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

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Abstract

Extremely contagious pathogens are a global biosecurity threat because of their high burden of morbidity and mortality, as well as their capacity for fast-moving epidemics that are

difficult to quell. Understanding the mechanisms enabling persistence of highly transmissible pathogens in host populations is thus a central problem in disease ecology. Through a combination of experimental and theoretical approaches, we investigated how highly contagious foot-and-mouth disease viruses persist in the African buffalo, which serves as their wildlife reservoir. We found that viral persistence through transmission among acutely infected hosts alone is unlikely. However, the inclusion of 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.

Outbreaks of highly contagious pathogens are 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 of 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 (reservoirs), whence they reemerge 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, which are typically of moderate size—far below the hundreds of thousands required to maintain pathogens such as measles, polio, and pertussis—remains enigmatic, as seasonal births exacerbate the risk of pathogen fade-out (*5*).

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 wildlife reservoir (*8*). FMDVs can infect numerous cloven-hoofed wildlife species as well as domestic livestock, where they cause substantial losses in production of meat and dairy (*9*). Temporal and spatial variation in FMDV antigenicity limit the efficacy of vaccination as a disease control strategy (*10*) under most circumstances (*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 global cost 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*), though maintenance in cattle may also occur (*14*). FMDVs maintain a high force of infection in free-ranging buffalo populations; serological surveys in endemic areas demonstrate that more than 98% of buffalo have been exposed to all three southern African territories (SAT) serotypes (SAT1, SAT2, and SAT3) by the time they are 2 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” that circulate 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 titers of virus are detected during persistent infection, and previous experiments attempting transmission from carrier buffalo to naïve 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.

