all humans were naive, as compared with subsequent years after immunity had built up, we tested for an effect of the density of infected mosquitoes (DIM) and year (either 2003, or all subsequent years combined) on the number of human WNND cases. To do this, we used a generalized linear mixed effects model with a negative binomial distribution and log link, treating county as a random effect, and using function glmmPQL in the MASS package in R, v. 3.0.2. We also used a generalized linear model to test for relationships between drought and vector abundance (using a negative binomial distribution) and vector WNV prevalence (using a binomial distribution) in each transmission season.

(e) Effective herd immunity

Previous research on fine-scale spatial variation in mosquito abundance suggests that 90% of transmission occurs in just 20% of locations for vector-borne infections (averaged from Woolhouse *et al*. [10]; figure 1*a*). While these data are for parasitic diseases within *Anopheles* mosquitoes, the general principle of heterogeneity has been found to be remarkably consistent across a range of disease systems [49]. If 90% of WNV-infected bites occur in a subset of 20% of a state's population, the effective herd immunity could be as much as 0.9/0.2, or 4.5 times, higher than the seroprevalence that is calculated by assuming that 100% of the population is at risk.

3. Results

Both intrinsic (immunity) and extrinsic (climate) drivers were important predictors of WNND incidence, with immunity and drought being the strongest predictors of the number of observed annual WNND cases at the national and state levels (figures 2 and 3; electronic supplementary material, S2–S6 and tables S1 and S2). Local data from Colorado, one of the states hit hardest by WNV, further support a mechanistic link between WNV incidence and drought and immunity. Drought was correlated with elevated infection prevalence in the two most important mosquito vectors in the state (*C. pipiens* and *C. tarsalis*), but was uncorrelated with mosquito abundance (electronic supplementary material, figure S7). Additionally, in the first year that WNV had spread across the full state of Colorado, when most of the population was naive, there were more human cases than expected for a given DIM [48] than in subsequent years (figure 3*c*; Year coeff. $= 1.7$, $t = 12.7$, $p < 0.001$; DIM coeff. $= 0.2$, $t = 13.8$, $p < 0.001$). For instance, when the DIM is one infected mosquito per trap-night, there were five predicted cases in the first year, compared with just one predicted case in subsequent years. Temperature-driven R_0 (calculated using May to September mean temperature), winter severity (no. of weeks below freezing) and total May-to-September precipitation were weakly significant predictors at the national level, and present in only 24%, 7% and 27% of states, respectively.

The explanatory power of state-level models was relatively high, except in the few states where variation in cases was uncorrelated with measures of climate and immunity. The null model was the best fit in states with relatively few cases (e.g. West Virginia and New Jersey), as well as in some large, climatically variable states (e.g. Texas, Arizona, New Mexico and Minnesota). Finer spatial-scale analyses of weather drivers in these larger states may reveal additional weather drivers whose effects may have been masked when averaged across a climatically variable state [27]. Additionally, some of the unexplained variation may be due to factors that we were unable to include in the model, such as vector control efforts, and changes in virus genetics, host resistance [50], or bird communities [51]. Models explained an average of 58% of the non-stochastic variance in the number of neuroinvasive WNV cases in the 38 states where the best model was not the null (electronic supplementary material, table S2). Similarly, cross-validation techniques using the model to predict data not used to build the model indicated that fitted models had a prediction accuracy of 65% across the 31 states where they were a better predictor than the null hypothesis value of the previous year's case burden (electronic supplementary material, table S2 and figure S8). Prediction accuracies were highest in states where immunity was a significant predictor. In addition, models for states where immunity was not significant occasionally predicted larger than observed epidemics in some years (electronic supplementary material, figure S8).

We used the fitted models described above, along with an ensemble of high-resolution climate model simulations [45], to estimate current and future WNND cases in each state. The models project an average of 991 ± 683 WNND cases each year under average current climate conditions and 2013 levels of acquired immunity, whereas up to 1331 ± 712 cases could occur in a relatively intense year (95th percentile of projected cases) driven by climate variation (figure 4*a*). Climate change is projected to nearly double the mean WNND burden (1814 ± 783 cases) by the mid-twenty-first century, while the 95th percentile is likely to increase by a factor of 2.5 (3297 ± 1123 cases), assuming current immunity levels and no viral evolution that substantially increases competence in hosts or vectors, or allows re-infection of previously exposed individuals.

