1 **Downgrading disease transmission risk estimates using terminal importations**

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47   **Abstract**
48   As emerging and re-emerging infectious diseases like dengue, Ebola, chikungunya, and Zika
49   threaten new populations worldwide, officials scramble to assess local severity and
50   transmissibility, with little to no epidemiological history to draw upon. Standard methods for
51   assessing autochthonous (local) transmission risk make either indirect estimates based on
52   ecological suitability or direct estimates only after local cases accumulate. However, an
53   overlooked source of epidemiological data that can meaningfully inform risk assessments prior
54   to outbreak emergence is the absence of transmission by imported cases. Here, we present a
55   method for updating *a priori* ecological estimates of transmission risk using real-time importation
56   data. We demonstrate our method using Zika importation and transmission data from Texas in
57   2016, a high-risk region in the southern United States. Our updated risk estimates are lower
58   than previously reported, with only six counties in Texas likely to sustain a Zika epidemic, and
59   consistent with the number of autochthonous cases detected in 2017. Importation events can
60   thereby provide critical, early insight into local transmission risks as infectious diseases expand
61   their global reach.
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Introduction

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92   The explosive emergence of Ebola in West Africa in 2014 and Zika in the Americas in
93   2016 caught the global health community by surprise. Officials scrambled not only to control the
94   diseases at their source but also to anticipate and rapidly contain global transmission via
95   infected travelers (1,2). The rate at which a newly introduced infectious disease spreads can
96   vary enormously, depending on the physical and social environment. For example, serological
97   surveys of dengue virus (DENV) exposure on either side of the Texas-Mexico border indicated
98   far higher DENV exposure in the Mexican community despite virtually identical climatic
99   conditions and even higher mosquito abundance in the Texan community (3).
100   Epidemiological risk assessment--estimating the severity and transmissibility of a
101   threatening disease--can be vital to successful mitigation with limited resources. Historical
102   outbreak data can provide invaluable insight into future epidemic risk. However, for a disease
103   yet to arrive or that has just begun to spread, we necessarily borrow epidemiological data from
104   other populations or related diseases, or to indirectly assess risk based on environmental
105   suitability. For example, as the first importations of Zika virus (ZIKV) arrived in the US in 2016,
106   early attempts to determine the likelihood and rate of local transmission relied primarily on
107   dengue epidemiological data from regions with markedly different climatic and socioeconomic
108   conditions (4–6).
109   These risk assessments provide information regarding the reproduction number of a
110   disease (R_0)---the expected number of secondary human infections resulting from a single
111   human infection--- which provides a meaningful and predictive measure of local epidemiological
112   risk. In a naive population, R_0 indicates whether importations can potentially ignite local
113   epidemics; if so, it also provides insight into the probability, magnitude, and speed of spread
114   (7,8). Once a disease begins to spread, R_0 can be directly estimated from early case data (9).
115   Here, we introduce a method for estimating R_0 prior to an outbreak in populations that
116   face the ongoing threat of infected travelers from affected regions. This approach was motivated
117   by recent introductions of ZIKV into the continental US. As hundreds of cases arrived from
118   affected regions throughout the Americas, officials sought to estimate risks of autochthonous
119   (local) transmission and identify high risk regions in the southern US. However, given the
120   novelty of ZIKV and the large proportion of ZIKV cases that go undetected, early estimates had
121   high uncertainty (6,10,11). Our method harnesses importation data---individual cases that arrive
122   in a naive location with or without subsequently infecting others---to update *a priori* estimates of
123   R_0, while explicitly modeling case reporting uncertainty. As a case study, we use the almost
124   complete absence of secondary transmission following 298 importations of ZIKV into the state
125   of Texas in 2016 and 2017 to reduce and narrow local estimates of R_0.
126
127   **Methods**
128   We used a two-step procedure to estimate the monthly R_0 for each of the 254 Texas
129   counties (hereafter county-month R_0): (1) estimate *a priori* county-month R_0 distributions using
130   published ecological models of ZIKV transmission (4,6), and (2) using these as Bayesian priors,
131   generate posterior R_0 distributions based on reported importations and subsequent local
132   transmission.
133
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135 *Data*
136   We analyzed all ZIKV importations into Texas from January 2016 to September of 2017,
137 including the county and notification date. County-level purchasing power parity (PPP) in US
138 dollars (12); daily temperature data at a 5 km x 5 km resolution for 2016-2017 and historical
139 averages from 1960-1990 (13,14) were also used as inputs to the transmission risk model. For
140 each county and month, we averaged daily temperatures across all 5 km x 5 km grid cells
141 whose center fell within the county; we aggregated 5 km x 5 km mosquito (*Aedes aegypti*)
142 occurrence probabilities similarly (15). Data available doi:10.18738/T8/HYZ53B.
143   In all, six mosquito-borne, autochthonous cases of ZIKV were reported in Texas in 2016
144 and two were reported in 2017 (25). For updating R_0 estimates, we analyzed 2016 data and
145 assumed that two autochthonous cases were detected in Cameron County--one in November
146 and one in December 2016; we excluded four nearby cases discovered during the November
147 follow-up investigation, because our model does not incorporate active surveillance. As
148 sensitivity analyses, we re-estimated R_0 assuming that no cases were detected and that all six
149 cases were detected (Fig S7). For validating our estimates, we analyzed 2017 data and
150 considered only one of the two reported autochthonous cases, as the second case occurred
151 outside the timeline of our 2017 importation data.
152
153 *A priori county-month R_0 estimates*
154   Following Perkins et al (6), we estimated R_0 using the Ross-Macdonald temperature-
155 dependent formulation:

