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A review of mechanistic models of viral dynamics in bat reservoirs for zoonotic disease

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ABSTRACT

The emergence of SARS-CoV-2, a coronavirus with suspected bat origins, highlights a critical need for heightened understanding of the mechanisms by which bats maintain potentially zoonotic viruses at the population level and transmit these pathogens across species. We review mechanistic models, which test hypotheses of the transmission dynamics that underpin viral maintenance in bat systems. A search of the literature identified only twenty-five mechanistic models of bat-virus systems published to date, derived from twenty-three original studies. Most models focused on rabies and related lyssaviruses (eleven), followed by Ebola-like filoviruses (seven), Hendra and Nipah-like henipaviruses (five), and coronaviruses (two). The vast majority of studies has modelled bat virus transmission dynamics at the population level, though a few nested within-host models of viral pathogenesis in population-level frameworks, and one study focused on purely within-host dynamics. Population-level studies described bat virus systems from every continent but Antarctica, though most were concentrated in North America and Africa; indeed, only one simulation model with no associated data was derived from an Asian bat-virus system. In fact, of the twenty-five models identified, only ten population-level models were fitted to data – emphasizing an overall dearth of empirically derived epidemiological inference in bat virus systems. Within the data fitted subset, the vast majority of models were fitted to serological data only, highlighting extensive uncertainty in our understanding of the transmission status of a wild bat. Here, we discuss similarities and differences in the approach and findings of previously published bat virus models and make recommendations for improvement in future work.

KEYWORDS

Bat virus; mechanistic model; SIR model; virus dynamics; zoonotic disease

Introduction

Bats have received much attention in recent years for their roles as reservoir hosts for several, highly virulent, emerging infectious diseases of humans, including rabies and related lyssaviruses, Ebola and Marburg filoviruses, Hendra and Nipah henipaviruses, and SARS, MERS, and now SARS-CoV-2 coronaviruses [1,2]. At the time of this writing, the SARS-CoV-2 virus, which causes the disease COVID-19, has infected more than 27 million people [3]. Though the exact phylogenetic ancestry of SARS-CoV-2 is still unknown [4], the virus is believed to have originated from a common ancestor of several closely related coronaviruses, circulating in wild populations of *Rhinolophus* spp. horseshoe bats, in south-central China [5,7–9].

Predicting and preventing zoonotic emergence – or the cross-species spillover of a pathogen from a wildlife reservoir to a human host – first requires understanding transmission and infection dynamics in the reservoir population. Despite the public health impact of bat-borne zoonoses, the mechanisms by which bats maintain pathogens at the population level, including the extent to which they experience within-host infection-induced morbidity or mortality, remain poorly characterized [10–12]. Understanding these mechanisms will be critical for predicting future cross-species spillover events, as well as informing strategies of possible public health intervention. Compartmental models offer an essential tool for elucidating the mechanisms underpinning reservoir bat transmission, as they can be applied to longitudinally collected field data from bat systems to test transmission hypotheses.

Mechanistic compartmental models of pathogen transmission originated in 1915 when Sir Ronald Ross first described the mathematical relationship between mosquito biting and human malaria incidence [13]. This early Ross model classed humans into infected or uninfected 'compartments', or categories, using a system of differential equations to track movements between them [14]. Later adapted this malaria model to construct a generalized framework of pathogen transmission in a population, known as the 'SIR Model', in which individuals move between susceptible ('S'), infected ('I'), and recovered ('R') compartments. Distinct from statistical models – which demonstrate associations between variables of interest – mechanistic models describe processes underlying observations through time, as defined by the

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mathematical relationships between compartments. The compartmental model framework has allowed researchers to move beyond statistical correlations to generate and compare hypotheses regarding the infection and transmission dynamics underlying observed patterns in pathogen incidence within a population [15].

The classic SIR model has been adapted to describe pathogen transmission in many different human and wildlife systems. For instance, stochastic compartmental models once used to predict yearly influenza epidemics are now being used to capture the transmission patterns of SARS-CoV-2 in human populations across the globe [16,17]. Mechanistic elucidation of viral transmission in bats has not been pursued with the same energy. Given that bats represent one of the most important source taxa for emerging zoonotic infections [18–20], mechanistic models of viral dynamics in bat reservoirs will play a vital role in efforts to predict or prevent the next spillover [21]. In this review, we identified and analyzed twenty-five mechanistic models elucidating the dynamics of viruses circulating in bat reservoir systems. We catalog model characteristics to compare the advantages and disadvantages of various modeling approaches, as well as identify gaps in the existing research on potentially zoonotic infections in bat hosts. We collate previous findings and highlight priorities for future research with the goal of advancing modeling efforts to elucidate within- and between-host dynamics of potentially zoonotic viruses in bat reservoirs – a critical step toward developing frameworks for predicting and preventing spillover to humans.

