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Genomic and epidemiological monitoring of yellow fever virus transmission potential

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The yellow fever virus (YFV) epidemic in Brazil is the largest in decades. The recent discovery of YFV in Brazilian *Aedes* species mosquitos highlights a need to monitor the risk of reestablishment of urban YFV transmission in the Americas. We use a suite of epidemiological, spatial, and genomic approaches to characterize YFV transmission. We show that the age and sex distribution of human cases is characteristic of sylvatic transmission. Analysis of YFV cases combined with genomes generated locally reveals an early phase of sylvatic YFV transmission and spatial expansion toward previously YFV-free areas, followed by a rise in viral spillover to humans in late 2016. Our results establish a framework for monitoring YFV transmission in real time that will contribute to a global strategy to eliminate future YFV epidemics.

Yellow fever (YF) is responsible for 29,000 to 60,000 deaths annually in South America and Africa (1) and is the most severe mosquito-borne infection in the tropics (2). Despite the existence of an effective YF vaccine since 1937 (3), an estimated >400 million unvaccinated people live in areas at risk

of infection (4). Yellow fever virus (YFV) is a member of the *Flaviviridae* family and is classified into four genotypes: East African, West African, South American I, and South American II (5–9). In the Americas, YFV transmission occurs mainly via the sylvatic cycle, in which nonhuman primates (NHPs)

are infected by tree-dwelling mosquito vectors such as *Haemagogus* spp. and *Sabethes* spp. (10, 11). YFV transmission can also occur via an urban cycle, in which humans are infected by *Aedes* spp. mosquitoes that feed mostly on humans (12, 13).

Brazil has recently experienced its largest-recorded YF outbreak in decades, with 2043 confirmed cases and 676 deaths since December 2016 (supplementary text and fig. S1) (14). The last YF cases in Brazil attributed to an urban cycle were in Sena Madureira, in the northern state of Acre, in 1942 (15). An intensive eradication campaign eliminated *Aedes aegypti* and YF from Brazil in the 1950s (16), but the vector became reestablished in the 1970s and *Aedes* spp. mosquitoes are now abundant across most of Brazil (17). The consequences of a reignition of urban cycle transmission in Brazil would be serious, as an estimated 35 million people in areas at risk for YFV transmission in Brazil remain unvaccinated (4). New surveillance and analytical approaches are therefore needed to monitor this risk in real time.

Yellow fever virus outbreak in Brazil, 2016–2017

Between December 2016 and the end of June 2017, there were 777 polymerase chain reaction (PCR)-confirmed human cases of YF across 10 Brazilian states—mostly in Minas Gerais (MG) (60% of cases), followed by Espírito Santo (32%), Rio de Janeiro (3%), and São Paulo (3%) (18). The fatality ratio of severe YF cases was estimated at 33.6%, comparable to previous outbreaks (19, 20). Despite the exceptional magnitude and rapid expansion of the outbreak, little is known about its genomic epidemiology. Further, it is uncertain how the virus is spreading through space, as well as between humans and NHPs, and analytical insights into the contribution of the urban cycle to ongoing transmission are lacking.

To characterize the 2017 YFV outbreak in Brazil, we first compared time series of confirmed cases in humans ($n = 683$) and NHPs ($n = 313$) reported until October 2017 by public health institutes in MG, the epicenter of the outbreak (Fig. 1, A and B, and fig. S2). The time series are strongly associated (cross-correlation coefficient = 0.97; $P < 0.001$). Both peak in late January 2017, and we estimate that human cases lag behind those in NHPs by 4 days (table S1). NHP cases are geographically more dispersed in MG than human cases, which are more concentrated in the Teófilo Ottoni and Manhuaçu municipalities (Fig. 1, D and E). Despite this, the numbers of human and NHP cases per municipality are positively correlated (Fig. 1F).

To establish whether human cases are acquired in proximity to potential sources of sylvatic infection, we estimated the distance between the municipality of residence of each human case and the nearest habitat of potential transmission, determined by using the enhanced vegetation index (EVI) (21) (supplementary materials). The average minimum

distance between areas with $EVI > 0.4$ and the residence of confirmed human cases is only 5.3 km. In contrast, a randomly chosen resident of MG lives, on average, ≥ 51 km away from areas with $EVI > 0.4$. Similarly, human YFV cases reside, on average, 1.7 km from the nearest NHP case, whereas the mean minimum distance of a randomly chosen MG resident to the nearest NHP case is 39.1 km. This is consistent with YF infection risk being greatest for people who reside or work in forested areas where sylvatic transmission occurs. We find that most human cases (98.5%) were reported in municipalities with estimated YFV vaccination coverage above the 80% threshold recommended by the World Health Organization (WHO). On average, human cases would need to travel 65 km from their place of residence to reach an area where vaccination coverage is $< 80\%$ (4).

