Title: Endemic persistence of a highly contagious pathogen: Foot-and-mouth disease in its wildlife host

Authors:

Anna Jolles*[†1,2], Erin Gorsich[†1,3,4], Simon Gubbins[5], Brianna Beechler[1], Peter Buss[6], Nick Juleff[7], Lin-Mari de Klerk-Lorist[8], Francois Maree[9,10], Eva Perez-Martin[5], OL van Schalkwyk[8,11, 12], Katherine Scott[9], Fuquan Zhang[13], Jan Medlock[1+], Bryan Charleston[5+]

Affiliations:

[1] Department of Biomedical Sciences, Oregon State University, Corvallis, OR, 97331, USA.

[2] Department of Integrative Biology, Oregon State University, Corvallis, OR, 97331, USA.

[3] Zeeman Institute for Systems Biology and Infectious Disease Epidemiology Research, University of Warwick, Coventry, CV4 7AL, United Kingdom.

[4] School of Life Sciences, University of Warwick, Coventry, CV4 7AL, United Kingdom.

[5] The Pirbright Institute, Ash Road, Pirbright, Surrey, GU24 0NF, United Kingdom.

[6] SANParks, Veterinary Wildlife Services, Kruger National Park, 1350 Skukuza, South Africa .

[7] Bill & Melinda Gates Foundation, Livestock Program, Seattle, WA, USA.

[8] Office of the State Veterinarian, Department of Agriculture, Land Reform and Rural Development, Government of South Africa, Skukuza, 1350, South Africa.

[9] Vaccine and Diagnostic Research Programme, Onderstepoort Veterinary Institute, Agricultural Research Council, Private Bag X05, Onderstepoort 0110, South Africa.

[10] South Africa Department of Microbiology and Plant Pathology, University of Pretoria, Pretoria, South Africa.

[11] Department of Veterinary Tropical Diseases, Faculty of Veterinary Science, University of Pretoria, Onderstepoort, South Africa.

[12] Department of Migration, Max Planck Institute of Animal Behavior, Am Obstberg 1

[13] Institute of Prion Diseases, University College London, London, WC1E 6BT, UK.

*Correspondence to: aejolles@gmail.com.

† These authors contributed equally to this work.

[+] These authors contributed equally to this work.

Abstract:

Extremely contagious pathogens are a global biosecurity threat because of their high burden of morbidity and mortality, and their capacity for fast-moving epidemics that are difficult to quell. Understanding the mechanisms enabling persistence of highly transmissible pathogens in their host populations is thus a central problem in disease ecology. Combining experimental and theoretical approaches, we investigated how highly contagious foot-and-mouth disease viruses persist in their wildlife reservoir, African buffalo. We found that viral persistence via transmission among acutely infected hosts alone is unlikely. However, including even very occasional transmission from persistently infected carriers reliably rescues the most infectious viral strain from fade-out. Additional mechanisms, such as antigenic shift, loss of immunity, or spillover among host populations, may be required for persistence of less transmissible strains.

One Sentence Summary:

Even sporadic transmission from chronically infected carrier hosts can allow highly contagious pathogens to persist in their host populations.

Main Text:

Outbreaks of highly contagious pathogens are notoriously difficult to predict, and their potential for explosive spread allows these infections to progress quickly from localized transmission events to disease emergencies of epidemic proportions(*1*, *2*). After initial invasion into susceptible host populations, highly contagious pathogens are prone to fade-out, as the force of infection quickly outstrips the supply rate of susceptible hosts. Yet, these pathogens persist endemically in some host populations — their reservoirs — whence they re-emerge to strike susceptible populations when the opportunity presents itself. Understanding the mechanisms that allow for pathogen persistence in reservoir host populations is thus fundamental to predicting and preventing outbreaks. Progress has been made in elucidating contagious pathogen persistence in large human populations(*3*)(*4*). However, persistence in animal populations, where seasonal births exacerbate the risk of pathogen fade-out(*5*), and which are typically of moderate size — far below the hundreds of thousands required to maintain pathogens such as measles, polio, and pertussis— remains enigmatic.