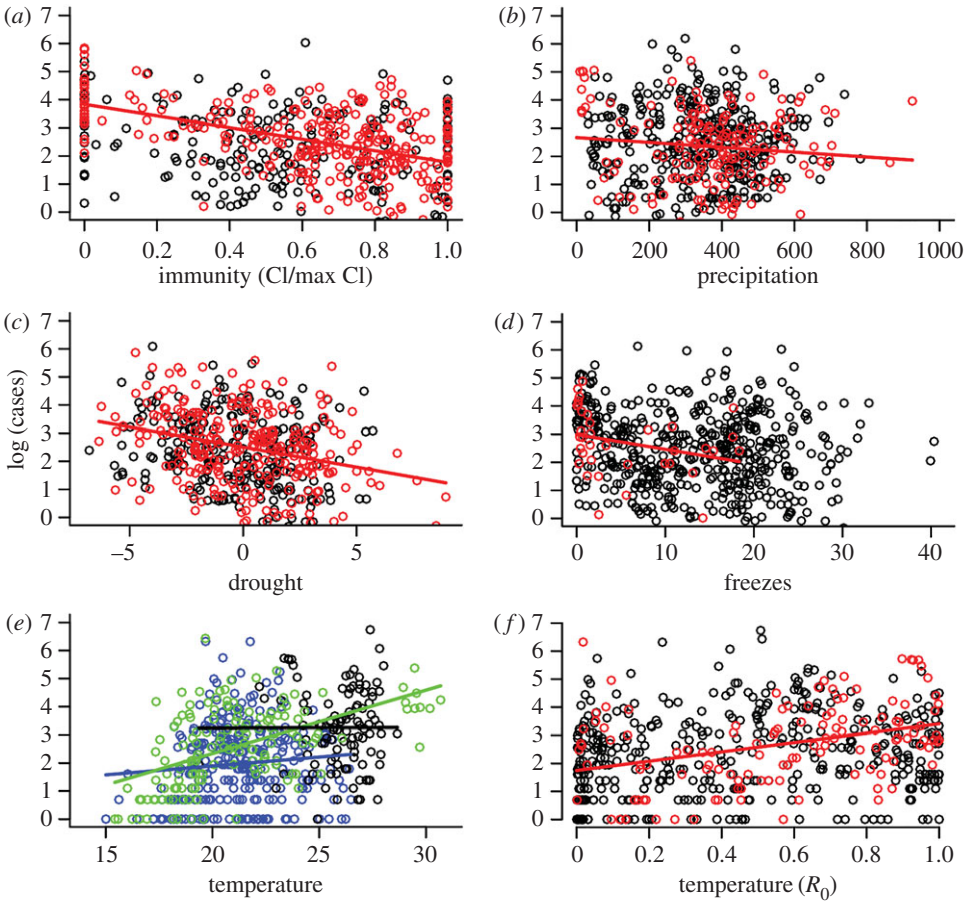

Figure 2. Climate and immunity correlations with annual state WNND cases. The effect of (*a*) immunity (cumulative incidence; coeff. = −2.05, $F_{1,300} = 96.42$, $p < 0.001$), (*b*) precipitation (coeff. = −0.0009, $F_{1,161} = 2.20$, $p = 0.14$), (*c*) drought (coeff. = −0.14, $F_{1,274} = 27.01$, $p < 0.001$), (*d*) winter severity (coeff. = −0.05, $F_{1,34} = 2.95$, $p = 0.09$), (*e*) temperature (PIP: coeff. = 0.06, $F_{1,276} = 2.58$, $p = 0.10$; TAR: coeff. = 0.22, $F_{1,144} = 53.59$, $p < 0.001$; QUI: coeff. = 0.002, $F_{1,104} = 0.0005$, $p = 0.98$) and (*f*) temperature modelled as the relative R_0 value at a given temperature (coeff. = 1.66, $F_{1,121} = 17.33$, $p < 0.001$) on the total logged number of WNND cases (adjusted for state random effects) in a given state and year (1999–2013). In (*a–d,f*), the filled points and fitted lines are univariate regressions for states in which that predictor was significant ($\alpha < 0.05$), while open points depict states in which the predictor is not present. In (*e*), crosses, open circles and triangles denote states where *C. tarsalis*, *C. pipiens* and *C. quinquefasciatus*, respectively, dominate transmission and the relationship is only significant for *C. tarsalis*. (Online version in colour.)

4. Discussion

WNV has been called 'unpredictable' because of enormous local and continental-scale variability in WNV incidence, and variation in avian host and mosquito vector ecology [14]. However, our results suggest that models that incorporate mechanistic hypotheses and both intrinsic and extrinsic drivers can improve the accuracy of predictions for complex multi-host, multi-vector pathogens like WNV. We found that the primary drivers of interannual variation in WNV across the USA include drought and immunity, and that increases in drought could potentially double WNV epidemic intensity nationally, with epidemics in areas of low immunity being even larger.