Materials and methods

Surveying the literature

We surveyed the literature for previous modeling studies of virus dynamics in bat reservoir hosts, querying both Web of Science and Google Scholar with the following search terms: 'bat virus model', 'bat virus transmission', 'bat virus dynamics', and 'bat virus mechanism'. We examined all results returned by Web of Science and the first fifty pages of results returned by Google Scholar and collected information on any study which reported a mechanistic model of virus transmission or infection dynamics in a bat reservoir host. We list all models of unique virus-host associations recovered from this search in Table 1, along with information on author, journal, publication year, broad virus taxonomic group (family or genus), virus species, bat host, study site, scale of model, and approach to data.

From these studies, we further identified a subset of eight publications that fitted compartmental models to field data from ten distinct host-virus systems with the aim of elucidating mechanisms of virus persistence in bat reservoir hosts at the population level (Table 2). From this data subset, we further collected information on the compartmental model structures tested, the modeling approach (continuous vs. discrete, deterministic vs. stochastic, frequency- vs. density-dependent transmission), the study design of the associated data, the method of model fitting, and the resulting conclusions – including estimation of the basic pathogen reproduction number (R_0) for the virus. R_0 describes the number of new infections generated by one existing infection in a completely naïve host population and is a key parameter in understanding a pathogen's intrinsic probability of persistence and transmissibility – including transmissibility across species [21]. For two continuous time fitted models of host-virus associations from our Table 2 subset which did not report R_0, we calculated R_0 from the system of equations and best-fit parameters reported in the corresponding article using a Next Generation Matrix (NGM) approach [22–24] (Supplementary Appendix 1 and 2). For two discrete time fitted models from our Table 2 subset that did not report R_0 [both from 25], we calculated R_0 following a discrete time approximation of the NGM approach, again using best-fit parameters reported in the corresponding article [24,26] (Supplementary Appendix 3). All maps and summary figures were generated using R v. 4.0.0 for Macintosh.

Results

Broad patterns across the literature

Our literature search identified twenty-three publications (published between 2007 and 2020) which presented results from mechanistic models applied to twenty-five distinct bat-virus systems [two of the studies – [25,27] – applied the same modeling framework to two different bat-virus associations, using data from the same field study] (Table 1). All models were focused in one discrete study system, the geographic locality of which ranged across every continent except Antarctica, and centered on a few particular species of bat host, which spanned both the major Yangochiropteran and Yinpteropchiropteran suborders of the bat clade (Figure 1). Each model was applied to one of the four major bat virus families/genera of interest, with the majority (eleven) focused on lyssaviruses (particularly rabies), followed by filoviruses (seven), henipaviruses (five), and, finally, coronaviruses (two).

The frequency of these studies increased across the timespan captured in our dataset, suggesting that research into the mechanisms underpinning bat virus dynamics is on the rise (Figure 2). While early studies tended to focus on the dynamics of lyssaviruses in North and South American systems, more recent work shows an emphasis on studies conducted in Africa, often with

Table 1. All published mechanistic models of virus dynamics in bat systems (2007–2020).

Virus Taxonomy	Virus	Publication	Bat Species	Study Site	Scale	Approach to Data
Lyssavirus	**RABV**	[28]	*Tadarida brasiliensis*	Mexico; Texas, USA	nested within-host/population-level	pure theory
		[30]	'North American bats'	Mexico; Texas, USA	nested within-host/population-level	pure theory
		[29]	*Tadarida brasiliensis, Eptesicus fuscus*	Mexico; Texas, USA	nested within-host/population-level	simulated with data-derived parameters
		[40]	*Eptesicus fuscus*	Colorado, USA	population-level	fitted to data
		[41]	*Desmodus rotundus*	Peru	population-level	fitted to data
		[34]	*Desmodus rotundus*	Peru	population-level	fitted to data
	EBLV-1	[32]	*Myotis myotis*	Spain	population-level	simulated with data-derived parameters
		[33]	*Myotis capaccinii, Myotis myotis, Miniopterus schreibersii, Rhinolophus ferrumequinum*	Balearic Islands, Spain	population-level	simulated with data-derived parameters
		[43]	*Myotis myotis, Miniopterus schreibersii*	Spain	population-level	fitted to data
	LBV	[27]	*Eidolon helvum*	Africa	population-level	fitted to data
		[47]	*Eidolon helvum*	Ghana	population-level	fitted to data
Filovirus	**EBOV**	[58]	*Rousettus aegyptiacus* and 'African bats'	Africa	population-level	simulated with data-derived parameters
		[56]	'African bats'	Africa	population-level	simulated with data-derived parameters
		[54]	'African bats'	Africa	population-level spillover	pure theory
		[55]	'African bats'	Africa	population-level spillover	pure theory
		[57]	'African bats'	Africa	population-level	pure theory
	Madagascar EBOV	[25]	*Pteropus rufus*	Madagascar	population-level	fitted to data
	rVSV-EBOV, rVSV-MARV	[31]	cells of: *Pteropus alecto, Rousettus aegyptiacus*	–	within-host	fitted to data
Henipavirus	**HeV**	[69]	*Pteropus alecto, Pteropus poliocephalus*	Australia	population-level	simulated with data-derived parameters
		[70]	*Pteropus alecto, Pteropus poliocephalus*	Australia	population-level	simulated with data-derived parameters
	GhV	[27]	*Eidolon helvum*	Africa	population-level	fitted to data
		[71]	*Eidolon helvum*	Ghana	population-level	fitted to data
	Madagascar NiV	[25]	*Eidolon dupreanum*	Madagascar	population-level	fitted to data
Coronavirus	**SARS-CoV-2**	[77]	*Rhinolophus* spp. bats	China	population-level spillover	simulated with data-derived parameters
	Alpha-CoV	[78]	*Myotis macropus*	Australia	population-level	fitted to data