Risk of YFV urban transmission

YFV was detected in *Aedes albopictus* mosquitoes caught in MG in January 2017 (22). Further, experiments suggest that *Aedes* spp. mosquitoes from southeast Brazil can transmit Brazilian YFV, although perhaps less effectively than vectors from elsewhere in the country (23, 24). It is therefore important to investigate whether YFV cases in MG occur where and when *Aedes* spp. vectors are active. To do so, we analyzed confirmed chikungunya virus (CHIKV) cases from MG (Fig. 1C).

CHIKV is transmitted by the urban mosquitoes *Ae. aegypti* and *Ae. albopictus* (25). There were 3755 confirmed CHIKV cases in MG during January 2015 to October 2017. The CHIKV epidemic in MG in 2017 began later and lasted longer than the YFV outbreak (Fig. 1C), consistent with the hypothesis that YFV and CHIKV in the region are transmitted by different vector species. However, 29 municipalities with human YFV cases also reported CHIKV cases (Fig. 1D and fig. S3), indicating that YFV is indeed present in municipalities with *Aedes* mosquitoes. The mean YFV vaccination rate in districts with both YFV and CHIKV cases is 72.6% (range = 61 to 78%) (4). Thus, relatively high vaccination rates in the locations in MG where YF spillover to humans occurs, and potentially lower vector competence (23, 24), may ameliorate the risk of establishment of an urban YFV cycle in the state. However, adjacent urban regions (including São Paulo and Rio de Janeiro) have lower vaccination rates (4), receive tens of millions of visitors per year (26), and have recently experienced many human YFV cases (20). Thus, the possibility of sustained urban YFV transmission in southern Brazil and beyond necessitates continual virological and epidemiological monitoring.

We sought to establish a framework to evaluate routes of YFV transmission during an outbreak from the characteristics of infected individuals. Specifically, we assessed whether an outbreak is driven by sylvatic or urban transmission by

comparing the age and sex distributions of observed YFV cases with those expected under an urban cycle in MG. For example, an individual's risk of acquiring YFV via the sylvatic cycle depends on their likelihood to travel to forested areas, an occurrence that is typically highest among male adults (27). In contrast, under an urban cycle, we expect more uniform exposure across age and sex classes, similar to that observed for urban cases in Paraguay (28) and Nigeria (29).

The male-to-female sex ratio of reported YFV cases in MG is 5.7 (85% of cases are male), and incidence is highest among males aged 40 to 49 (Fig. 2). We compared this distribution to that expected under two models of urban cycle transmission (supplementary materials). In model M1, age and sex classes vary in vaccination status but are equally exposed to YFV, a scenario that is typical of arboviral transmission (30). Under model M1, predicted cases are characterized by a sex ratio ~1, and incidence peaks among individuals aged 20 to 25 (Fig. 2). In model M2, we assume that the pattern of YFV exposure among age and sex classes follows that observed for CHIKV. The sex ratio of reported CHIKV cases in MG is 0.49 (33% of cases are male) (fig. S4). Under model M2, predicted incidence is highest in females aged >30. The discrepancy between the observed distribution and that predicted under the two urban cycle models indicates that the YF epidemic in MG is dominated by sylvatic transmission. This method shows that age- and sex-structured epidemiological data can be used to qualitatively evaluate the mode of YFV transmission during an outbreak.