The projected future increase in WNV incidence is primarily due to a doubling of the drought index. The positive relationship between drought and WNV infection prevalence in Colorado mosquitoes suggests that drought alters transmission in this state not by reducing mosquito abundance, but by increasing infection prevalence. This could occur if lower avian reproduction [52] increases the vector-to-host ratio, or if patterns of host–vector contact are altered due to congregation [24] or avian stress [53]. Similarly, dry summer soil moisture conditions have been positively correlated with WNV prevalence in *Culex* mosquitoes in New York [39] as well as with spatial variation in the prevalence of the closely related Usutu flavivirus in *Culex* mosquitoes in Italy [54]. Increased aridity is projected in many regions of the USA in spite of increases in mean precipitation [55,56], highlighting the importance of considering moisture availability directly rather than relying on precipitation as a proxy measure, because precipitation alone was a poor predictor of WNV cases in most states.

The impact of immunity at both the national and state levels was evident through a large reduction in human cases in response to increasing cumulative incidence. At a local level, during the first year that WNND reached epidemic levels across Colorado (and a majority of humans were naive), the number of human cases for a given DIM was higher than in subsequent years (figure 3*c*). This difference in human cases at the same level of entomological risk suggests that human immunity rather than bird immunity was driving the decrease in incidence, because bird immunity can only affect human infections via mosquito infection, and this is already taken into account by using DIM as the predictor. Because humans are dead-end hosts for WNV, human immunity does not reduce transmission between mosquitoes and birds, but reduces human WNV cases by depleting the susceptible human population. Human immunity has frequently been dismissed as a factor in patterns of WNV

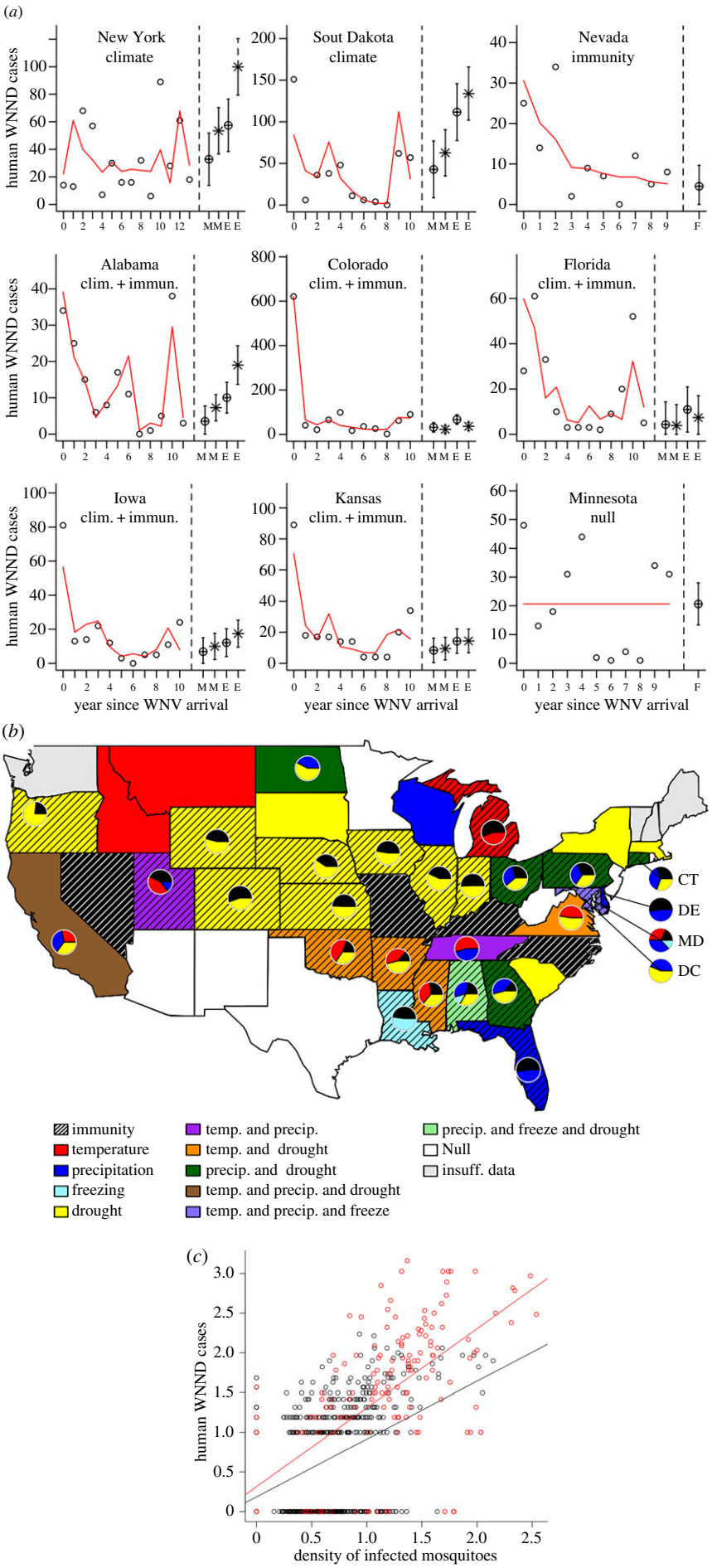

Figure 3. (*Caption opposite.*)