The 25 studies analyzed in this review are organized by viral taxonomy and approach to data. [25,27], occupy two entries in this table to reflect the two discrete transmission models for different bat-virus systems investigated in each paper.

Table 2. Summary of data-fitted models investigating virus transmission dynamics.

Virus	Publication	Data Description	R_0 Estimate	Best Fit Model Description	Other Models tested?	Key Conclusions
RABV	[40]	• Transmission rate estimated from 5-yr serological study of RABV in *E. fuscus* bats in Colorado, using data from recaptured individuals. • Sample size not reported • Frequency of sampling not reported • Number of sites not reported	0–64.8*	• Three season-specific submodels: (1) main transmission summer season; (2) winter hibernation season with no transmission; (3) spring early transmission season with slower disease progression. • All submodels have the same epidemic classes: S(EiI)ErR. • Exposed individuals can either become infectious and die, or recover and acquire lifelong immunity. • Four age classes • Seropositive epidemic class = R • Infection-induced mortality assumed	• Tested three alternative models with altered dynamics but no change in epidemic classes: (1) no transmission or disease progression during early transmission spring season (2) no transmission but slow disease progression during early transmission season (3) no density-dependence in demographic rates	• Hibernation supports viral maintenance by preserving rabies infections, through suppressed viral activity (prolonged incubation periods) and reduced mortality, until the next birth pulse replenishes the pool of susceptibles in the following year.
	[41]	• 4-year serological study across 17 sites • yearly sampling • 1436 *D. rotundus* bats binned into broad (juvenile, adult) age classes	0.61 (mean across four regions)	• SE(INIR)RS • Exposed bats either acquire immunity and temporary immunity, or become infected, beginning with a subclinical noninfectious phase and progressing to a rabid infectious phase which always results in death • Seropositive epidemic class = I, R • Infection-induced mortality tested & supported	• Tested three alternative models: (1) SE(INIR)RS: infection not always lethal (2) SE(INIR)RS with immune boosting in R-class based on the force of infection (3) SE(INIR)R: lifelong immunity	• Migration and temporarily immunizing nonlethal infections are needed to explain rabies persistence.
EBLV-1	[43]	• 4-year serological study across 2 sites • Twice yearly sampling • 279 *M. schreibersii* sampled • 25 *M. myotis* sampled	0.53–1.6	• SEIRS metapopulation model • Non-lethal infection and waning immunity with migration and cross-species transmission between sites • Seropositive epidemic class = R • No infection-induced mortality assumed; nonlethal infections supported	• Presented two alternative model forms in simulations but did not evaluate fit to data: (1) SE(I)RS: progression to infectious rabies always lethal; recovery only from noninfectious exposure confers temporary immunity (2) SE(I)R: progression to infectious rabies always lethal; recovery from noninfectious exposure confers permanent immunity	• EBVL-1 persistence depends on migration between roosts, cross- species transmission, and survival (followed by temporary immunity) of infected bats

(*Continued*)

Table 2. (Continued).