$$R_0(T) = m\frac{bca^2e^{-\mu(T)n(T)}}{\mu(T)\tau},$$

156
157 with parameters as defined in Table 1. We calculated relative abundance of the ZIKV vector
158 based on *Ae. aegypti* occurrence probabilities as -ln(1-occurrence probability), and interpret this
159 as a relative (rather than absolute) abundance, which is sufficient for our R_0 estimation (6). We
160 derived *a priori* county-month R_0 distributions by drawing 1,000 Monte Carlo samples from each
161 underlying parameter distribution, with the appropriate county and month data. Finally, we fit
162 gamma distributions to each probability distribution for use as an informative priors.
163
164 Table 1: Parameters of prior R_0 estimates.

Parameter	Description	Distribution	Value (CI)	Citation
b	Mosquito-to-human transmission probability	Constant	0.4	(16)
c/r	Human-to-mosquito transmission probability times the duration of human infectiousness	Constant	3.5	(17)
a	Mosquito biting rate	Constant	0.67	(18)
μ(T)	Mosquito daily mortality rate	Non-parametric GAM	0.115[1]	(19,20)

$n(T)$	Extrinsic incubation period in Mosquitoes	Exponential	6.1 (3.4, 9.9)[2]	(21)
m	Economic mosquito-human contact factor	Monotonic decreasing SCAM	Fit to monte carlo samples	(6)

165   1.   Fit to data from mark-recapture study occurring between 20-34 C
166   2.   At 30 C
167
168
169   *Autochthonous transmission likelihood*
170   Following (22), we developed a likelihood function describing the expected outbreak size
171   following an importation. We assumed that the secondary case distribution for each infected is
172   negative binomial with mean R_0, and dispersion parameter, k. Assuming all cases are detected,
173   the probability of an outbreak of chain size, j, is given by:

$$s(j, R_0, k) = \frac{\Gamma(kj+j-1)}{\Gamma(kj)\Gamma(j+1)} \frac{(R_0/k)^{j-1}}{(1+(R_0/k))^{kj+j-1}}$$

174
175   where $\Gamma(n) = (n-1)!$. However, not all cases are detected and the imported index case is always
176   detected and correctly classified as an importation, so the probability of detecting a chain of
177   size, j, from a given importation is given by:
178

$$s^*(j, R_0, k, p_d) = \sum_{l=j}^{\infty} s(l, R_0, k) \cdot \binom{l-1}{j-1} \cdot p_d^{j-1} \cdot (1-p_d)^{l-j}$$

179
180   where p_d is the case detection probability. Importantly, this allows for local, undetected cases.
181   We take the product of all likelihoods for each imported case as

$$L(\vec{O}|\alpha, \vec{R_0}, k, p_d) = \prod_{i=1}^{\text{length}(\vec{O})} s^*(O_i, \alpha R_{0_{\gamma_i, \omega_i}}, k, p_d)$$