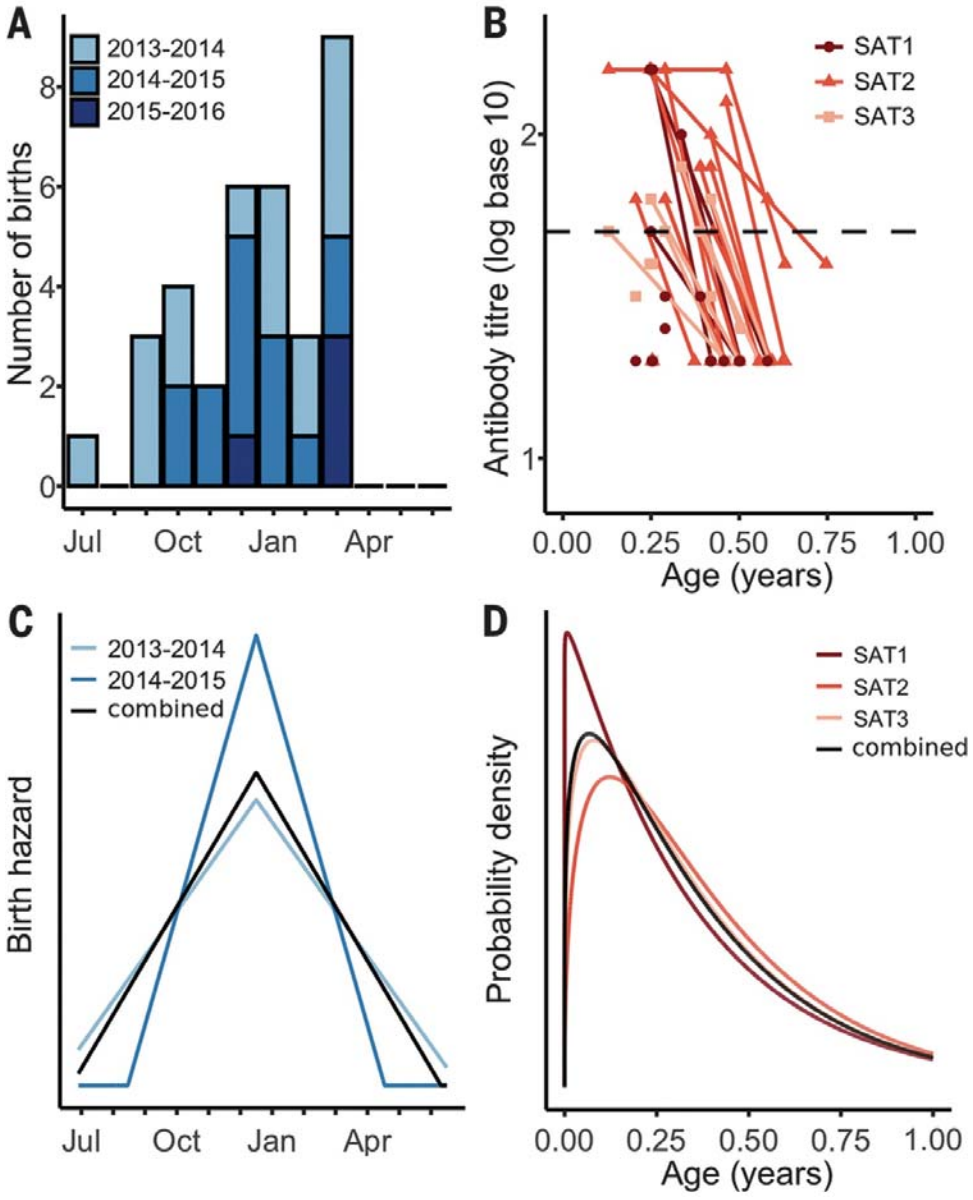

Fig. 1. Data and model parameters defining the annual birth pulse and waning of maternally derived antibodies.

(**A**) Births observed during the cohort study. (**B**) FMDV antibody titers in young calves. Lines connect longitudinally sampled titers in individual buffalo. The dashed line indicates the threshold for protective antibodies. (**C**) Birth hazard functions. (**D**) Maternally derived immunity duration density functions.

We conducted a 3-year cohort study on a buffalo herd in Kruger National Park (KNP), South Africa, 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 to 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, with the number of births peaking between December and March (Fig. 1A). Maternally derived antibodies to FMDVs waned around 5 months of age [mean 4.8 months, confidence interval (95% CI): 3.6 to 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 and tables S1 and S2). Animals susceptible to FMDVs thus entered the buffalo population annually throughout a prolonged period, peaking from May to August. Notably, the seasonal timing of births resulted in a lapse of ≥150 days 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 the three FMDV strains (SAT1, SAT2, and 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 30 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 (figs. S4B and S5). During primary infection, all SAT serotypes were readily transmitted from experimentally infected buffalo to naïve hosts. Our data support transmission models that include a latent period, as well as serotype-specific parameters (transmission rate, incubation period, and infectious period) for FMDVs in buffalo (Fig. 2 and tables S1 and S2). We estimated the fraction of buffalo that become carriers after primary infection, duration of carrier status, and transmission rates from carriers, revealing substantial variation in carrier dynamics between the three viral strains (Fig. 2 and table S1). On the basis of these parameters, the basic reproductive number(R_0) for the tested strains in models that included transmission from both acutely infected buffalo and carriers is 23.8 (95% CI: 8.2 to 73.3) for SAT1, 7.8 (95% CI: 2.1 to 41.7) for SAT2, and 7.2 (95% CI: 2.3 to 36.1) for SAT3. Models assuming transmission from only acutely infected hosts yielded notably lower basic reproductive numbers for SAT1 (15.8; 95% CI: 4.1 to 65.6) and SAT3 (5.2; 95% CI: 1.3 to 34.1), but not for SAT2 (7.5; 95% CI: 1.9 to 41.5).