Virus	Publication	Data Description	R_0 Estimate	Best Fit Model Description	Other Models tested?	Key Conclusions
LBV	[27]	• Cross-sectional age- seroprevalence data from six regions collected across different years • 603 *E. helvum* bats sampled and aged via dentition	1.6	• MSIRS: A parameterized proportion of individuals are born with maternal antibody-mediated immunity, which wanes to susceptibility. Infection results in antibody-mediated recovery which wanes back to susceptibility • Age-structured to match precisely aged data from bat dentition. • Seropositive epidemic class = I,R • No infection-induced mortality assumed; nonlethal infections supported	• MSIR also tested. Weak support recovered for waning immunity	• Maternally-derived immunity and waning adult immunity are necessary to reproduce observed serological dynamics. • Hypothesized that some bats must experience prolonged infections or latency to recover viral persistence. • The effect of maternal immunity on persistence varies based on other transmission parameters.
	[47]	• 4 year serological study across 6 sites • Sporadic intervals • 1167 *E. helvum* bats sampled, binned into broad (juvenile, adult) age classes	1.903*	• MSE(I)R: Maternal immunity wanes to susceptibility, exposed bats either become infectious and die or recover with lifelong immunity • Broad age-structured (juvenile/adult) • R-class mothers produce M-class juveniles • Seropositive epidemic class = R • Infection-induced mortality assumed and supported	None	• Long incubation periods and low pathogen-induced mortality promote low population-level persistence. • Serological data suggests lifelong immunity.
Madagascar EBOV	[25]	• 18 month serological study at one site • ~five annual ampling sessions per month • Models fit to 123 *Pteropus rufus* bats aged via dentition	0–0.742*	• MSIRN: Maternal immunity (M) wanes to susceptibility, recovered bats wane in antibody signature but maintain immunity (N). • R-/N- class mothers produce M- class juveniles. • 20 age classes • Seropositive epidemic class = R • Infection-induced mortality discussed, not tested	• Multiple alternative hypotheses tested: MSIR, MSIRS, MS(R)IR, MSI[RN] • Some support for recovered immunity waning back to susceptibility (MSIRS).	• Support for waning immunity and possible longterm infections • Decreasing seroprevalence reported in older age class bats
GhV	[27]	• Cross-sectional age- seroprevalence data from six regions collected across different years • 791 *E. helvum* bats sampled and aged via dentition	2.1	• MSIRS: A parameterized proportion of individuals are born with maternal antibody-mediated immunity, which wanes to susceptibility. Infection results in antibody-mediated recovery which wanes back to susceptibility • Precisely age-structured to match data. • Seropositive epidemic class = I,R • No infection-induced mortality assumed; nonlethal infections supported	• MSIR also tested. Support much stronger for assumptions of waning immunity	• Maternally-derived immunity and waning immunity are necessary to reproduce observed serological dynamics. serological dynamics • Hypothesized that some bats must experience prolonged infections or latency to recover viral persistence. • The effect of maternal immunity on persistence varies based on other transmission parameters.

(*Continued*)

Table 2. (Continued).

Virus	Publication	Data Description	R_0 Estimate	Best Fit Model Description	Other Models tested?	Key Conclusions
	[71]	• 9 years of longitudinal serology from captive colony of *E. helvum*. • Sampling intervals sporadic • Models fit to data from 1890 individual bat captures, including multiple recaptured individuals	For SEI+: 2; For R+: 66.7	• SEIRS: Bat progresses from susceptible to exposed (seroconverting in the process), then can return to S immediately or progress into an infectious cycle with periods of latency. • Infectious bats are favored to survive infection and recontribute to later transmission, different from RABV. • Models fitted under two different assumptions with respect to serology: (1) EIR+: whereby E,I, and R classes are all seropositive (2) R+: whereby only R class bats are seropositive • No infection-induced mortality assumed; nonlethal infections supported	• All possible combinations of S,E,I, and R tested under both EIR+ and R + assumptions.	• Reinfection is necessary to explain viral persistence at the population-level. • Strong support for persistent, recrudescent infections, and short-lived immunity under both assumptions of serology.
Madagascar NiV	[25]	• 18 month serological study at one site • five annual sampling sessions per year • Models fit to data from 72 *Eidolon dupreanum* bats aged via dentition	0–0.585*	• MSIRN: Maternal immunity (M) wanes to susceptibility, recovered bats wane in antibody signature but maintain immunity (N), age-structured. R-, and N-class mothers produce M-class juveniles. • Seropositive epidemic class = R • Infection-induced mortality discussed, not tested	• Multiple alternative hypotheses tested: MSIR, MSIRS, MS(R)IR, MSI[RN] • Some support for recovered immunity waning back to susceptibility (MSIRS).	• Support for waning immunity and possible longterm infections • Decreasing seroprevalence reported in older age class bats
Alpha-CoV	[78]	• 12-week mark- recapture study at one maternal roost • Real-time CoV detection determined via PCR • Models fit to data from 42 individually recaptured bats	1.59	• SIt(Ip)RS: Bats can become either transiently or persistently infectious, prior to achieving temporary immunity and returning to susceptible status	• Alternative SIRS model also tested, allowing for only one transient infectious class (no persistent infections). • Better support achieved for SIt(Ip)RS	• Support recovered for models allowing bats to become transiently or persistently infectious, while maintaining an option to progress to recovery and return to susceptibility

* **R_0 values for** [25,40,47] were not reported in the original articles but were calculated for this paper. For [40,47], we used a Next Generation Matrix approach [23] (Supplementary Appendix 1 and 2), and for [25], we used the discrete time approximation of this methodology [22,24,26] (Supplementary Appendix 3).

M = Maternally-derived immunity; S = Susceptible; E = Exposed; $I_{(T/P)}$ = Infected (Transiently/Persistently); R = Recovered; N = Non-antibody-mediated immunity or sub-seropositive antibody titers.