182
183   where the vector, O, contains the observed outbreak sizes for each importation (terminal
184   importations have an outbreak size of one),   denotes the county (   )-month (   ) R_0 for the
185   location and time that the importation occurred, and α is a statewide scaling factor applied to
186   each   . The introduction of the state-wide scaling factor allows for localized importations to
187   inform statewide estimates, but assumes that biases in the *a priori* R_0 estimation procedure are
188   constant across counties and months. Details of simulations and validation of the likelihood can
189   be found in supplemental section I (Fig S1).
190
191   *Estimating the dispersion parameter*
192   The negative binomial dispersion parameter governs the variability in secondary cases
193   following each importation, with values near zero meaning that most importations yield few or no
194   cases while a few "superspreaders" produce many. We assume that ZIKV secondary case
195   distributions resemble that of dengue virus (DENV) (23). Padmanabha *et al.* describe the
196   relationship between regional R_0 and the percentage of DENV cases generating over 20

197 secondary infections (p_{20}), as $R_0 = 0.63 \times 100 \times (p_{20}) + 0.58$. We assumed that $p_{20} = $ 1e-8 for
198 $R_0 < 0.58$, and found that a single dispersion parameter captures this relationship for all R_0 values
199 and thus used k=0.12 for all analyses (Fig S2).
200
201 *Updating posterior R_0 estimates*
202   We estimated posterior distributions for α, and each county-month R_0 for each day with a
203 new importation between January 2016 and January 2017. We assumed a uniform prior for α of
204 U~(0,2), and used a blocked Gibbs sampling algorithm of MCMC. For each MCMC step we
205 provide the detected imported cases to date and propose each county-month R_0, a single α, and
206 a p_d. County-month R_0 proposals were normally distributed around the previous sample with
207 standard deviation of 0.1, α proposals were distributed U~(0,2), and we used a previously
208 estimated distribution for the reporting rate, $p_d \sim$ N(5.74%, sd=1.49%), which we assumed to not
209 vary spatiotemporally (24). We used the Metropolis-Hastings probability to accept or reject
210 proposals. Our chains consisted of 200,000 samples with a burn-in duration of 100,000; thinning
211 every 10 steps. Further algorithmic details and code are available on Github
212 (https://github.com/sjfox/rnot_updater).
213
214 *Validating posterior* county-month R_0 *estimates*
215   We derived the expected number of autochthonous cases from the importations data
216 through September of 2017 (at that time, the most recent importation was detected in mid-May)
217 and compared the estimates to the actual reported autochthonous cases. We integrated
218 uncertainty into our estimates by sampling from the posterior county-month R_0 distributions and
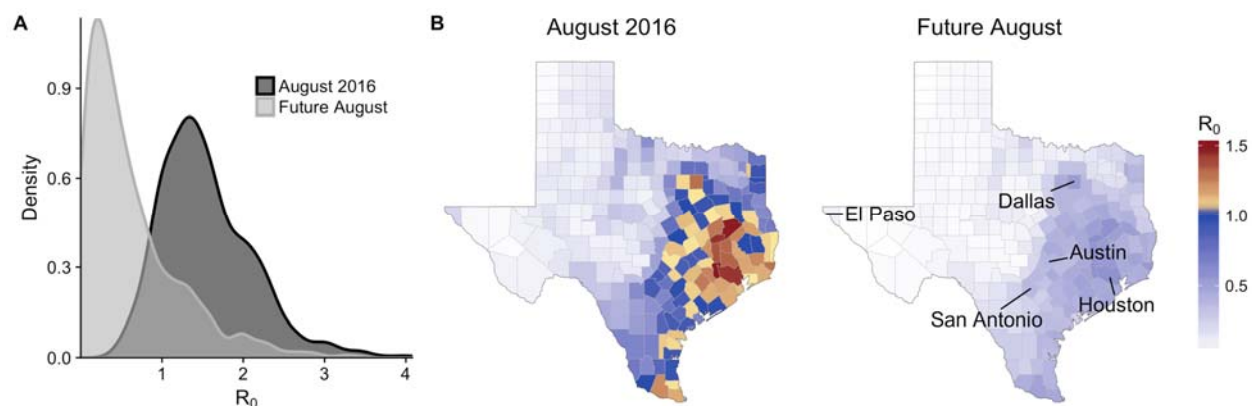219 simulating outbreaks accordingly (full details in supplemental section II).
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223 **Figure 1**: R_0 updating using importation data. Consider a hypothetical scenario in which the first
224 15 terminal ZIKV importations into Texas arrive in Harris County (which includes Houston)
225 during August 2016. **(A)** Estimated Harris County R_0 for August 2016 *a priori* (dark grey) and
226 after accounting for the 15 (light grey) terminal importations (Future August). **(B)** Median R_0
227 estimates for August before (August 2016) and following (Future August) the importation-based
228 update.
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231 **Results**