We investigated endemic persistence of foot-and-mouth-disease viruses (FMDVs), one of the most contagious groups of pathogens(*6*, *7*), in African buffalo, their wildife reservoir(*8*). FMDVs can infect numerous cloven-hoofed wildlife species, as well as domestic livestock, where they cause significant production losses(*9*). Temporal and spatial variation in FMDV antigenicity limit the efficacy of vaccination as a disease control strategy(*10*), but see (*11*); consequently, international trade restrictions forbid movement of livestock and meat products from FMD-endemic to FMD-free countries. As such, FMD is the most important livestock disease restricting international trade, and its colossal global impact is disproportionately borne by developing countries(*12*). In sub-Saharan Africa, control of FMD is further complicated by the role of the African buffalo as a reservoir(*13*), but see (*14*). FMDVs maintain a high force of infection in free-ranging buffalo populations: serological surveys in endemic areas demonstrate that over 98% of buffalo have been exposed to all three local serotypes —Southern African Territories (SAT) serotypes SAT1, 2, 3 — by the time they are two years old(*8*).

We consider two putative mechanisms for the persistence of FMDVs in buffalo populations. First, FMDVs might be maintained as typical “childhood infections”, circulating through each year’s susceptible calves, with the latest born calves of one year sparking the new epidemic in the earliest born of the following cohort(*15*). Second, persistently-infected carrier buffalo may play a role in preventing

fade-out of FMDVs between successive calf cohorts. Buffalo can maintain viable FMDVs for months(*16*) to years(*17*). However, only low titres of virus are detected during persistent infection, and previous experiments attempting transmission from carrier buffalo to naive animals(*18–24*) have suggested that transmission events are rare at best. The role of carrier buffalo in natural FMDV transmission dynamics thus remains unknown (*25*). We used a cohort study and experimental infections to parameterize an individual-based stochastic model, and investigate the role of transmission from acutely infected calves and carrier animals in the dynamics of endemic FMDV infection in African buffalo populations.

Working on a buffalo herd in Kruger National Park, South Africa, we conducted a 3-year cohort study to measure the temporal distribution of births, and duration of maternally-derived immunity to FMDVs in buffalo calves (*26*). The study herd consisted of 49-70 buffalo of mixed age and sex, which were captured five times per year for FMDV testing. Buffalo calves were born between September and April, peaking between December and March (Fig. 1a). Maternally-derived antibodies to FMDVs waned around 5 months of age (mean 4.8, CI: 3.6-6.0 months; Fig. 1b). A triangular birth function captured the timing and duration of births in the cohort, including the period from May to August when births did not tend to occur (Fig. 1c). Our data did not support differences among serotypes in waning of maternally-derived immunity (Fig. 1d; Table S1, S2). Animals susceptible to FMDVs thus entered the buffalo population annually throughout a prolonged period peaking May–August. Importantly, the seasonal timing of births resulted in a lapse of 150 days or more between pulses of susceptible recruitment.

We conducted an experimental challenge study to quantify epidemiological parameters for FMDV transmission in buffalo during primary (acute) infection and from carrier hosts for three FMDV strains (SAT1, SAT2, SAT3; (*26*)). To study primary transmission, we allowed four naïve buffalo to contact four experimentally infected animals, using separate groups for each FMDV serotype; thus the primary infection experiment involved a total of 12 naïve recipient buffalo and 12 needle-infected viral donor buffalo for a period of thirty days (Fig. S4a). We assessed transmission from carrier buffalo by monitoring infections in two groups of buffalo. Each group included two carriers for each serotype sourced from the primary infection experiment, plus six naïve buffalo. The carrier experiment thus included a total of 12 carriers and 12 naïve animals, monitored for 6.5 months (Fig. S4b, Fig. S5). During primary infection, all SAT serotypes were readily transmitted from experimentally infected buffalo to naïve hosts. Our data support transmission models including a latent period, and serotype-specific parameters (transmission rate, incubation period, infectious period) for FMDVs in buffalo (Fig. 2, Tables S1, S2). We estimated the fraction of buffalo that become carriers following primary infection, the duration of the carrier status, and transmission rates from carriers, revealing striking variation in carrier dynamics between the three viral strains (Fig. 2, Table S1). Based on these parameters, the basic reproduction number for the strains we tested, in models including transmission from both acutely infected buffalo and carriers, is 23.8 (95%CI 8.2, 73.3) for SAT1, 7.8 (95%CI 2.1-41.7) for SAT2 and 7.2 (95%CI 2.3-36.1) for SAT3. Models assuming transmission from acutely infected hosts only, yield notably lower basic reproductive numbers for SAT1 (15.8; 95%CI 4.1, 65.6) and SAT3 (5.2, 95%CI 1.3, 34.1), but not for SAT2 (7.5; 95%CI 1.9, 41.5).