Genomic surveillance of Brazilian YFV outbreak

During a YF outbreak, it is important to undertake virological surveillance to (i) track epidemic origins and transmission hotspots, (ii) characterize genetic diversity to aid molecular diagnostics, (iii) detect viral mutations associated with disease severity, and (iv) exclude the possibility that human cases are caused by vaccine reversion. We generated 62 complete YF genomes from infected humans ($n = 33$) and NHPs ($n = 29$) from the most affected Brazilian states, including MG ($n = 51$), Espírito Santo ($n = 8$), Rio de Janeiro ($n = 2$), and Bahia ($n = 1$) (Fig. 3 and table S3). We also report two genomes from samples collected in 2003 during a previous YFV outbreak in MG from 2002 to 2003 (31). Genomes were generated in Brazil using a combination of methods (tables S5 to S7); half were generated in MG using a MinION portable YFV sequencing protocol adapted from (32) (tables S4 and S5). This protocol was made publicly available in May 2017 after the completion of pilot sequencing experiments using a cultured vaccine strain (supplementary materials). Median genome coverages were similar for samples obtained from NHPs [99%; median cycle threshold value (Ct) = 11] and from human cases (99%; median Ct = 16) (tables S5 to S7).

To put the newly sequenced YFV genomes in a global

context, we added our genomes to a pool of 61 publicly available genomes (33, 34). We developed and applied an automated online phylogenetic tool to identify and classify YFV gene sequences (also publicly available, see supplementary materials). Phylogenies estimated by this tool, along with maximum likelihood and Bayesian methods, consistently place the Brazilian outbreak strains in a single clade within the South America I (SA1) genotype with maximum statistical support (bootstrap = 100%; posterior probability > 0.99) (Fig. 3A and fig. S5).

The outgroup to the outbreak clade is strain BeH655417, a human case sampled in Alto Alegre, Roraima, north Brazil, in 2002. In contrast, isolates sampled during the previous outbreak in MG in 2003 are more distantly related to the outbreak clade within the SA1 genotype (Fig. 3A). Thus, the 2017 outbreak was more likely caused by a YFV strain introduced from an endemic area, possibly northern or center-west Brazil (35), than by the reemergence of a lineage that had persisted in MG. Although low sampling densities mean that this conclusion is provisional, similar scenarios have been suggested for previous Brazilian epizootics (36). The 14-year gap between the current outbreak and the date of the most closely related nonoutbreak strain agrees with the reported periodicity of YF outbreaks in northern Brazil (37), thought to be dictated by vector abundance and the accumulation of susceptible NHP hosts (19, 38).

At least seven humans from MG with PCR-confirmed YFV received a YF vaccine before the onset of symptoms. To test that these occurrences were caused by natural infection, and not by vaccine reactivation, we sequenced the YFV genomes from three of these cases (Fig. 3A and table S3). Our phylogenetic analysis clearly shows that these represent natural infections caused by the ongoing outbreak and are conclusively not derived from the 17DD vaccine strain (which belongs to the West African YFV genotype) (Fig. 3A and fig. S6).

Unifying YFV epidemiology and molecular evolution

Virus genomes are a valuable source of information about epidemic dynamics (39) but are rarely used to investigate specific YFV outbreaks in detail. Here we show how a suite of three analytical approaches, which combine genetic, epidemiological, and spatial data, can provide insights into YFV transmission.

First, we used a Bayesian method (40) to explore potential covariates of fluctuations in the effective population size of the YFV outbreak in 2017. After finding that genetic divergence in the outbreak clade accumulates over the time scale of sampling (Fig. 3B and fig. S6), albeit weakly, we sought to determine which epidemiological time series best describe trends in inferred YFV effective population size. We found that effective population size fluctuations of the YFV outbreak are well explained by the dynamics of both human and

NHP YFV cases (inclusion probability: 0.37 for human cases and 0.63 for NHP cases) (table S8). These two YFV time series explain the genetic diversity dynamics of the ongoing outbreak 10^3 times more effectively than CHIKV incidence (inclusion probability <0.001), which represents transmission by *Aedes* spp. vectors. One benefit of this approach is that epidemiological data contribute to estimation of the outbreak time scale. By incorporating YFV incidence data into evolutionary inference, we estimate the time of the most recent common ancestor (TMRCA) of the outbreak clade to be late July 2016 [95% Bayesian credible interval (BCI): March to November 2016] (Fig. 3C and fig. S7), consistent with the date of the first PCR-confirmed case of YFV in a NHP in MG (Jul 2016). The uncertainty around the TMRCA estimate is reduced by 30% when epidemiological and genomic data are combined, compared with genetic data alone (Fig. 3C).