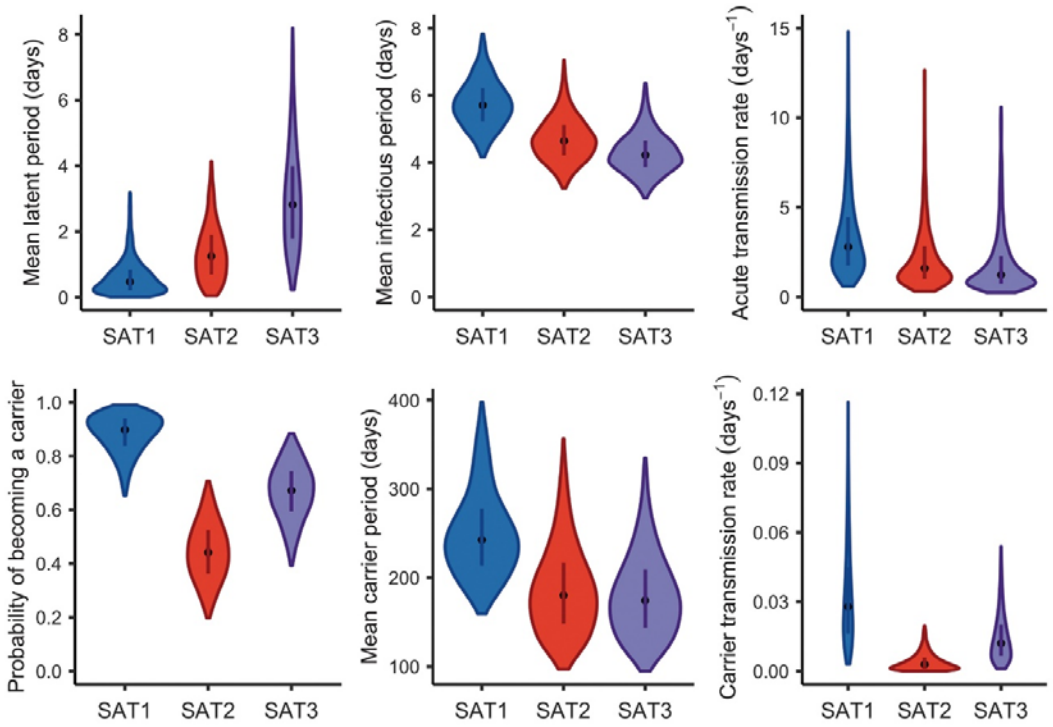

Fig. 2. Epidemiological parameters for acute infection (top) and FMDV carriers (bottom).

Black dots indicate posterior median for the parameter; lines show the interquartile range for the posterior distribution; colored shapes show the posterior distribution for each parameter estimate.

We modeled the dynamics of FMDV infections in African buffalo (i) under the null hypothesis that infection persists stochastically between birth pulses, and (ii) 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 was scaled to balance mortalities.

We extended the susceptible-exposed-infectious-recovered (SEIR) class of models to include calves that are temporarily not susceptible to infection because they are protected by maternally derived immunity, as well as carrier hosts that transmit FMDV at reduced rates (Fig. 3A). For the model with transmission during primary infection only, our simulations showed that the number of infected hosts rapidly declined to zero, and all three strains faded 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 with different initial conditions (figs. S1 and S2). When transmission from carrier buffalo is included 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; however, our models predict that SAT2 fails to persist, even with carriers (Fig. 3C), as a result of its very low estimated carrier transmission rate.