232 *Importation-based updates of transmission risk*

233   Hypothetically, suppose that the first 15 imported cases of Zika into Texas arrived in
234 August into Harris County (which contains Houston) without any detected autochthonous
235 transmission. Prior to these importations, environmental suitability models yielded a relatively
236 high local risk estimate with median Harris county R_0 above the epidemic threshold of one
237 (Figure 1A - dark grey). The lack of secondary cases following all 15 importations suggests that
238 R_0 may be lower. Indeed, our updated estimates suggest that the Harris county R_0 is likely
239 below one (Figure 1A - light grey). Our method leverages such county-level importation data to
240 update R_0 estimates throughout the state (via a scaling factor), based on the assumption that
241 any *a priori* biases will be similar across counties (Figure 1B).

242

243 *Baseline importation and transmission risks in Texas*

244   Prior to making importation-based updates, our initial median estimates of R_0 across
245 Texas' 254 counties in 2016 range from approximately 0 to 1.5 throughout the year with July
246 and August having the highest transmission risk (Figure 2A). Throughout the manuscript, we
247 conduct a one-sided test at a 1% significance level and thus consider counties with 99
248 percentiles (upper bounds) that include one to be at risk for an epidemic ($R_0 > 1$). Initial upper
249 bound estimates reach as high as three, and 119 (47%) of Texas counties are expected to be at
250 risk of a local outbreak in at least one month of the year (Figure 2A, S2). When we considered
251 historic average temperatures rather than 2016 temperatures, the projected 2017 risks were
252 consistently lower, with the largest differences occurring during the unseasonably warm 2017
253 winter (Fig S4). Case importations peaked in July, August, and September of 2016, with 164
254 (55%) of the 298 total 2016 importations arriving then (Figure 2B). The few detected
255 autochthonous cases occurred in November and December, when expected risk was relatively
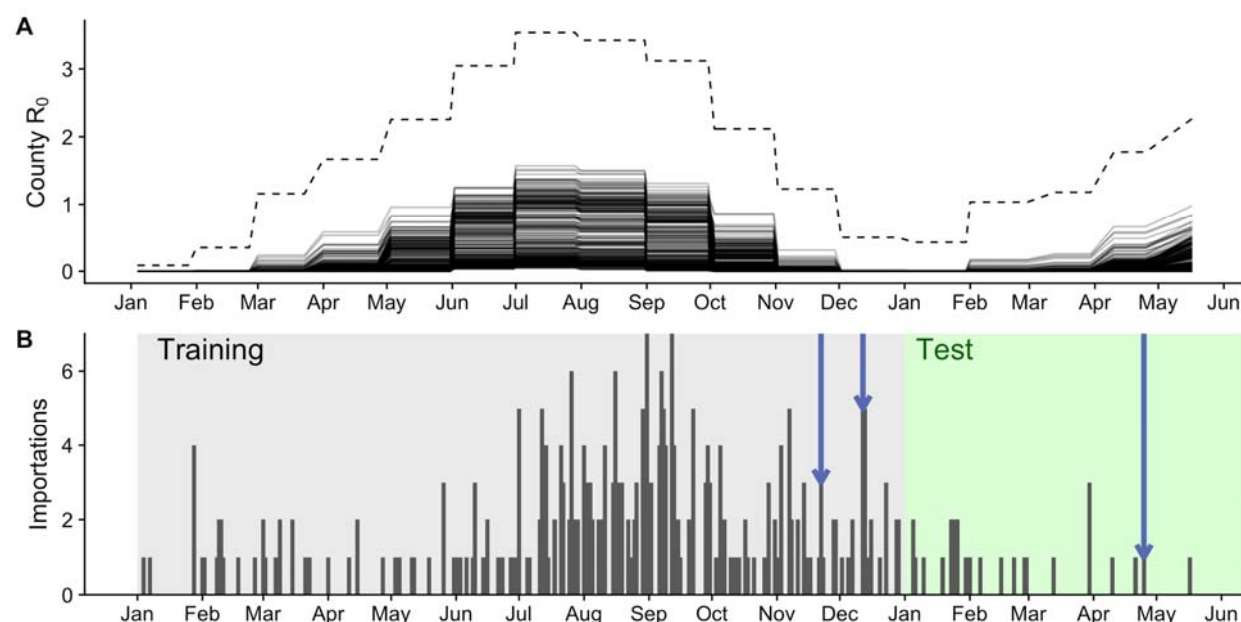256 low but not negligible.