Second, to better understand YFV transmission between humans and NHPs, we measured the movement of YFV lineages between the NHP reservoir and humans, using a phylogenetic structured coalescent model (41). Although previous studies have confirmed that YFV is circulating in five neotropical NHP families (Aotidae, Atelidae, Callitrichidae, Pitheciidae, and Cebidae) (Fig. 4A), thus far NHP YFV genomes during the 2017 outbreak have been recovered only from *Alouatta* spp. (family Cebidae) (33). In this analysis, we used the TMRCA estimate obtained above (Fig. 3C) to inform the phylogenetic time scale (Fig. 4B). All internal nodes in the outbreak phylogeny whose host state is well supported (posterior probability >0.8) are inferred to belong to the NHP population, consistent with an absence of urban transmission and in agreement with the large number of NHP cases reported in southeast Brazil (20). Despite this, we argue that hypotheses of human-to-human transmission linkage should not be tested directly using phylogenetic data alone, owing to the large undersampling of NHP infections. Notably, the structured coalescent approach reveals substantial changes in the frequency of NHP-to-human host transitions through time, rising from zero around November 2016 and peaking in February 2017 (Fig. 4C). This phylogenetic trend matches the time series of confirmed YFV cases in MG (Fig. 1, A and B), demonstrating that viral genomes, when analyzed using appropriate models, can be used to quantitatively track the dynamics of zoonosis during the course of an outbreak (42).

Third, we used a phylogenetic relaxed random walk approach to measure the outbreak's spatial spread (43) (supplementary materials and methods and table S9). When projected through space and time (Fig. 4, D and E, and movie S1), the phylogeny shows a southerly dissemination of virus lineages from their inferred origin in MG toward densely populated areas, including Rio de Janeiro and São Paulo (where YF vaccination was not recommended until July 2017 and January 2018, respectively). We estimate that virus

lineages move, on average, 4.25 km/day (95% BCI: 2.64 to 10.76 km/day) (44). This velocity is similar when human YFV terminal branches are removed (5.3 km/day) and therefore most likely reflects YFV lineage movement within the sylvatic cycle and not the movement of asymptomatic infected humans. These rates are higher than expected given the distances typically travelled by NHPs in the region (45) and suggest the possibility that YFV lineage movement may have been aided by human activity—e.g., transport of infected mosquitoes in vehicles (46) or hunting or illegal trade of NHPs in the Atlantic forest (47, 48). The epidemic wavefront (maximum distance of phylogeny branches from the inferred epidemic origin) expanded steadily between August 2016 and February 2017 at an estimated rate of ~ 3.3 km/day. Therefore, by the time YF was declared a public health emergency in MG (13 January 2017; dashed lines in Fig. 4, B to D), the epidemic had already expanded ~ 600 km (Fig. 4D) and caused >100 reported cases in both humans and NHPs (Fig. 1). Notably, the first detection in humans in December 2016 was concomitant with the outbreak's spatial expansion phase (Fig. 4D) and the rise in estimated NHP-to-human zoonoses (Fig. 4C); both were likely driven by an increase in the abundance of sylvatic vectors. Thus, the outbreak lineage appeared to circulate among NHPs in a widening geographic area for several months before human cases were detected.

Conclusion

Epidemiological and genomic surveillance of human and animal populations at risk is crucial for early detection and rapid containment of YFV transmission. The YFV epidemic in Brazil continues to unfold with an increase in cases since December 2017. Longitudinal studies of NHPs are needed to understand how YFV lineages disseminate across South America between outbreaks and how epizootics are determined by the dynamics of susceptible animals in the reservoir. To achieve the WHO's goal to eliminate YF epidemics by 2026, YF surveillance necessitates a global, coordinated strategy. Our results and analyses show that rapid genomic surveillance of YFV, when integrated with epidemiological and spatial data, could help anticipate the risk of human YFV exposure through space and time and monitor the likelihood of sylvatic versus urban transmission. We hope that the toolkit introduced here will prove useful in guiding YF control in a resource-efficient manner.