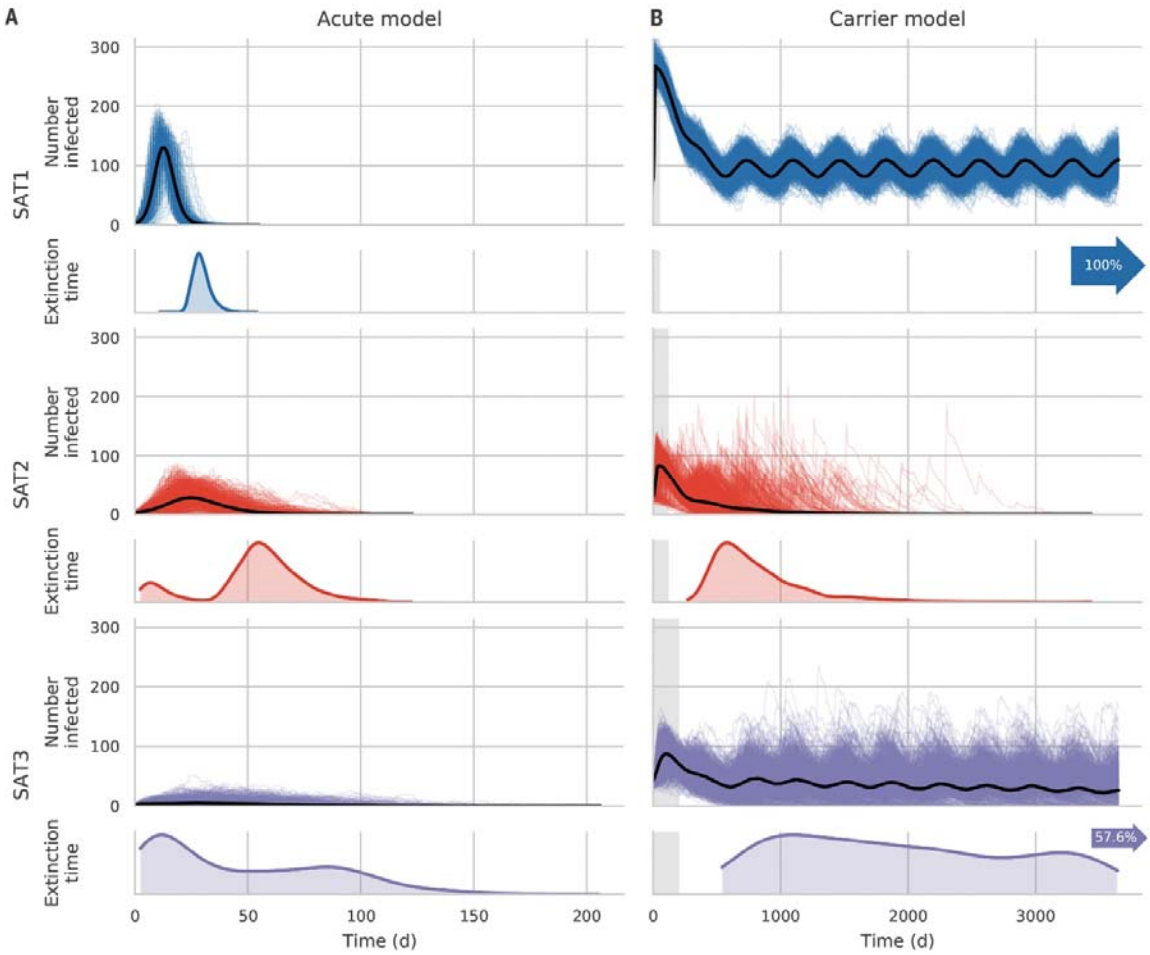

Fig. 3. Dynamics of FMDV infection for SAT1, SAT2, and SAT3.

This includes (**A**) acute transmission only, and (**B**) transmission from both acutely infected and carrier hosts. In the graphs showing the number of infected individuals, the thin, colored curves show the number infected versus time for individual simulations, whereas 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 >10 years, and the gray boxes show the longest persistence time for the model with acute transmission only to highlight the difference in scale.

Sensitivity analyses (supplementary materials section S5) revealed population size thresholds for each serotype: SAT1 required only moderate-sized populations (~400 buffalo) to persist reliably, SAT3 attained long-term persistence in populations with >2000 buffalo, and SAT2 required very large populations (~10,000 buffalo) for continued circulation, on the basis of 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 with those of the other two serotypes, suggesting that SAT1's epidemiological parameters are tuned near optimally for persistence in buffalo populations through 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.