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Figure 2: Texas importations and baseline transmission risk estimates for 2016-17. **(A)** Initial ZIKA R_0 estimates using ecological risk models parameterized with actual 2016-2017 temperatures. Each solid line shows median values for one of Texas' 254 counties. Dashed line shows the highest upper bound (99th percentile) across all counties. **(B)** Daily ZIKV importations into Texas. Blue arrows indicate importations that produced detected autochthonous transmission; shading indicates training (2016) and testing (2017) periods.

Updated transmission risks in Texas

Based on all importations and autochthonous cases that occurred in Texas prior to January 2017, we estimate that all Texas counties have a median posterior R_0 below one (Fig 3). Median estimates range from 0 to 0.29; upper-bound estimates range from 0 to 1.12, with only six (5%) of the original 119 high-risk counties maintaining epidemic potential (Fig S5). When we assume historic averages rather than 2016 temperatures, we obtain similar results (Fig S6).

In a sensitivity analysis that assumes ~20 times more *undetected* importations, we found that the estimated risks decreased further (Fig S7). We also varied the number of detected autochthonous cases in November: as they decrease from one to zero, the estimated risks decrease considerably; as they increase to five, estimated risks increase, with 83 counties becoming at risk for a local outbreak (Fig S7).
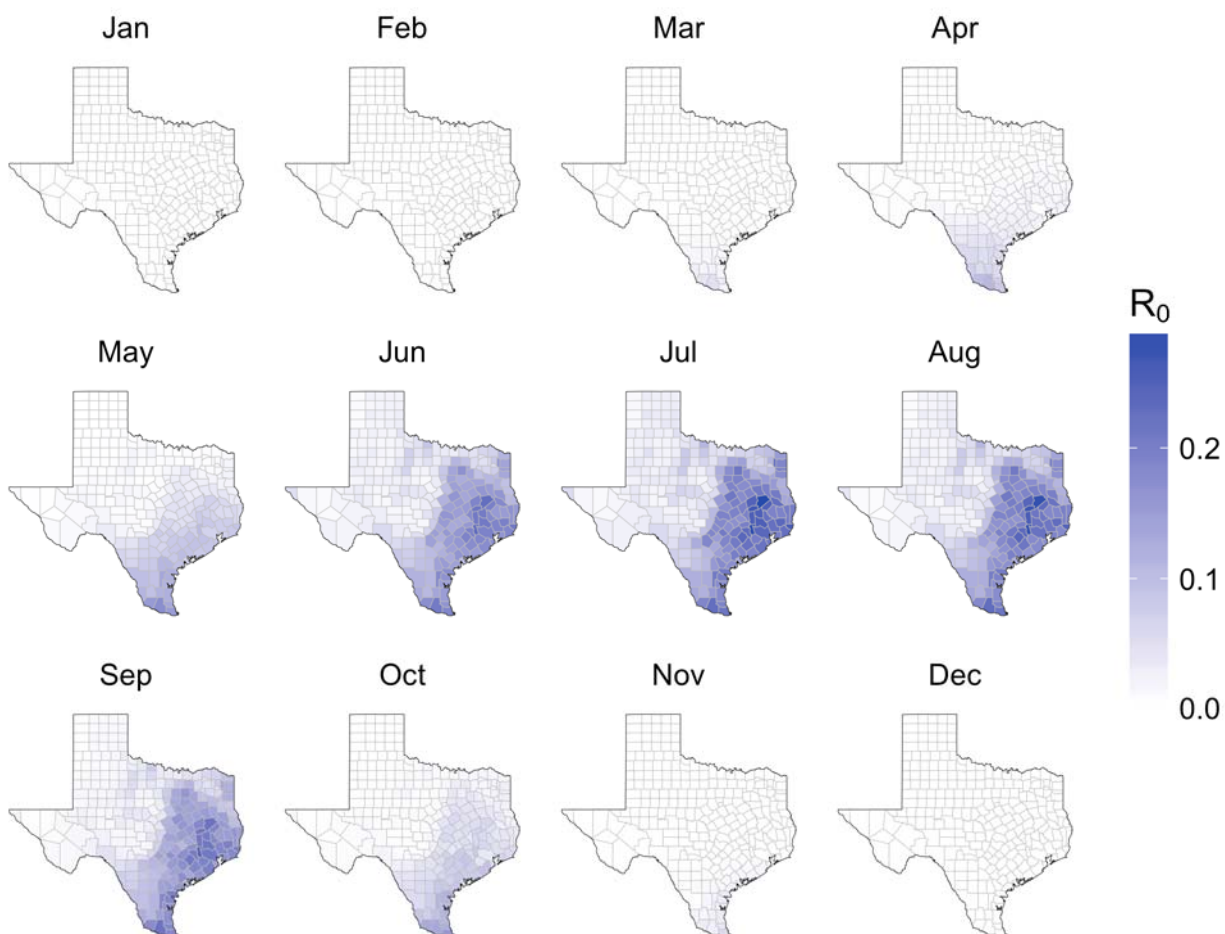
Figure 3: Posterior median county R_0 estimates for Texas, based on ZIKV importations through January 2017. This assumes that all importations were terminal except for a two autochthonous cases detected in Cameron County in late 2016.