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SUPPLEMENTARY MATERIALS

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Materials and Methods

Supplementary Text

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Movie S1

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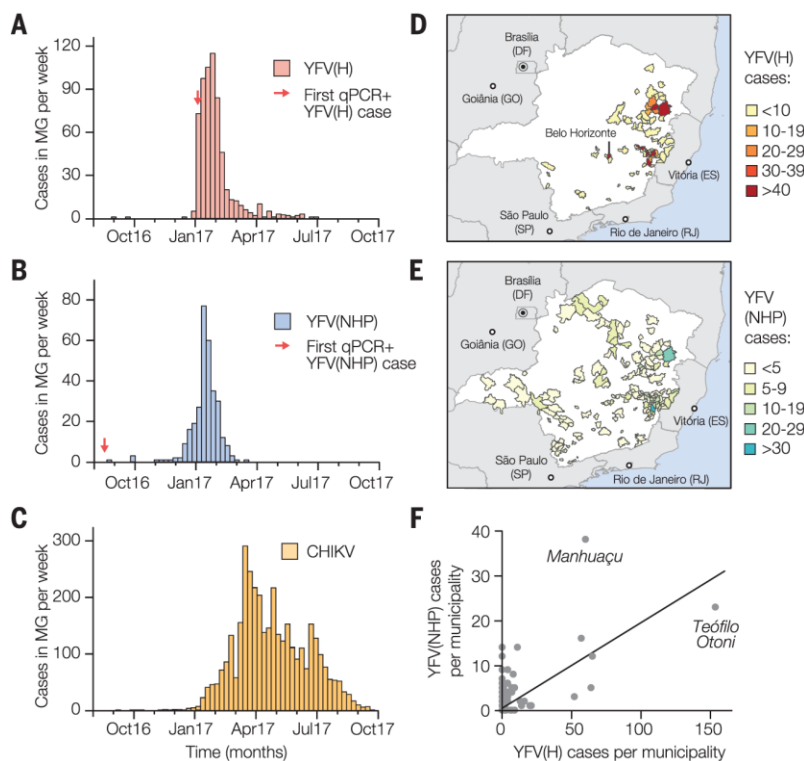


Fig. 1. Spatial and temporal epidemiology of YFV and CHIKV in Minas Gerais (MG). (A) Time series of human (H) YFV cases in MG (676 cases across 61 municipalities)—confirmed by serology, reverse transcription quantitative PCR (RT-qPCR), or virus isolation—during the first YFV epidemic wave (August 2016 to October 2017). (B) Same as in (A) but showing NHP YFV cases (313 cases across 90 municipalities) confirmed by RT-qPCR. (C) Same as in (A) but showing human CHIKV cases (3668 cases across 129 municipalities). (D) Geographic distribution of human YFV cases in MG. (E) Geographic distribution of NHP YFV cases in MG. Fig. S3 shows the corresponding geographic distribution of CHIKV cases. (F) Association between the number of human and NHP cases in each municipality of MG (Pearson's $r = 0.62$; $P < 0.0001$; nonparametric Spearman's rank $\rho = 0.32$; $P < 0.05$).

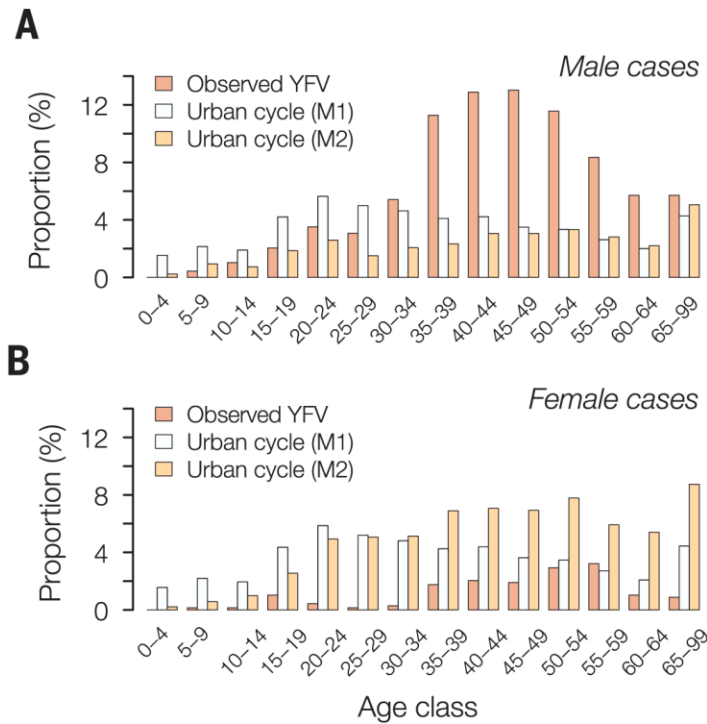


Fig. 2. Age and sex distribution of YFV cases in MG, 2016–2017. Red bars show the proportion of observed YFV cases in MG that occur in each age class, in (A) males and (B) females. These empirical distributions are different from those predicted under two models (M1, pale blue bars; M2, orange bars) of urban cycle transmission (see text for details).