Figure 3. (*Opposite.*) Climate, immunity and WNND cases. (*a*) Yearly WNND cases and fitted model (line) in nine representative states, and projections of the number of future cases under mean (M) or extreme (E—95th percentile) climate conditions for either current (cross-hatch) or future (star) climate projections. Error bars include both the standard error of the mean projected values and the standard deviation of the residuals between current projected and actual values. (*b*) Colours/shading indicate the significant variables in the fitted models by state with pie-charts showing their relative importance. (*c*) Human WNND cases and abundance of infected mosquitoes in Colorado when all humans were naive (2003, filled points, coeff = 0.99, $F_{1,175} = 173.1$, $p < 0.001$) and in subsequent years (2004–2008, open points, coeff = 0.72, $F_{1,787} = 285.5$, $p < 0.001$). Variables were power transformed (1/4) to equalize leverage and linearize the relationship. (Online version in colour.)

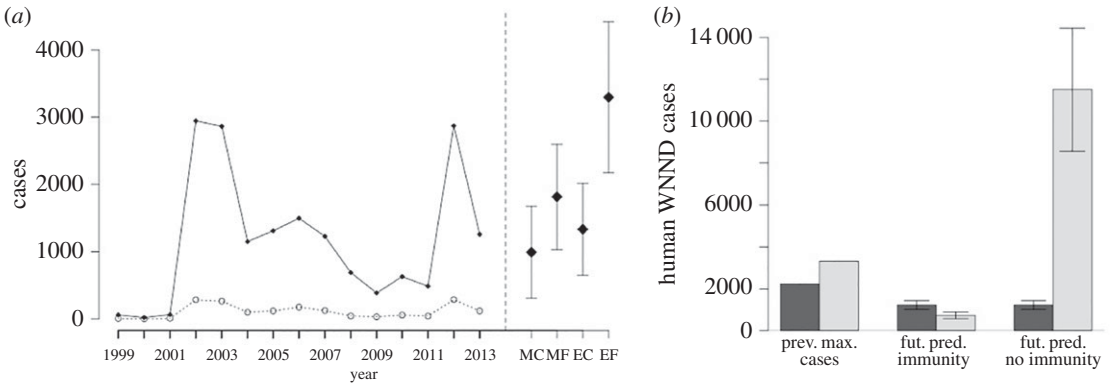

Figure 4. National historical and projected WNND cases. Interannual variation in human WNV encephalitis cases (filled circle, solid line) and deaths (open circle, dashed line) in the USA and projections of WNND cases under mean current (MC), extreme current (EC—95th percentile) mean future (MF) or extreme future (EF) conditions (*a*). Error bars include both the standard error of the mean projected values and the standard deviation of the residuals between current projected and actual values. Summed totals of current maximum number of yearly cases and projected future cases with and without immunity in states where immunity was (grey) or was not (black) significant (*b*). Q3

incidence, because estimates of population-wide seroprevalence are uniformly low (less than 14%) [57,58], indicating most of the population remains susceptible. However, heterogeneity in the risk of mosquito exposure means that only a small subset of the population is likely at risk for WNV, and the effective seroprevalence may be 4.5-fold higher [10] (see Material and methods).

Although increased drought severity could approximately double the number of WNV cases annually, the projected increase would have been even greater without the limiting role of immunity, and the actual increase in WNV incidence may be smaller if herd immunity in human populations increases before drought increases. Without the observed build-up of human immunity, the number of projected future cases would be sixfold higher nationally ($11\,673 \pm 1921$ cases; figures 2 and 4*b*). Nonetheless, despite accumulating immunity, the number of WNND cases in each state does not always decline over time, because entomological risk varies from year to year [48], and both transmission and the build-up of herd immunity is spatially heterogeneous. In states where acquired immunity is already relatively high, intense future WNND epidemics are unlikely (electronic supplementary material, figure S9). For example, no more than 18 WNND cases are projected to occur in Wyoming under current or future climate conditions, which is less than 20% of the previous maximum of 92 cases. This state recorded only five and two WNND cases in 2014 and 2015, respectively, years not used to build the models [59]. However, states with above-average immigration or birth rates, or changes in human behaviour or age structure that increase their exposure to vectors or likelihood of developing the neuroinvasive form of the disease [57], and thus the at-risk population, could lead to more cases than projected in regions with high estimated immunity. Additionally, viral mutations that would allow WNV to re-infect previously exposed individuals could limit the effect of immunity. Furthermore, in states where there was little evidence of accumulated human immunity, such as Virginia, models suggest that up to 163 WNND cases could occur in an extreme year under future climate conditions, which is over eight times higher than the previous maximum of 20 cases. Our results thus identify states most likely to experience future WNV epidemics, which could be used by federal agencies to allocate control resources, as they did during the initial years following WNV invasion. An important question for future research is how population immunity in humans will change with variable yearly WNV transmission, and population turnover through births, deaths and immigration.