Importation events had variable impacts on the posterior estimates, depending on their timing and location (Fig 4). Terminal importations early in the year, when *a priori* R_0 estimates were low, had little effect; those arriving in the summer months, when high *a priori* R_0 estimates suggested that transmission should have occurred, led to sharp decreases and a shrinking confidence interval. By early November, the median α decreased from 1.0 to 0.06 with a narrow 95% CI of 0.002-0.30. However, the two secondary transmission events detected in November and December increase R_0 estimates and widen the confidence intervals. Incorporating all data up to January 2017, our best estimate is that R_0 values across the state are roughly one fifth the original estimates (median: 0.19, 95% CI: 0.05-0.48).
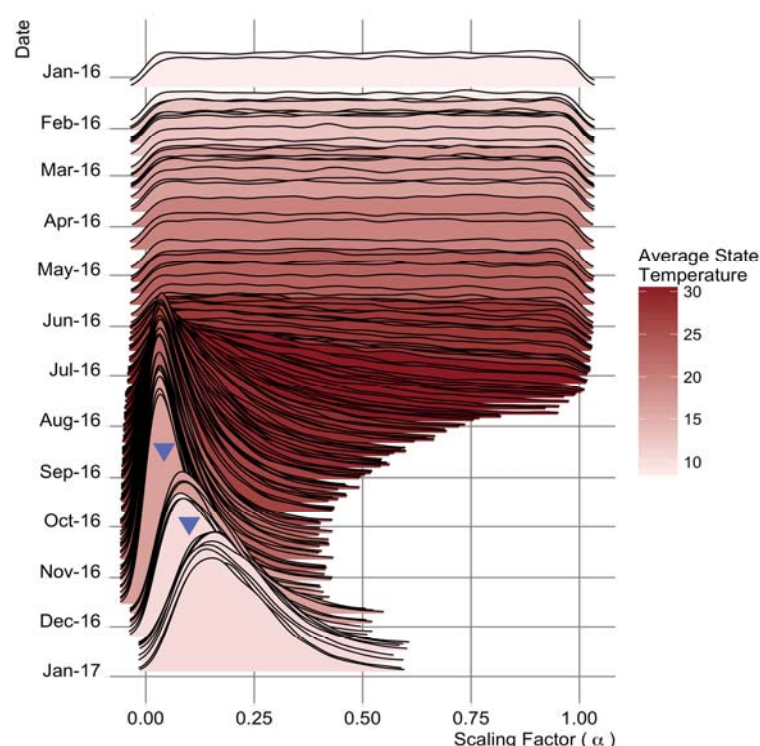
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302 **Figure 4: Evolving posterior distribution of statewide scaling factor for R_0.** Zika
303 importations, both with and without subsequent detected autochthonous transmission, provide
304 insight into local transmission potential, via a statewide scaling factor, $α$. This shows the
305 posterior distributions of $α$, for each day of 2016 that had at least one imported case. Median
306 estimates reach a minimum in early November, just before the detected autochthonous
307 transmission events (upside-down blue triangles). Red shading indicates the average statewide
308 monthly temperature. Note: the scaling factor is never less than zero.