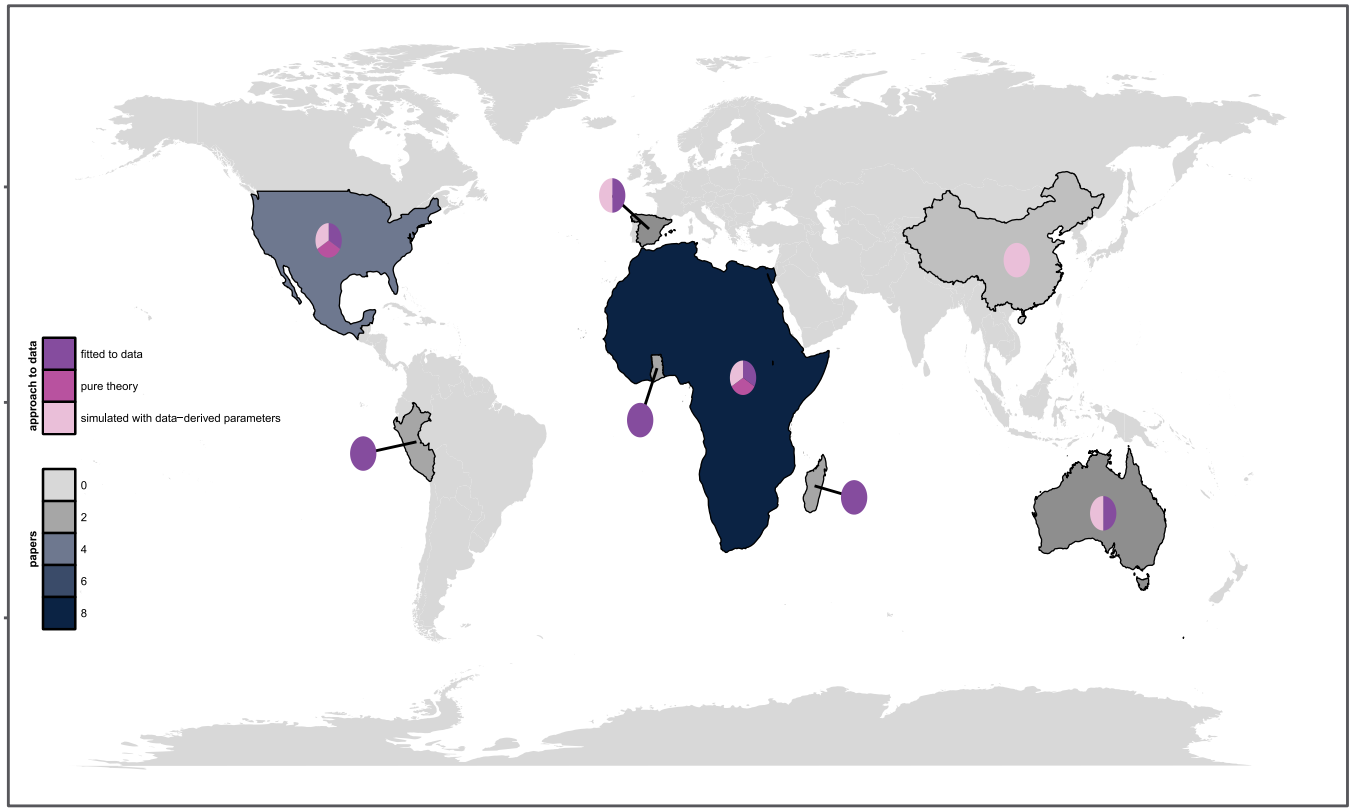

Figure 1. Distribution of bat virus modeling studies to date. Shading hue indicates the number of bat virus modeling studies conducted to date. Colored pie-charts indicate each model's approach to data (by percentage) for each locality, whether purely theoretical, simulated using data-derived parameters, or explicitly fitted to data. For theoretical models that did not specify a distinct locality, the continent (i.e. Africa) is shaded instead.