The effects of temperature observed at finer spatial scales in other studies may be less apparent at the state level, or after accounting for immunity, and warmer temperatures may increase incidence in areas that are on the edge of being suitable for transmission [27,35] (electronic supplementary material), as is the case for malaria [4]. Previous studies have demonstrated positive effects of temperature and precipitation on vector abundance [60–63], which can affect vector-borne disease transmission [64]; however, the strong effects of drought on infection prevalence in mosquitoes may overwhelm these effects in some areas (electronic supplementary material).

The anticipated regional variability in which predictors were most important can be partly explained by vector ecology and geography. For instance, temperature-driven R_0 values tended to explain WNND cases in the northern range limits of *C. quinquefasciatus*, as well as in several far northern states (e.g. Montana, Idaho and Michigan). This is consistent with the idea that warming at northern boundary edges will push temperatures into more optimal ranges for transmission [3,5]. Winter freezes appear to be most important in extreme southern portions of the USA where vectors may be more

poorly adapted to freezing temperatures. Precipitation had generally positive effects in the eastern portion of the country, and negative effects in the west, consistent with the idea that container-breeding mosquitoes may benefit from rain that fills containers, while excessive rain could increase predation on wetland-breeding mosquitoes [22,23]. Additionally, irrigation appears to influence WNV transmission in the western USA [65], which could alter the importance of rainfall for mosquito populations there.

Our model, which incorporated laboratory-derived temperature–R_0 relationships, and immunity as a key intrinsic driver, has allowed us to uncover the dominant drivers of WNV incidence across the USA. The projected future increase in WNV in the USA indicates a need for increased resources for WNV surveillance, mitigation and research, at a national scale. Furthermore, our results can improve allocation of WNV mitigation resources in areas where drought is a major driver, because the drought index (PDSI) is calculated in real-time. Because drought severity is likely to alter transmission of other vector-borne diseases in ways not captured by analyses of temperature and precipitation alone, variations and changes in drought severity should be examined as potential drivers of disease dynamics.

Ethics. The research described conforms to all current laws of the USA, and no vertebrate animals were used in this research.

Data accessibility. Human WNND case data are available from the Centers for Disease Control at https://www.cdc.gov/westnile/statsmaps/finalmapsdata/index.html. The NARR climate data are available from NOAA at http://www.esrl.noaa.gov/psd/. Colorado mosquito analysis data are available through Dryad at http://dx.doi.org/10.5061/dryad.t0027 [66].

Authors' contributions. A.M.K., S.H.P., N.S.D. and L.D.K. conceived the ideas. S.H.P. and A.M.K. performed analyses and wrote the manuscript. M.A. and D.R. performed the climate model simulations. D.E.H., N.S.D., M.A. and D.R. performed the climate analyses, and contributed to the text. All authors gave final approval for publication.

Competing interests. We declare we have no competing interests.