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311 *Expected autochthonous transmission in Texas*
312   We use transmission risk estimates based on importations through December 2016 to
313 estimate the number of autochthonous cases we would expect to detect in Texas in 2017.
314 Assuming first that only the reported importations occurred in 2017 (26 total), we estimate that
315 there should have been 0.08 (95%CI: 0-1) detected autochthonous cases in the state; assuming
316 that many importations went undetected, according to the reporting probability (26 / p_d ≈ 453
317 total), we estimate 1.3 (95% CI: 0-7) detected autochthonous cases. These estimates are
318 consistent with the single autochthonous case detected in Texas in 2017 (Fig 5).
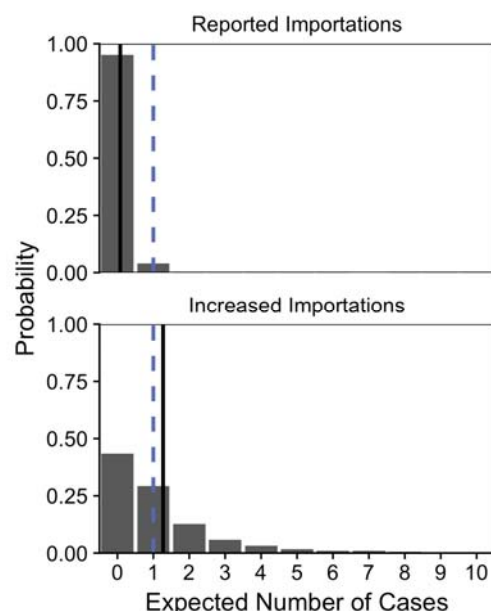
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322 **Figure 5:** Expected autochthonous cases in 2017, assuming revised county R_0 estimates and
323 reported importations through September 2017. The probability distributions are built from
324 10,000 simulations, each randomly drawing from the R_0 posterior distributions. The dashed blue
325 line indicates the actual number of detected autochthonous cases in state (one), and the solid
326 black lines indicate means for the baseline importation scenario, in which only the reported
327 importations occurred (top) and the increased importation scenario, in which a large fraction of
328 importations went undetected (bottom).

329

330 **Discussion**

331 The global expansion of ZIKV was declared a Public Health Emergency of International
332 Concern in February 2016, and caused more than 565,000 confirmed or probable cases and
333 over 3,352 documented cases of congenital Zika syndrome. Although it is receding in most
334 regions of the world, ecological risk assessments suggest that previously unaffected or
335 minimally affected areas may remain at risk for future emergence, including parts of Asia and
336 South America (26–28). Differentiating regions that can sustain a ZIKV epidemic ($R_0 > 1$) from
337 those that cannot is vital to effective planning and resource allocation for future preparedness
338 plans. To address this challenge, we have developed a simple method for refining uncertain risk
339 assessments with readily available data on disease importations.

340 We applied the method to update ZIKV R_0 estimates for each of the 254 counties in
341 Texas, and found that only six counties have non-negligible probabilities of sustained local
342 transmission. This is a substantial downgrade in expected risk, given that 43% of the 254
343 counties were previously thought to be vulnerable to ZIKV outbreaks. These estimates suggest
344 that there should have been roughly one detected case of locally acquired ZIKV between
345 January and September of 2017, closely corresponding to the single transmission event actually
346 detected in Cameron County in July 2017 (Figure 5). Our sensitivity analysis suggests that, if we
347 underestimated case-reporting in November, 77 additional counties have non-negligible but low
348 risks of summer outbreaks. Given comparable importation and climatic data, this approach