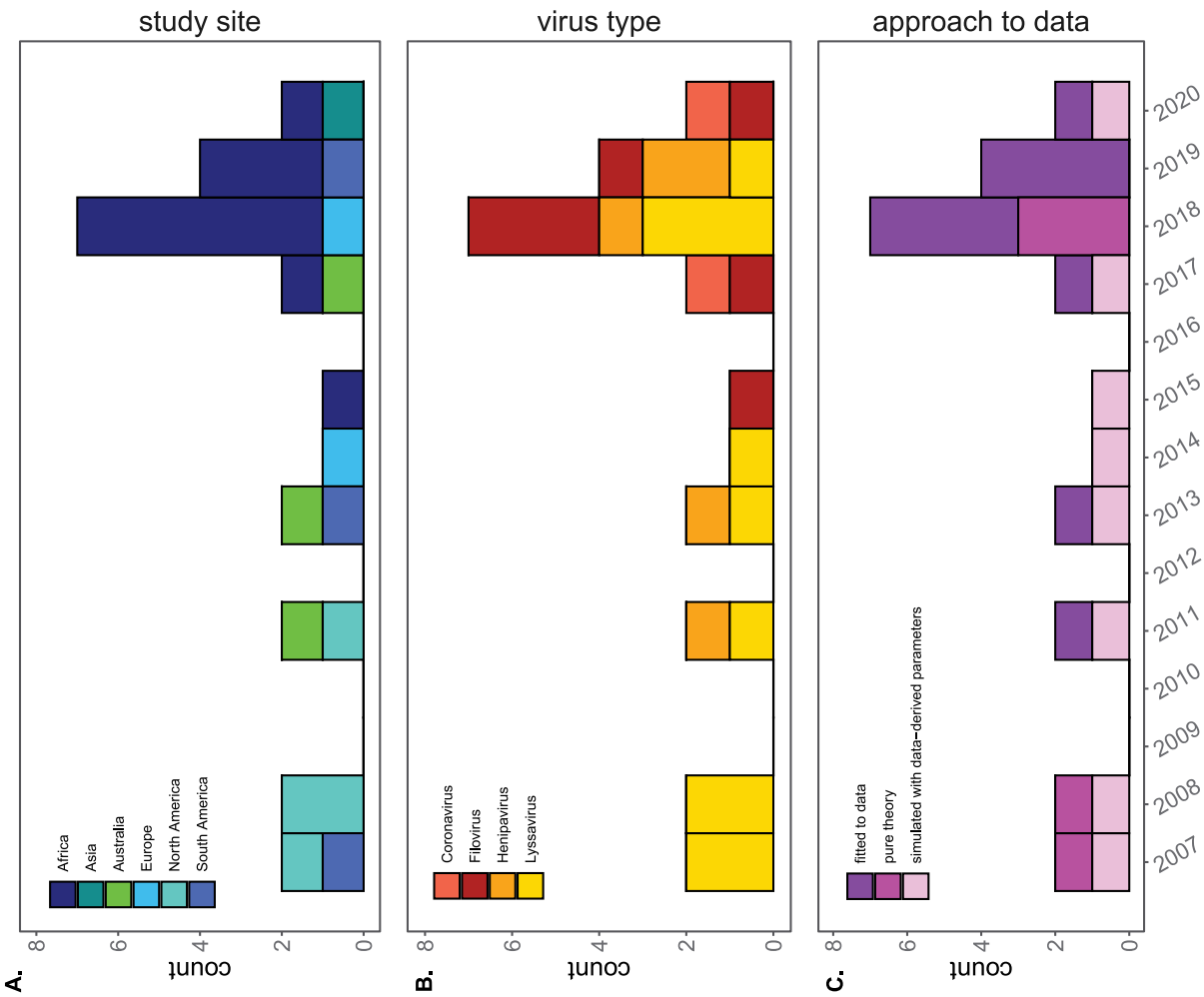

Figure 2. Trends in mechanistic modeling of bat-virus systems. Histogram of timeline of publication for mechanistic models of bat-virus systems, organized by (a) Locality of focal study site, (b) Taxonomy of virus studied, and (c) Approach to data, as shown in Figure 1.

a focus on filoviruses (Figure 2(a,Figure 2b)). Of the twenty-five systems modeled, twenty-one were focused at the population-level, while four described the within-host dynamics of viral pathogenesis in a bat immune system (Table 1). Among the within-host studies, three of the four embedded the within-host model into a population-level framework to explore how within-host metrics, such as viral load or antibody titer, translated to population-level processes, such as transmission and mortality [28–30]. The fourth model kept the analysis focused at the level of within-host viral dynamics [31].

Across the entire dataset, thirteen of twenty-five models were purely theoretical or based on simulations using data-derived parameters from previous publications or analysis of field data external from the model construction [32,33]. The remaining twelve models were explicitly fitted to data, using a variety of statistical techniques. Notably, we observed that data-fitted models have increased in frequency in recent years (Figure 2(c)), suggesting that these studies represent a new research focus. Of these fitted models, one [31] was a within-host model fitted to *in vitro* data in bat cell tissue culture, while the other eleven were fitted to field data. One of the field-based models [34] was used to evaluate the efficacy of a proposed intervention (a transferable, orotopical rabies vaccine), while the remaining ten all aimed to identify the transmission dynamics underlying pathogen persistence in various bat systems – with a particular focus on four zoonotic bat virus taxa of interest: lyssaviruses, filoviruses, henipaviruses, or coronaviruses (Table 2). We summarize modeling insights across this taxa in the following sections.