We modeled the dynamics of FMDV infections in African buffalo (1) under the null hypothesis that infection persists stochastically between birth pulses, and (2) including transmission from carrier hosts (*26*). Individual variation in the timing of births, the period of maternally-derived immunity, and epidemiological parameters were incorporated into the model according to our estimates from empirical data. Age-specific death rates of buffalo were estimated from prior studies in KNP(*27*, *28*), and the seasonal birth rate scaled to balance mortalities.

We extended the SEIR (susceptible-exposed-infectious-recovered) class of models to include calves that are temporarily not susceptible to infection because they are protected by maternally-derived immunity, and carrier hosts that transmit FMDV at reduced rates (Fig. 3a).

For the model including transmission during primary infection only, our simulations show that the number of infected hosts rapidly declines to zero, and all three strains fade out within 50 (SAT1), 100 (SAT2), or 150 (SAT3) days (Fig. 3b). These findings indicate that FMDVs are unlikely to persist in their reservoir populations through acute transmission among calves alone, because the duration of epidemics in a given susceptible calf cohort is shorter than the gap between birthing seasons (150+ days). Sensitivity analyses demonstrate the robustness of this result, even in very large buffalo herds, with more evenly distributed births, and different initial conditions (Fig. S1, S2). When we include transmission from carrier buffalo in our models, we find highly predictable dynamics and robust persistence of SAT1 in buffalo populations. Carrier transmission also tends to allow SAT3 to persist; but our models predict that SAT2 fails to persist, even with carriers (Fig. 3c), due to its very low estimated carrier transmission rate.

Sensitivity analyses (Supplement section S5) revealed population size thresholds for each serotype, with SAT1 requiring only moderate sized populations of ~400 buffalo to persist reliably, SAT3 attaining long-term persistence in populations larger than ~2000 buffalo, and SAT2 requiring very large populations (~10,000 buffalo) for continued circulation, based on the transmission mechanisms included in our models (Fig. 4a). Viral persistence time for all strains was far more sensitive to variation in carrier parameters than in parameters describing acute transmission (Fig. 4b). Sensitivities across all epidemiological parameters were small for SAT1 compared to the other two serotypes, suggesting that SAT1's epidemiological parameters are tuned near-optimally for persistence in buffalo populations, via combined transmission from acutely infected calves and carrier hosts. By comparison, SAT2 and SAT3 appear less well adapted for endemic persistence mediated by these transmission mechanisms.

Our experiments reveal striking variation in epidemiological parameters among the three southern African FMDV serotypes, resulting in contrasting transmission dynamics and persistence patterns. Rapid transmission among acutely infected calves and less frequent transmission from carrier hosts can explain the long-term persistence of SAT1 in African buffalo populations. SAT1's transmission rate from carriers was two orders of magnitude lower than from acutely infected hosts. Even this modest carrier transmission rate, coupled with a carrier state duration that exceeds the interval between buffalo birth cohorts, and minimal risk of early stochastic fade-out once infection has been sparked, was sufficient to ensure robust year-to-year persistence of SAT1. SAT2 and especially SAT3 transmitted at a considerably more moderate pace during acute transmission, leading to slower - but still inevitable - fade-out than SAT1 when considering transmission from acutely infected hosts only. Like SAT1, SAT3 transmitted from carrier buffalo at an approximately 100-fold reduced rate compared to its acute transmission rate. Its combination of slower fade-out and occasional transmission from carriers, allowed SAT3 to persist for more than ten years in about 60% of model runs. More reliable persistence was prevented by a non-trivial risk of early stochastic fade-out (visible as an early peak in extinctions, Fig. 3b) at the start of each new transmission chain. However, larger population sizes, as found in Kruger National Park, mitigate this risk, and our models predict long-term persistence of SAT3 in buffalo populations exceeding about 2000 animals (Fig. 4a). We did not observe any transmission of SAT2 from carriers in our experiments, resulting in a low upper boundary for the carrier transmission rate. Coupled with less efficient generation of carriers from acutely infected animals, and shorter duration of the carrier state, this results in a very low probability of persistence of SAT2 in buffalo populations, based on the transmission mechanisms considered here. While we cannot be certain that the strains we used in our experiments are typical of their serotypes, FMDV transmission data from our cohort study support our experimental findings: Our study herd has been largely isolated in its enclosure since its establishment in 1998, and there is clear serological evidence that all FMDV serotypes were originally present in the herd. However, during three

and a half years of repeatedly testing the entire herd for FMDV infection, we detected no primary or chronic SAT2 infections, suggesting that SAT2 may have gone extinct in our study herd. By contrast, SAT1 was transmitting regularly, and SAT3 intermittently (*29*).— consistent with the idea that additional mechanisms not yet addressed in our study may be necessary for viral persistence of SAT2 and in smaller buffalo populations, SAT3.