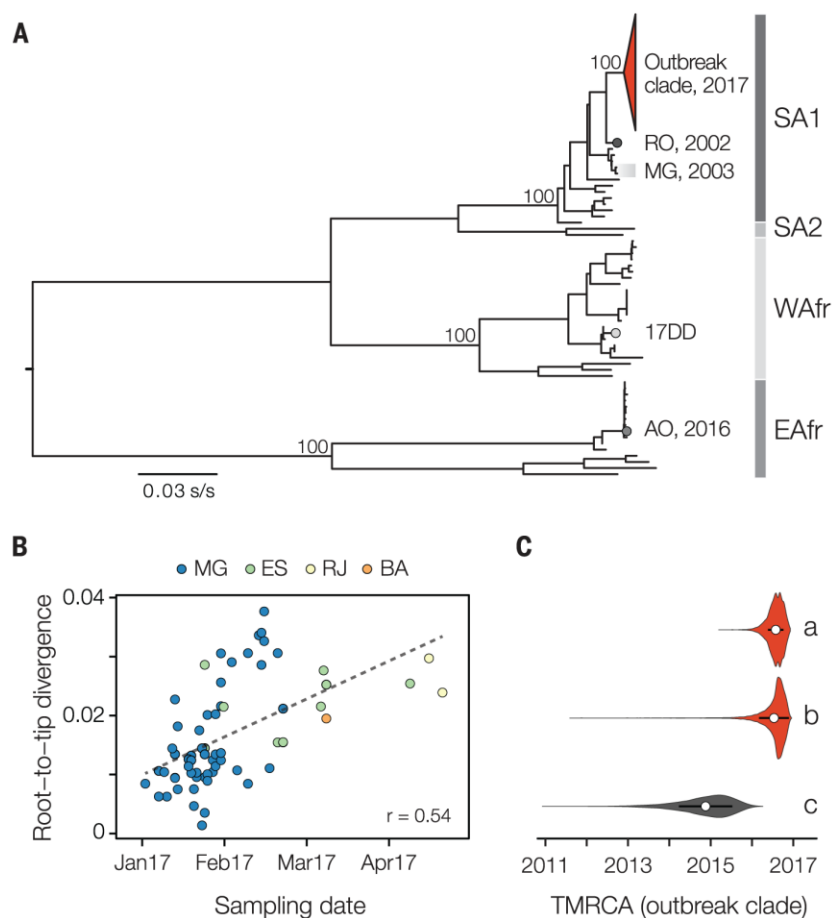


Fig. 3. Molecular phylogenetics of the Brazilian YFV epidemic. (A) Maximum likelihood phylogeny of complete YFV genomes showing the outbreak clade (red triangle) within the South American I (SA1) genotype (Fig. 4 and fig. S6). SA2, WAfr, and EAfr indicate the South America II, West Africa, and East Africa genotypes, respectively. For clarity, five YFV strains introduced to Venezuela from Brazil (49) are not shown. The scale bar is in units of substitutions per site (s/s). Node labels indicate bootstrap support values. RO 2002, strain BeH655417 from Roraima; MG 2003, two strains from the previous YF outbreak in MG in 2003; 17DD, the vaccine strain used in Brazil; AO 2016, YFV outbreak Angola in 2015–2016 (13). (B) Root-to-tip regression of sequence sampling date against genetic divergence from the root of the outbreak clade (fig. S6). Sequences are colored according to sampling location (MG, Minas Gerais; ES, Espírito Santo; RJ, Rio de Janeiro; BA, Bahia). (C) Violin plots showing estimated posterior distributions (white circles denote means) of the time of the most common ancestor (TMRCA) of the outbreak clade. Estimates were obtained using two different datasets (gray, SA1 genotype; red, outbreak clade) and under different evolutionary models: a, uncorrelated lognormal relaxed clock (UCLN) model with a skygrid tree prior with covariates (specifically, the time series data shown in Fig. 1, A to C; also see fig. S7); b, UCLN model with a skygrid tree prior without covariates; c, fixed local clock model (see supplementary materials).

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