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References

1. Morens DM, Folkers GK, Fauci AS. 2004 The challenge of emerging and re-emerging infectious diseases. *Nature* **430**, 242–249. (doi:10.1038/nature08554)
2. Patz JA, Campbell-Lendrum D, Holloway T, Foley JA. 2005 Impact of regional climate change on human health. *Nature* **438**, 310–317. (doi:10.1038/nature04188)
3. Altizer S, Ostfeld RS, Johnson PTJ, Kutz S, Harvell CD. 2013 Climate change and infectious diseases: from evidence to a predictive framework. *Science* **341**, 514–519. (doi:10.1126/science.1239401)
4. Siraj AS, Santos-Vega M, Bouma MJ, Yadeta D, Ruiz Carrascal D, Pascual M. 2014 Altitudinal changes in malaria incidence in highlands of Ethiopia and Colombia. *Science* **343**, 1154–1158. (doi:10.1126/science.1244325)
5. Rogers DJ, Randolph SE. 2000 The global spread of malaria in a future, warmer world. *Science* **289**, 1763–1766. (doi:10.1126/science.289.5478.391b)
6. Lindgren E, Andersson Y, Suk JE, Sudre B, Semenza JC. 2012 Monitoring EU emerging infectious disease risk due to climate change. *Science* **336**, 418–419. (doi:10.1126/science.1215735)
7. Shaman J, Day JF, Stieglitz M. 2005 Drought-induced amplification and epidemic transmission of West Nile virus in southern Florida. *J. Med. Entomol.* **42**, 134–141. (doi:10.1603/0022-2585(2005)042[0134:DAAETO]2.0.CO;2)
8. Rohani P, Earn DJ, Grenfell BT. 1999 Opposite patterns of synchrony in sympatric disease metapopulations. *Science* **286**, 968–971. (doi:10.1126/science.286.5441.968)
9. Wearing HJ, Rohani P. 2006 Ecological and immunological determinants of dengue epidemics. *Proc. Natl Acad. Sci. USA* **103**, 11 802–11 807. (doi:10.1073/pnas.0602960103)
10. Woolhouse MEJ. 1997 Heterogeneities in the transmission of infectious agents: Implications for the design of control programs. *Proc. Natl Acad. Sci. USA* **94**, 338–342. (doi:10.1073/pnas.94.1.338)
11. Koelle K, Rodó X, Pascual M, Yunus M, Mostafa G. 2005 Refractory periods and climate forcing in cholera dynamics. *Nature* **436**, 696–700. (doi:10.1038/nature03820)
12. Petersen LR, Brault AC, Nasci RS. 2013 West Nile virus: review of the literature. *JAMA* **310**, 308–315. (doi:10.1001/jama.2013.8042)
13. Kilpatrick AM. 2011 Globalization, land use, and the invasion of West Nile virus. *Science* **334**, 323–327. (doi:10.1126/science.1201010)
14. Petersen L, Fischer M. 2012 Unpredictable and difficult to control—the adolescence of West Nile virus. *N. Engl. J. Med.* **367**, 1281–1284. (doi:10.1056/NEJMp1208347)
15. Reisen WK, Milby MM, Presser SB, Hardy JL. 1992 Ecology of mosquitoes and St. Louis encephalitis virus in the Los Angeles Basin of California, 1987–1990. *J. Med. Entomol.* **29**, 582–598. (doi:10.1093/jmedent/29.4.582)
16. Ciota AT, Matacchiero AC, Kilpatrick AM, Kramer LD, Matacchiero AMYC. 2014 The effect of temperature on life history traits of *Culex* mosquitoes. *J. Med. Entomol.* **51**, 55–62. (doi:10.1603/ME13003)
17. Reisen W. 1995 Effect of temperature on *Culex tarsalis* (Diptera, Culicidae) from the Coachella and San Joaquin valleys of California. *J. Med. Entomol.* **32**, 636–645. (doi:10.1093/jmedent/32.5.636)
18. Kilpatrick AM, Meola MA, Moudy RM, Kramer LD. 2008 Temperature, viral genetics, and the transmission of West Nile virus by *Culex pipiens* mosquitoes. *PLoS Pathog.* **4**, e1000092. (doi:10.1371/journal.ppat.1000092)
19. Reisen WK, Fang Y, Martinez VM. 2006 Effects of temperature on the transmission of West Nile virus by *Culex tarsalis* (Diptera: Culicidae). *J. Med. Entomol.* **43**, 309–317. (doi:10.1093/jmedent/43.2.309)
20. Mordecai EA *et al.* 2013 Optimal temperature for malaria transmission is dramatically lower than previously predicted. *Ecol. Lett.* **16**, 22–30. (doi:10.1111/ele.12015)
21. Koenraadt ACJM, Harrington LC. 2008 Flushing effect of rain on container-inhabiting mosquitoes *Aedes aegypti* and *Culex pipiens* (Diptera: Culicidae). *J. Med. Entomol.* **45**, 28–35. (doi:10.1093/jmedent/45.1.28)
22. Landesman WJ, Allan BF, Langerhans RB, Knight TM, Chase JM. 2007 Inter-annual associations between precipitation and human incidence of West Nile virus in the United States. *Vector Borne Zoonotic Dis.* **7**, 337–343. (doi:10.1089/vbz.2006.0590)
23. Chase JM, Knight TM. 2003 Drought-induced mosquito outbreaks in wetlands. *Ecol. Lett.* **6**, 1017–1024. (doi:10.1046/j.1461-0248.2003.00533.x)
24. Shaman J, Day JF, Stieglitz M. 2002 Drought-induced amplification of Saint Louis encephalitis virus, Florida. *J. Med. Entomol.* **8**, 575–580.
25. Hamer GL *et al.* 2008 Rapid amplification of West Nile virus: the role of hatch-year birds. *Vector Borne Zoonotic Dis.* **8**, 57–67. (doi:10.1089/vbz.2007.0123)
26. Kermack W, McKendrick A. 1927 A contribution to the mathematical theory of epidemics. *Proc. R. Soc. Lond. A* **115**, 700–721. (doi:10.1098/rspa.1927.0118)