Several additional persistence mechanisms are plausible for FMDVs. First, titers of neutralizing antibody against FMDV wane over time(*17*, *30*), and seasonal stressors modulate immune responses in free-living populations(*31*), possibly resulting in temporal variability in acquired immune protection. Indeed, our data suggest that antibody titers to FMDVs, especially SAT3, are highly variable within individual hosts over time(*32*), which may contribute to maintaining viral endemic persistence in buffalo populations. Second, RNA viruses including FMDVs evolve quickly(*33–35*). Antigenic shift may allow for reinfection of previously exposed buffalo, especially by SAT2, which has notably high nonsynonymous mutation rates(*36*). Third, interactions among different pathogens can affect transmission dynamics (*28*, *37*, *38*), but we have yet to assess interactions among the three SAT serotypes. . Finally, buffalo population structure is fluid (*39*), with a high rate of dispersal among groups(*40*). As such, FMDVs may persist by traveling through the buffalo metapopulation, causing asynchronous epidemics across subpopulations. Indeed, since FMDVs can infect a broad range of ungulate species, transmission networks may not be limited to buffalo, but include other members of the diverse southern African ungulate assemblage(*41*, *42*) and livestock (*43*).

Our estimates for the basic reproductive numbers of the three SAT serotypes in buffalo (SAT1: 23.8; SAT2: 7.8; SAT3: 7.2) confirm FMDVs as one of the most contagious known groups of pathogens (FMDV R_0 in cattle(*7*, *44*) 20- 30; cf. measles(*45*) 12-18, pertussis(*46*) 5.5; SARS-CoV2(*47*) 3.8-8.9). Understanding the conditions that allow for persistence of highly contagious pathogens underlies concepts of critical community size (*3*, *4*) and strategies for limiting disease impacts in human and animal populations. This requires leveraging insights from multiple host-pathogen systems, including human infection dyamics (*48–50*) and animal infections subject to seasonal demographics (*5*) and inter-species transmission in diverse host communities (*51*, *52*). Our study reveals distinct life histories, population dynamics and strategies for persistence even within a closely related group of highly transmissible respiratory pathogens.

Figure Legends:

Fig. 1. Data (A,B) and model parameters (C,D) defining the annual birth pulse (A,C) and waning of maternally-derived antibodies (B,D). (A) Births observed during the cohort study. (B) FMDV antibody titres in young calves. Lines connect longitudinally sampled titres in individual buffalo. The dashed line indicates the threshold for protective antibodies. (C) Birth hazard functions. (D) Maternally-derived immunity duration density functions.

Fig. 2. Epidemiological parameters for acute infection (top row) and FMDV carriers (bottom row). Black dots indicate posterior median for the parameter and lines show the interquartile range for the posterior distribution. Coloured shapes show the posterior distribution for each parameter estimate.

Fig. 3. Dynamics of FMDV infection for SAT1, SAT2, and SAT3, including (b) acute transmission only, and (c) transmission from acutely infected and carrier hosts.. In the graphs of number infected, thin colored curves show the number infected vs. time for individual simulations; the thick black curve is the mean over the simulations. The graphs of FMDV extinction time show the distribution of extinction times over the simulations. In (b), for SAT1 and SAT3, arrows show the proportion of simulations that persisted longer than 10 years and the gray boxes show the longest persistence time for the model with acute transmission only to highlight the difference in scale.

Fig. 4. The sensitivity of extinction time to (a) buffalo population size, and (b) transmission parameters, for models including acute and carrier transmission. (a) The top row shows the distribution of FMDV extinction times. The bottom row shows the proportion of simulations where FMDV persisted in the buffalo population for the whole simulated 10-year period. (b) Sensitivity is measured by the partial rank correlation coefficient (PRCC).

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Author contributions:
AJ, BC, JM, BB and NJ designed the study.
BB, AJ and PB managed the cohort study; LKL and OvS managed the experimental study.
BB, PB, BC, LKL, EG, AJ, NJ, FM, EPM, KS, OvS and FZ collected field data.
FM, BC, EPM, KS and FZ designed and conducted diagnostic testing.
SG and EG led statistical analyses estimating epidemiological parameters from empirical data.
JM and EG created and analyzed FMDV transmission models.
AJ, EG, JM, KS, SG and EPM wrote the manuscript, which was edited by all authors.