349   could readily update ZIKV transmission risk estimates for all counties in the continental US and
350   elsewhere.
351   Our estimation method relies on several simplifying assumptions. We assumed that the
352   shape of the secondary case distribution resembles that of dengue. Although we have no
353   evidence to the contrary, this should be updated as ZIKV-specific estimates become available
354   (23). We also assumed that transmission is equally likely from imported and locally acquired
355   cases. Imported cases may be less infectious than locally acquired cases for two reasons,
356   leading us to underestimate local transmission risks. First, they may be more likely to receive
357   care or education that limits subsequent transmission, although most ZIKV cases are inapparent
358   or mild, and do not require medical care (11); second, if they arrive already infectious, their local
359   infectious periods may be shorter than those of autochthonous cases. Next, we treat all
360   importations as independent. However, spatiotemporal heterogeneity in case detection
361   probabilities or clustering of cases (e.g., testing of travel companions) could bias risk estimates.
362   Furthermore, when secondary clusters are detected, we assume they share a transmission tree
363   stemming from a single detected importation. In fact, the low ZIKV detection rate suggests that
364   both primary importations and secondary cases are likely to be missed. If the detection rates are
365   roughly similar, our results hold. When we assume, in sensitivity analysis, that importations are
366   detected at higher rates than secondary cases, then the resulting risk estimates will be higher;
367   when we assume the reverse, they are lower. The additional assumption, that clusters are
368   epidemiologically connected, seems reasonable for the small contained outbreaks detected in
369   Texas, but may not be appropriate for importation-fueled arbovirus outbreaks in Florida, for
370   example. In such cases, molecular data might enable estimation of transmission clusters
371   (32,33). We also rely on informative Bayesian priors and a statewide scaling factor, which
372   allows us to use local importations to inform risk estimates elsewhere, but implies that our prior
373   county-month transmission risk estimates are correct relative to each other. Given additional
374   importation data, we could potentially estimate each county-month R_0 independently. Finally, we
375   do not consider possibility of sexual transmission of ZIKV. While sexual transmission has
376   occurred and may be important for specific populations (29), we assumed that mosquito-borne
377   transmission is the dominant mode of infection.
378   During the height of the ZIKV threat, public health agencies in the US rapidly
379   implemented both preventative measures (e.g., vector control and educational campaigns) and
380   response measures (e.g. laboratory testing and epidemic trigger plans), particularly in high risk
381   southern states. Decision makers sought to identify and narrow the spatiotemporal scope of
382   outbreak risk to enable targeted responses, efficiently allocate resources, and avoid false
383   alarms (10,30). Our method facilitates such rapid, real-time geographic risk estimation from
384   typical early outbreak data, and suggests that only 3% of the Texas population is at risk for a
385   local outbreak. Critically, we can conclude neither that all initial ecological risk assessments for
386   ZIKV will overestimate risk, although this seems to be the case for ZIKV in Texas, nor that
387   public health preparations and interventions for ZIKV are no longer necessary in Texas or the
388   southern US. Rather, our results suggest that sustained ZIKV outbreaks are unlikely, but not
389   impossible, and provide more robust and localized estimates of ZIKV risk that can inform more
390   targeted surveillance and reactions to future ZIKV importations.
391   This framework can be applied to update any R_0 estimates using importation data,
392   regardless of the *a priori* method of estimation. For example, a new approach combining

393　epidemiological and molecular analyses suggests that transmission risk in Florida is subcritical
394　(i.e., $R_0 < 1$) (31,32). Given that Florida experienced thousands of introductions, only a few of
395　which sparked large outbreaks, coupling such outbreak-driven estimation with our terminal
396　importation method may provide a powerful real-time risk assessment framework for exploiting
397　all available data.
398　　　　We presented a simple and rational method for continuously updating transmission risk
399　estimates for populations experiencing infectious disease importations, with or without
400　secondary transmission. As we demonstrated for ZIKV in Texas, large numbers of terminal
401　importations can profoundly lower both estimated risks of transmission and uncertainty in prior
402　estimates, particularly those derived from ecological suitability or other models that borrow
403　inputs from related pathogens in other parts of the world. Although the threat of ZIKV
404　emergence in the continental US motivated this study, this new framework can be widely
405　applied to improve transmission risk assessments when a disease newly threatens a population
406　via regular introductions with minimal secondary transmission. For example, importation-fueled
407　MERS-CoV transmission risk, or highly pathogenic avian influenza (34,35). This method can
408　also be used to assess disease transmission risk during elimination scenarios, such as
409　assessing risk for measles transmission in vaccinated populations or malaria in non-endemic
410　regions (36,37).
411

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Author Contributions

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426　SEB, LAM, and SJF developed the conceptual modelling framework. SJF completed the
427　analyses and created the figures. SJF, TAP, and MAJ reviewed published literature. All authors
428　contributed to the interpretation and presentation of results. SJF wrote the first draft, and all
429　authors contributed to writing and approval of the final report.
430

Data and code availability

432　Texas county-level importation data has not been given approval for public release, but all other
433　necessary data can be found online (http://dx.doi.org/10.18738/T8/HYZ53B) and the code can
434　be found on github (https://github.com/sjfox/rnot_updater). These data and code repositories
435　contain fake importation data that can be used to fully understand the statistical methods

436   presented here. Please contact Texas DSHS directly for access to the real county-level
437   importation data used in the analysis.
438
439   **Competing interests**
440   The authors have no competing interests.
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