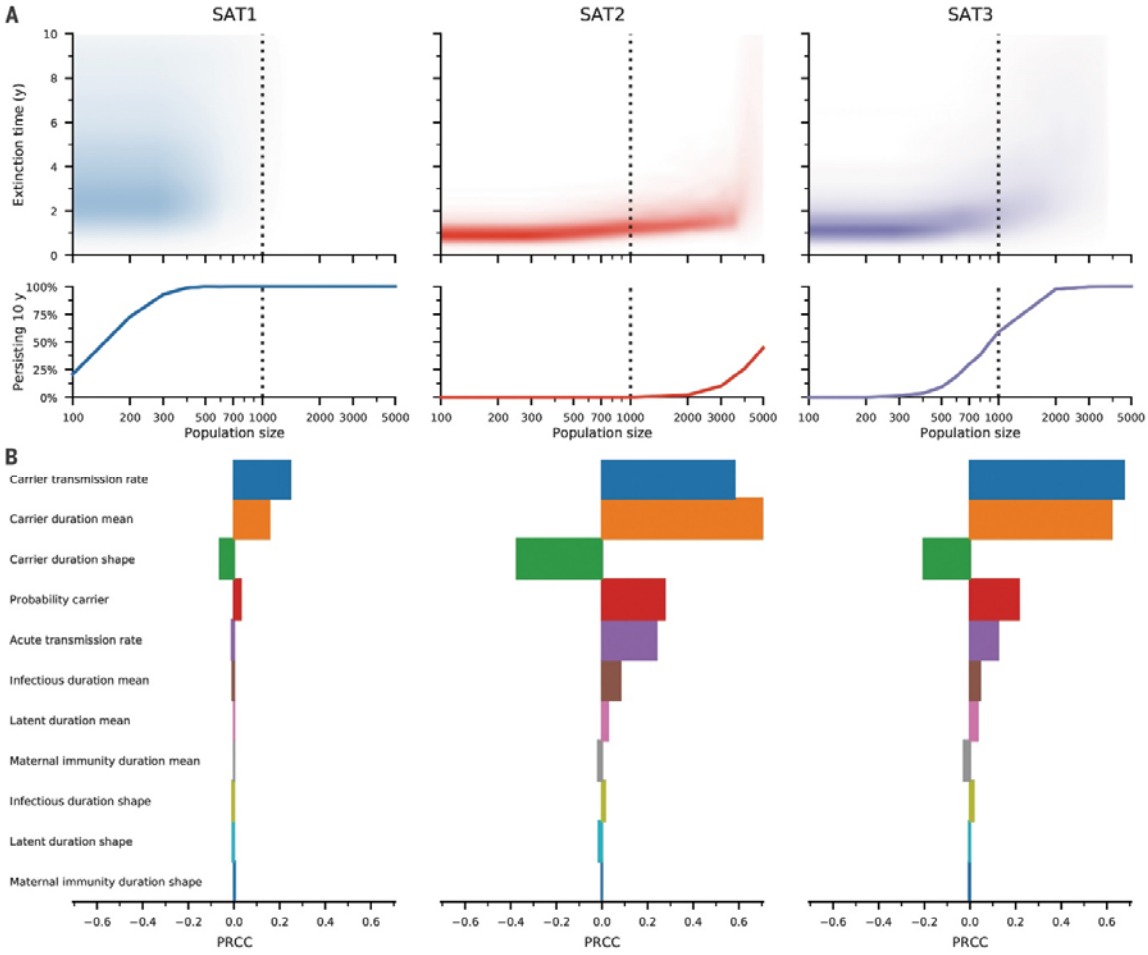

Fig. 4. Sensitivity of extinction time to buffalo population size and transmission parameters for models including acute and carrier transmission.

(**A**) The top row shows the distribution of FMDV extinction times. The bottom row shows the proportion of simulations in which FMDV persisted in the buffalo population for the whole simulated 10-year period. (**B**) Sensitivity is measured by the partial rank correlation coefficient (PRCC).

Our experiments reveal substantial 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. The transmission rate of SAT1 from carriers was two orders of magnitude lower than that from acutely infected hosts. 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 compared with that of SAT1 when considering transmission from acutely infected hosts only. Similar to SAT1, SAT3 transmitted from carrier buffalo at an approximately 100-fold reduced rate compared with its acute transmission rate. A combination of slower fade-out and occasional transmission from carriers allowed SAT3 to persist for more than 10 years in ~60% of model runs. More reliable persistence was prevented by a nontrivial 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 KNP, mitigate this risk, and our models predict long-term persistence of SAT3 in buffalo populations with >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, the result is a very low probability of persistence of SAT2 in buffalo populations, on the basis of the transmission mechanisms considered here. Although we cannot be certain that the strains 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, the entire herd was repeatedly tested for FMDV infection over 3.5 years (2014 to 2017), and no primary or chronic SAT2 infections were detected, which suggests that SAT2 may have gone extinct in our study herd. By contrast, SAT1 was transmitting regularly and SAT3 intermittently (*29*). This is 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, ongoing work examines the potential role of highly variable antibody titers, especially to SAT3, in the maintenance of viral endemic persistence. Second, RNA viruses, including FMDVs, evolve quickly (*32*–*34*) and antigenic shift may allow for reinfection of previously exposed buffalo, especially by SAT2, which has notably high nonsynonymous mutation rates (*35*). Third, interactions among different pathogens can affect transmission dynamics (*28*, *36*, *37*), but we have yet to assess interactions among the three SAT serotypes. Finally, buffalo population structure is fluid (*38*) and there is a high rate of dispersal among groups (*39*). As such, FMDVs may persist by traveling through the buffalo metapopulation, causing asynchronous epidemics across subpopulations. Indeed, because FMDVs can infect a broad range of ungulate species, transmission networks may not be limited to buffalo but may include other members of the diverse southern African ungulate assemblage (*40*, *41*) as well as livestock (*42*).

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: 20 to 30 (*7*, *43*); compare with values for measles (12 to 18) (*44*), pertussis (5.5) (*45*), and SARS-CoV2 3.8 to 8.9 (*46*)]. 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 dynamics (*47–49*) and animal infections subject to seasonal demographics (*5*) and interspecies transmission in diverse host communities (*50*, *51*). Our study reveals distinct life histories, population dynamics, and strategies for persistence even within a closely related group of highly transmissible respiratory pathogens.

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