Competing interests: Authors declare no competing interests.

Data and materials availability: Code for our parameter analyses and model simulations are available online (*53*, *54*). All data will be uploaded to github.

List of Supplementary materials:

Supplementary Materials:

References and Notes:

(Refs 55+ appear only in the Supplementary Materials)

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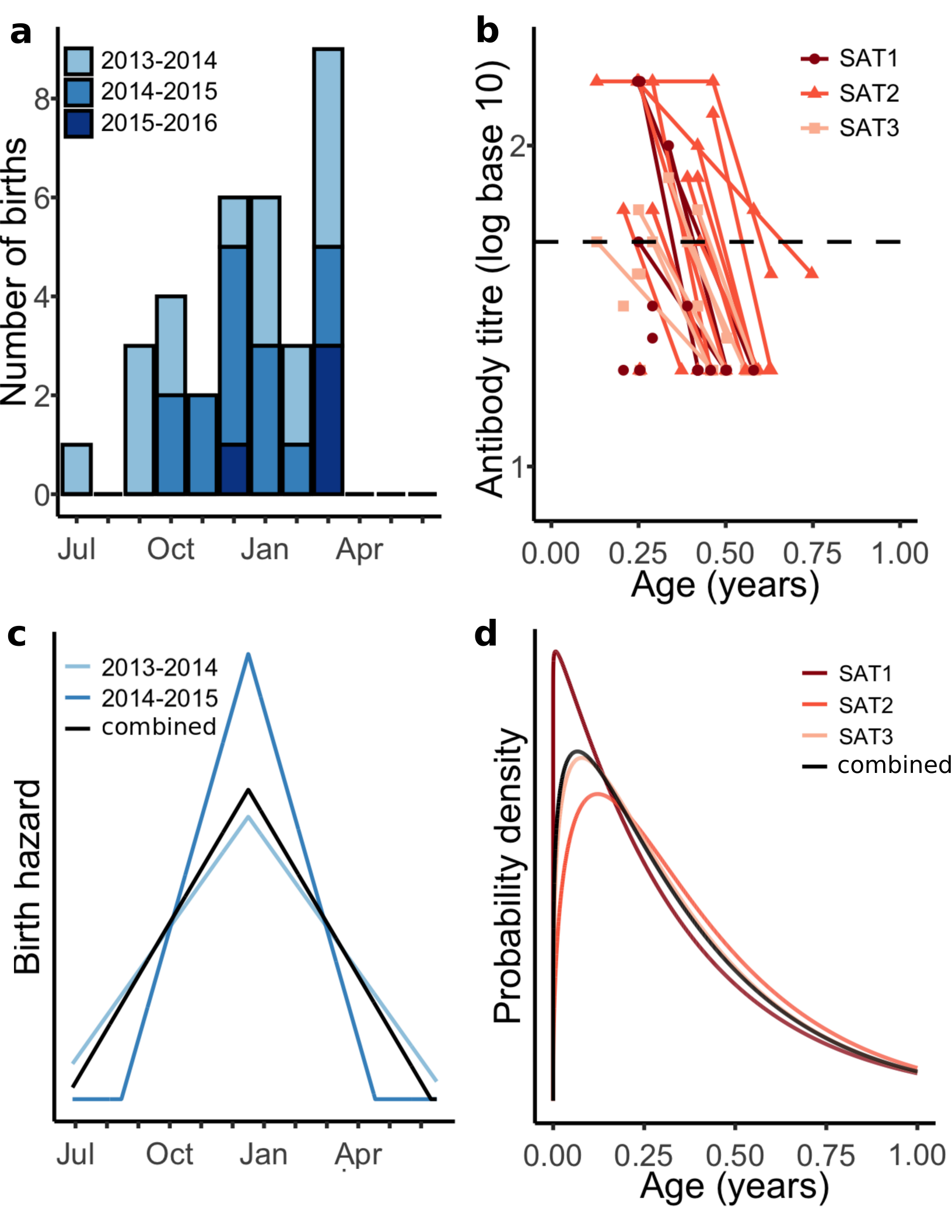
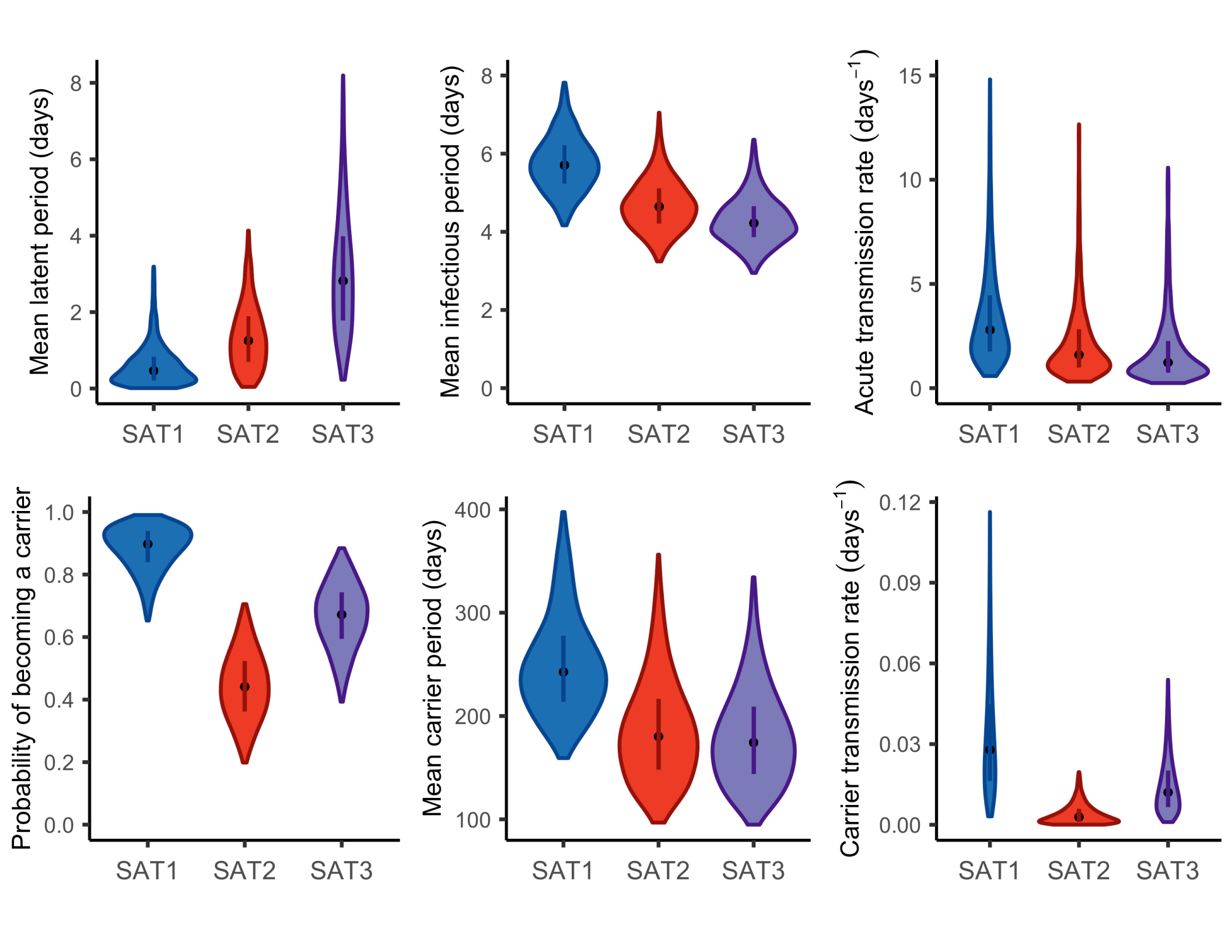
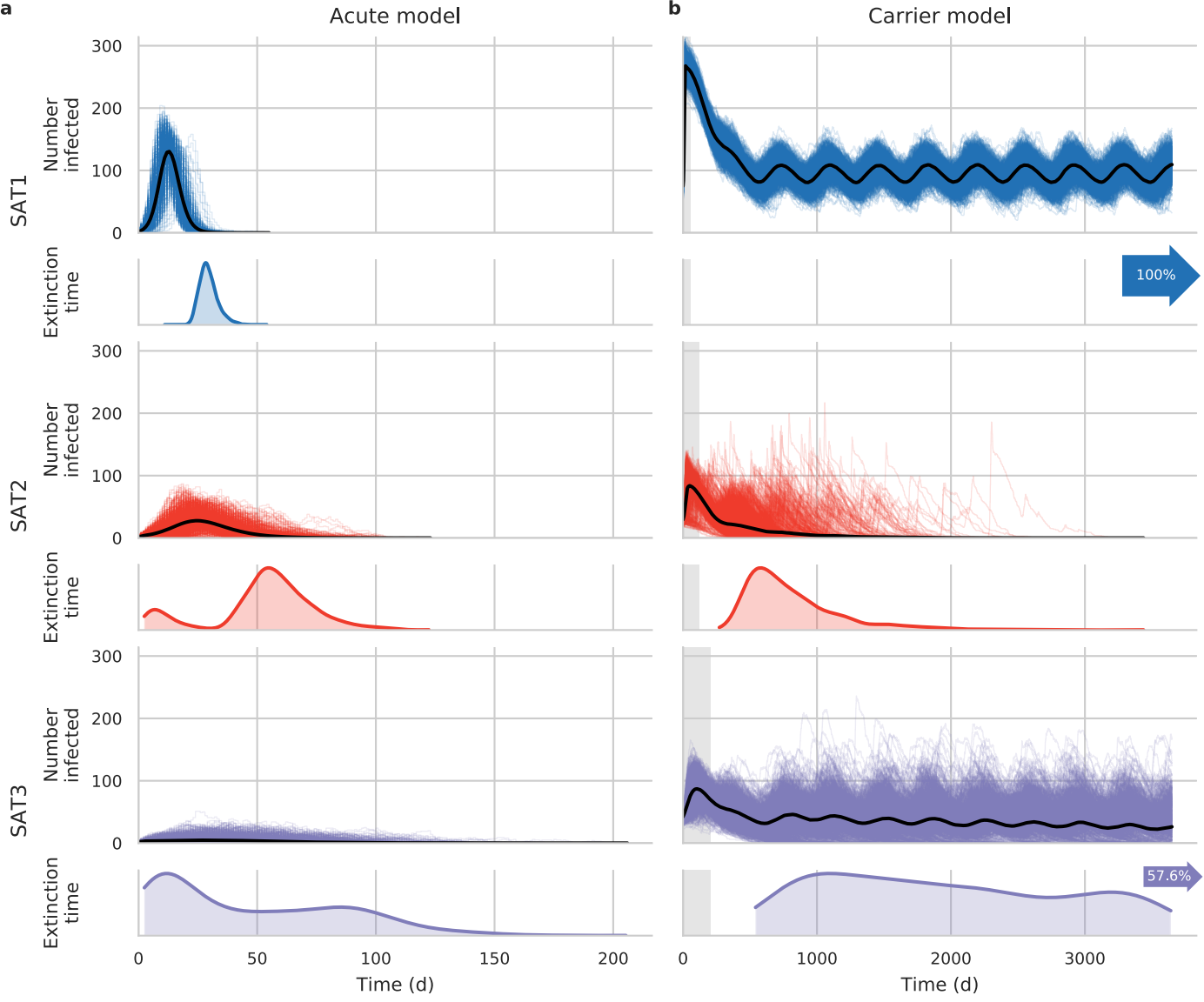
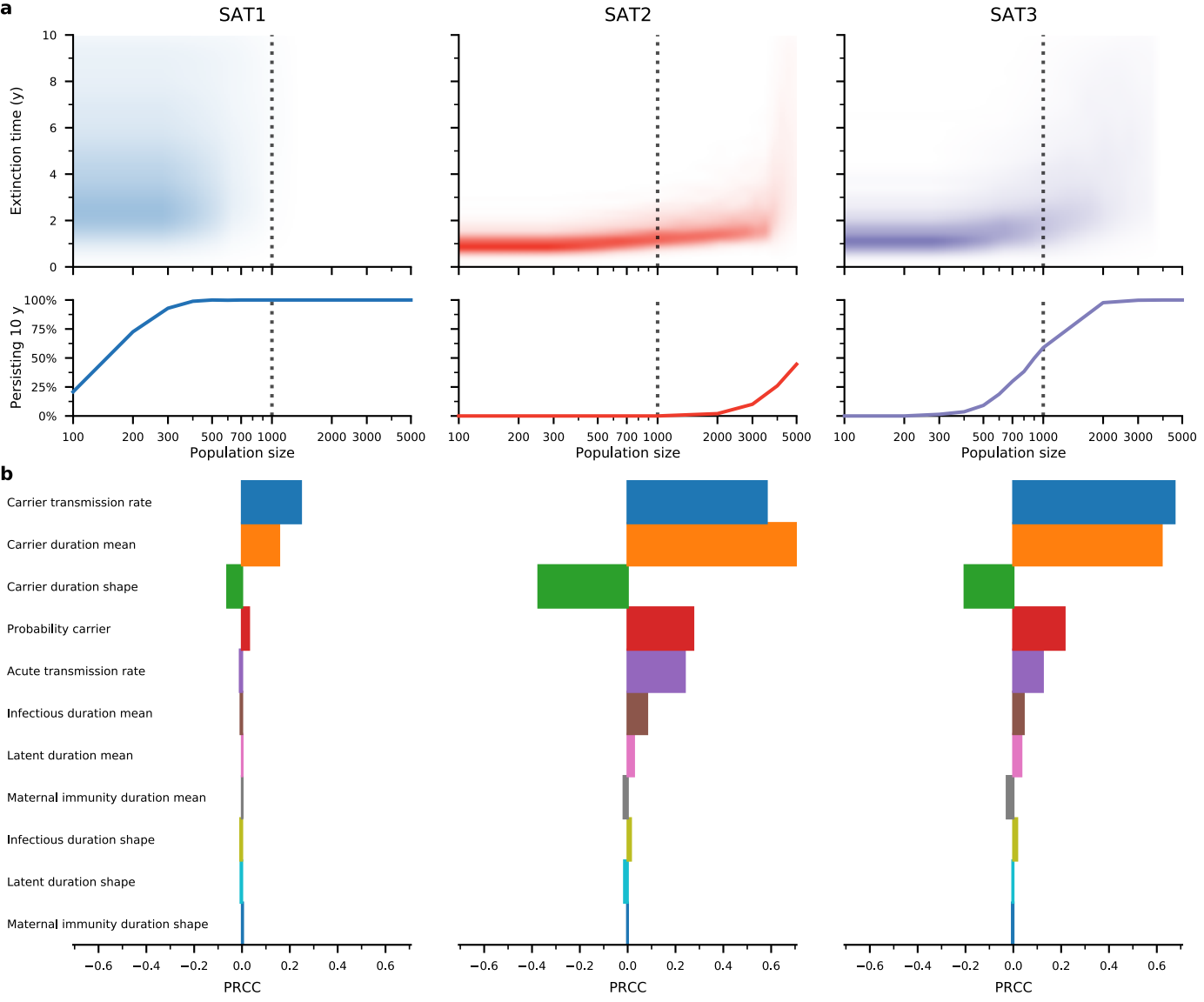