Lyssaviruses

Lyssaviruses are non-segmented, single-stranded, negative-sense RNA viruses in the family Rhabdoviridae, order Mononegavirales [35]. Lyssaviruses can be classed into three distinct phylogroups, which all show a strong association with bats [36]. Lyssaviruses in phylogroup I include rabies virus (RABV), one of the oldest known viral zoonoses that accounts for over 60,000 human deaths per year [37]. Though most RABV infections in humans are sourced from domestic dog populations [37], the virus also persists in wild, Yangochiropteran bats across the New World, and bat-sourced infections account for the majority of RABV cases annually in the United States [38]. Outside of the Americas, both Yinpterochiropteran and Yangochiropteran bats maintain a suite of diverse lyssaviruses; besides RABV, several other phylogroup 1 lyssaviruses with bat origins are known to infect humans, including Australian bat lyssavirus (ABLV), European bat lyssavirus (EBLV), and Duvenhage lyssavirus (DDUV) [36]. Though all lyssaviruses are presumed to have some zoonotic capacity [39], bat-borne lyssaviruses in phylogroup 2 (i.e. Lagos Bat Virus, LBV) or phylogroup 3 (i.e. Leida bat lyssavirus, LLBV) have not yet been identified infecting humans.

In our review, we identified eleven models describing the dynamics of bat-borne lyssaviruses, the majority of which (six) were focused on RABV infections in Yangochiropteran bats in the New World, while three others explored EBLV-1 dynamics in European Yangochiropterans, and two others investigated LBV dynamics in Yinpterochiropterans in Africa (Table 1). Of the RABV studies, three hailed from the same research group [28–30], which used theoretical, within-host models to explain how heterogeneity in individual-level immune responses could promote population-level maintenance of rabies virus in New World Yangochiropteran bats. The authors found that models allowing for disparate dynamical outcomes based on the viral load of an initial infection were critical to obtaining population-level viral persistence; in particular, models allowing low-dosed bats to clear infections and progress to a state of temporary immunity prior to a return to susceptible status best supported viral maintenance within the population.

In addition to these within-host theoretical simulations, we identified three compartmental models of RABV infections in bat populations, all of which were fitted to field data to explore the dynamics underpinning RABV persistence in North American *Eptesicus fuscus* [40] or Peruvian *Desmodus rotundus* [41], or to assess the efficacy of communicable vaccines for RABV elimination in Peruvian *D. rotundus* [34]. Like the within-host models, the population-level models demonstrated an important role for heterogeneous immune responses in rabies virus maintenance: [40] fit season-specific susceptible-exposed-infectious-recovered SE(I)R models – in which exposed bats can either become infectious and die or recover and acquire lifelong immunity – to a five-year mark-recapture time-series tracking serological status of wild, *Eptesicus fuscus* in Colorado and demonstrated support for elevated mortality rates in infected individuals. Importantly, the authors determined that viral persistence was only possible in this population when models allowed for reduced mortality rates, and long viral incubation times across the winter hibernation period that 'preserved' infections until the summer birth pulse replenished the pool of susceptibles. Our R_0 calculations from this study highlight the intense seasonal variation in the probability of viral persistence: we estimated R_0 at 64.8 during the summer transmission period immediately following the peak birth pulse and at zero during winter hibernation and early summer transmission seasons (Table 2; Supplementary Appendix 1).

Like [40, 41] modeled two outcomes of viral exposure when fitting models to field data on vampire bat rabies in Peru – one resulting in seroconversion without progression to an infectious state and a second by

which exposure resulted in infectious rabies disease and eventual virus-induced mortality. However, since *D. rotundus* do not hibernate, they were unable to adopt the same seasonal variation in mortality rates and the long incubation periods that supported rabies persistence in the Colorado study. Instead, bats that seroconverted without progression to a diseased state acquired temporary – as opposed to lifelong – immunity with eventual return to a susceptible state (Figure 3). Even still, [41 reported a range of site-specific R_0 values <1 for their system (Table 2), suggesting that the virus cannot be maintained at the population level in the absence of immigration within a spatially-structured metapopulation. Finally, in the last mechanistic model of RABV dynamics identified in our system, [34], built on the model published by [41], to investigate the efficacy of communicable, orotopical rabies vaccines for reducing rabies virus outbreaks in Peruvian *D. rotundus* bats. The authors found that realistic levels of vaccine uptake and transfer would be likely to reduce the probability, size, and duration of an outbreak. In particular, they highlighted advantages of immunization over bat culling as a strategy for reducing transmission – unlike vaccination, culling may increase recruitment of susceptible juveniles into the system, making the intervention ineffective or counterproductive [34,42].