27. Chung WM, Buseman CM, Joyner SN, Hughes SM, Fomby TB, Luby JP, Haley RW. 2013 The 2012 West Nile encephalitis epidemic in Dallas, Texas. *J. Am. Med. Assoc.* **310**, 297–307. (doi:10.1001/jama.2013.8267)
28. Ruiz MO, Chaves LF, Hamer GL, Sun T, Brown WM, Walker ED, Haramis L, Goldberg TL, Kitron UD. 2010 Local impact of temperature and precipitation on West Nile virus infection in *Culex* species mosquitoes in northeast Illinois, USA. *Parasit. Vectors* **3**, 19. (doi:10.1186/1756-3305-3-19)
29. Liu A, Lee V, Galusha D, Slade MD, Diuk-Wasser M, Andreadis T, Scotch M, Rabinowitz PM. 2009 Risk factors for human infection with West Nile Virus in Connecticut: a multi-year analysis. *Int. J. Health Geogr.* **8**, 67. (doi:10.1186/1476-072X-8-67)
30. Walsh MG. 2012 The role of hydrogeography and climate in the landscape epidemiology of West Nile virus in New York State from 2000 to 2010. *PLoS ONE* **7**, e30620. (doi:10.1371/journal.pone.0030620)
31. Shaman J, Day JF, Komar N. 2010 Hydrologic conditions describe West Nile virus risk in Colorado. *Int. J. Environ. Res. Public Health* **7**, 494–508. (doi:10.3390/ijerph7020494)
32. Semenza JC, Tran A, Espinosa L, Sudre B, Domanovic D, Paz S. 2016 Climate change projections of West Nile virus infections in Europe: implications for blood safety practices. *Environ. Health* **15**, 28. (doi:10.1186/s12940-016-0105-4)
33. Soverow JE, Wellenius GA, Fisman DN, Mittleman MA. 2009 Infectious disease in a warming world: how weather influenced West Nile virus in the United States (2001–2005). *Environ. Health Perspect.* **117**, 1049–1052. (doi:10.1289/ehp.0800487)
34. Manore CA, Davis JK, Christofferson RC, Wesson DM, Hyman JM, Mores CN. 2014 Towards an early warning system for forecasting human West Nile virus incidence. *PLoS Curr. Outbreaks* **2**, 1–21. (doi:10.1371/currents.outbreaks.f0b3978230599a56830ce30cb9ce0500.Abstract)
35. Hahn MB, Monaghan AJ, Hayden MH, Eisen RJ, Delorey MJ, Lindsey NP, Nasci RS, Fischer M. 2015 Meteorological conditions associated with increased incidence of West Nile virus disease in the United States, 2004–2012. *Am. J. Trop. Med. Hyg.* **92**, 1013–1022. (doi:10.4269/ajtmh.14-0737)
36. Harrigan RJ, Thomassen HA, Buermann W, Smith TB. 2014 A continental risk assessment of West Nile virus under climate change. *Glob. Change Biol.* **20**, 2417–2425. (doi:10.1111/gcb.12534)
37. Morin CW, Comrie AC. 2013 Regional and seasonal response of a West Nile virus vector to climate change. *Proc. Natl Acad. Sci. USA* **110**, 15 620–15 625. (doi:10.1073/pnas.1307135110)
38. National Climatic Data Center. See http://www7.ncdc.noaa.gov/CDO/CDODivisionalSelect.jsp#.
39. Shaman J, Harding K, Campbell SR. 2011 Meteorological and hydrological influences on the spatial and temporal prevalence of West Nile virus in *Culex* mosquitoes, Suffolk County, New York. *J. Med. Entomol.* **48**, 867–875. (doi:10.1603/ME10269)
40. Zuur AF, Ieno EN, Walker NJ, Saveliev AA, Smith GM. 2009 *Mixed effects models and extensions in ecology with R*. New York, NY: Springer.
41. ArboNET. See https://www.cdc.gov/westnile/resourcepages/survresources.html.
42. NARR. See http://www7.ncdc.noaa.gov/CDO/CDODivisionalSelect.jsp#.
43. Diffenbaugh NS, Scherer M. 2013 Using climate impacts indicators to evaluate climate model ensembles: temperature suitability of premium winegrape cultivation in the United States. *Clim. Dyn.* **40**, 709–729. (doi:10.1007/s00382-012-1377-1)
44. Prism. See http://www7.ncdc.noaa.gov/CDO/CDODivisionalSelect.jsp#.
45. Ashfaq M, Rastogi D, Mei R, Kao S-C, Gangrade S, Naz BS, Touma D. 2016 High-resolution ensemble projections of near-term regional climate over the continental U.S. *J. Geophys. Res.* **141**, 9943–9963. (doi:10.1002/2016JD025285)
46. Peters GP, Andrew RM, Boden T, Canadell JG, Ciais P, Le Quéré C, Marland G, Raupach MR, Wilson C. 2013 The challenge to keep global warming below 2°C. *Nat. Clim. Change* **3**, 4–6. (doi:10.1038/nclimate1783)
47. Horton DE, Harshvardhan, Diffenbaugh NS. 2012 Response of air stagnation frequency to anthropogenically enhanced radiative forcing. *Environ. Res. Lett.* **7**, 44034. (doi:10.1088/1748-9326/7/4/044034)