a
2013-2014
2014-2015
2015-2016
Number of births
0
2
4
6
8
Jul
Oct
Jan
Apr
b
SAT1
SAT2
SAT3
Antibody titre (log base 10)
1
2
0.00
0.25
0.50
0.75
1.00
Age (years)
c
2013-2014
2014-2015
combined
Birth hazard
Jul
Oct
Jan
Apr
d
SAT1
SAT2
SAT3
combined
Probability density
0.00
0.25
0.50
0.75
1.00
Age (years)


Mean latent period (days)
0
2
4
6
8
SAT1
SAT2
SAT3
Mean infectious period (days)
0
2
4
6
8
SAT1
SAT2
SAT3
Acute transmission rate (days^{-1})
0
5
10
15
SAT1
SAT2
SAT3
Probability of becoming a carrier
0.0
0.2
0.4
0.6
0.8
1.0
SAT1
SAT2
SAT3
Mean carrier period (days)
100
200
300
400
SAT1
SAT2
SAT3
Carrier transmission rate (days^{-1})
0.00
0.03
0.06
0.09
0.12
SAT1
SAT2
SAT3


a
Acute model
b
Carrier model
SAT1
SAT2
SAT3
Number infected
Extinction time
300
200
100
0
100%
57.6%
0
50
100
150
200
1000
2000
3000
Time (d)


a
SAT1
SAT2
SAT3
Extinction time (y)
0
2
4
6
8
10
Persisting 10 y
0%
25%
50%
75%
100%
100
200
300
500
700
1000
2000
3000
5000
Population size
b
Carrier transmission rate
Carrier duration mean
Carrier duration shape
Probability carrier
Acute transmission rate
Infectious duration mean
Latent duration mean
Maternal immunity duration mean
Infectious duration shape
Latent duration shape
Maternal immunity duration shape
−0.6
−0.4
−0.2
0.0
0.2
0.4
0.6
PRCC