48. Kilpatrick AM, Pape WJ. 2013 Predicting human West Nile virus infections with mosquito surveillance data. *Am. J. Epidemiol.* **178**, 829–835. (doi:10.1093/aje/kwt046)
49. Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. 2005 Superspreading and the effect of individual variation on disease emergence. *Nature* **438**, 355–359. (doi:10.1038/nature04153)
50. Duggal NK *et al.* 2014 Evidence for co-evolution of West Nile virus and house sparrows in North America. *PLoS Negl. Trop. Dis.* **8**, e3262. (doi:10.1371/journal.pntd.0003262)
51. LaDeau SL, Kilpatrick AM, Marra PP. 2007 West Nile virus emergence and large-scale declines of North American bird populations. *Nature* **447**, 710–713. (doi:10.1038/nature05829)
52. Albright TP, Pidgeon AM, Rittenhouse CD, Clayton MK, Flather CH, Culbert PD, Wardlow BD, Radeloff VC. 2010 Effects of drought on avian community structure. *Glob. Change Biol.* **16**, 2158–2170. (doi:10.1111/j.1365-2486.2009.02120.x)
53. Gervasi SS, Burkett-Cadena N, Burgan SC, Schrey AW, Hassan HK, Unnasch TR, Martin LB. 2016 Host stress hormones alter vector feeding preferences, success and productivity. *Proc. R. Soc. B* **283**, 20161278. (doi:10.1098/rspb.2016.1278)
54. Calzolari M *et al.* 2012 Mosquito, bird and human surveillance of West Nile and Usutu viruses in Emilia-Romagna region (Italy) in 2010. *PLoS ONE* **7**, e38058. (doi:10.1371/journal.pone.0038058)
55. Diffenbaugh NS, Swain DL, Touma D. 2015 Anthropogenic warming has increased drought risk in California. *Proc. Natl Acad. Sci. USA* **112**, 3931–3936. (doi:10.1073/pnas.1422385112)
56. Dai A. 2010 Drought under global warming: a review. *Wiley Interdiscip. Rev. Clim. Change* **2**, 45–65. (doi:10.1002/wcc.81)
57. Petersen LR, Carson PJ, Biggerstaff BJ, Custer B, Borchardt SM, Busch MP. 2012 Estimated cumulative incidence of West Nile virus infection in US adults, 1999–2010. *Epidemiol. Infect.* **141**, 1–5. (doi:10.1017/S0950268812001070)
58. Murphy T, Grandpre J, Novick S, Seys S, Harris R, Musgrave K. 2005 West Nile virus infection among health-fair participants, Wyoming 2003: assessment of symptoms and risk factors. *Vector borne zoonotic Dis.* **5**, 246–251. (doi:10.1089/vbz.2005.5.246)
59. West Nile virus. See http://www.cdc.gov/westnile/.
60. Lebl K, Brugger K, Rubel F. 2013 Predicting *Culex pipiens/restuans* population dynamics by interval lagged weather data. *Parasit. Vectors* **6**, 1–11. (doi:10.1186/1756-3305-6-129)
61. Carrieri M, Fariselli P, Maccagnani B, Angelini P, Calzolari M, Bellini R. 2014 Weather factors influencing the population dynamics of *Culex pipiens* (Diptera: Culicidae) in the Po Plain Valley, Italy (1997–2011). *Environ. Entomol.* **5**, 482–490. (doi:10.1603/EN13173)
62. Karki S, Hamer GL, Anderson TK, Goldberg TL, Kitron UD, Krebs BL, Walker ED, Ruiz MO. 2016 Effect of trapping methods, weather, and landscape on estimates of the *Culex* vector mosquito abundance. *Environ. Health Insights* **10**, 93–103. (doi:10.4137/EHI.S33384.TYPE)
63. Ewing DA, Cobbold CA, Purse BV, Nunn MA, White SM. 2016 Modelling the effect of temperature on the seasonal population dynamics of temperate mosquitoes. *J. Theor. Biol.* **400**, 65–79. (doi:10.1016/j.jtbi.2016.04.008)
64. Guo S, Ling F, Hou J, Wang J, Fu G, Gong Z. 2014 Mosquito surveillance revealed lagged effects of mosquito abundance on mosquito-borne disease transmission: a retrospective study in Zhejiang, China. *PLoS ONE* **9**, e112975. (doi:10.1371/journal.pone.0112975)
65. DeGroote JP, Sugumaran R. 2012 National and regional associations between human West Nile virus incidence and demographic, landscape, and land use conditions in the coterminous United States. *Vector Borne Zoonotic Dis.* **12**, 657–665. (doi:10.1089/vbz.2011.0786)
66. Paull SH, Horton DE, Ashfaq M, Rastogi D, Kramer LD, Diffenbaugh NS, Kilpatrick AM. 2017 Data from: Drought and immunity determine the intensity of West Nile virus epidemics and climate change impacts. Dryad Digital Repository. (doi:10.5061/dryad.t0027)