In addition to RABV, our review of the literature recovered three mechanistic models of the dynamics of EBLV-1 infection in European Yangochiropterans. [32] estimated R_0 (reported at 1.706) and the average duration of infection from a twelve-year longitudinal serological study of EBLV-1 dynamics in *Myotis myotis* bats in Spain, and then, using these estimates combined with parameters gleaned from the literature, simulated viral dynamics in a standard susceptible-infectious-recovered (SIR) framework (Table 1). Though data-inspired, the authors did not explicitly fit their transmission model to their data, making it impossible to assess the efficacy of this transmission structure in maintaining the virus in the Spain field system. [33] took a similar approach in modeling the

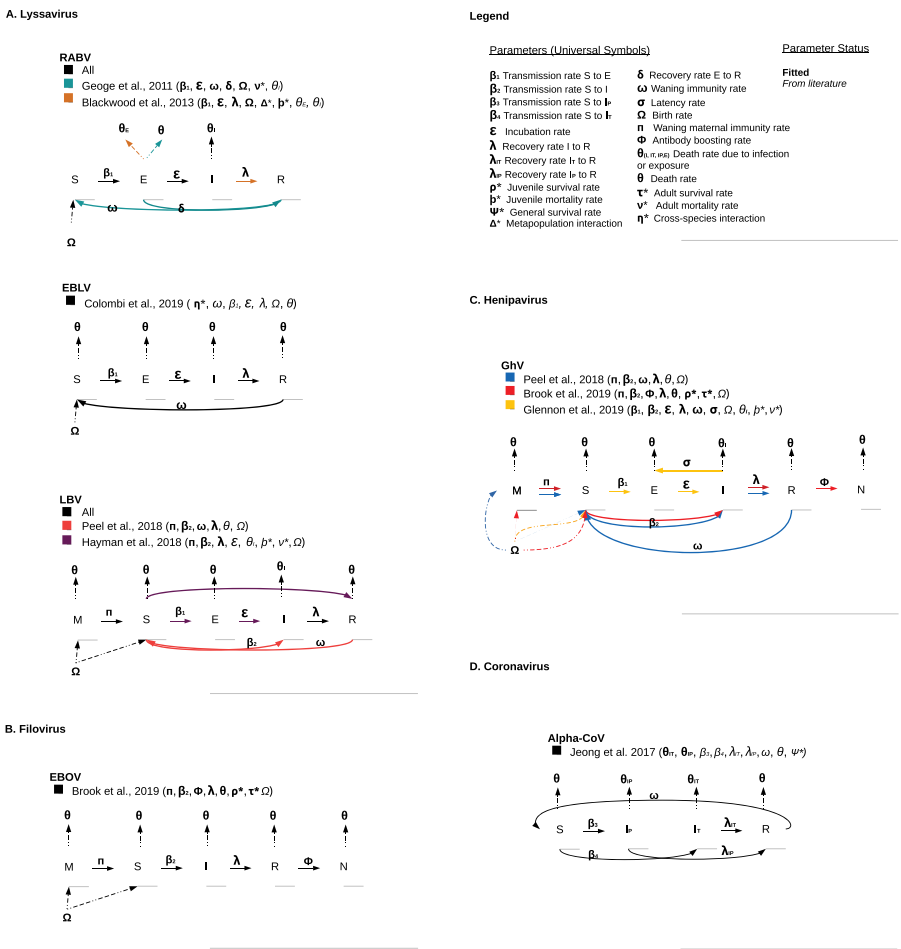

Figure 3. Universal compartmental model structure for models fitted to data. Compartmental model structure of each viral taxonomic group: (a) Lyssaviruses, (b) Filoviruses, (c) Henipaviruses, and (d) Coronaviruses. For lyssaviruses, structure is shown separately for rabies (RABV), European bat lyssavirus-1 (EBLV-1), and Lagos bat virus (LBV). For all diagrams, universal pathways are depicted in black, and those unique to a specific published model are depicted in color. Each parameter's status (fitted or drawn from the literature) is indicated adjacent to the author by the font face (bold or italicized) of the text. Age-structure and metapopulation dynamics are not depicted in the compartmental diagrams depicted here, but parameters specific to these more complex dynamics are listed adjacent to the author with an asterisk.*

dynamics of EBLV-1 infection and cross-species transmission among three Yangochiropteran (*Myotis capaccinii, Myotis myotis, Miniopterus schreibersii*) and one Yinpterochiropteran [*Rhinolophus ferrumequinum*) bat species in a three-site metapopulation in Mallorca, Spain. The authors simulated viral persistence and extinction under a suite of different R_0 values in a multi-species, metapopulation SEIRS framework and reported a heightened role for *M. schreibersii* in sourcing cross-species transmissions in the system – largely as a result of the high population density and rapid migration rates used for this species in the simulations. As with [32], the lack of validation of the [33] model against field-derived data made it impossible to assess its validity. [43] compared simulations of spatially explicit, multi-species metapopulation models of EBLV-1 transmission in *Miniopterus schreibersii* and *Myotis myotis* with and without virus-induced mortality. The authors found support for an SEIRS model structure which assumed – as previously modeled by [32,33] – no virus-induced mortality in bats infected with EBLV-1 (Figure 3). However, in contrast to the purely simulation-focused studies discussed above, [43] then fit this SEIRS framework to data from a four-year field survey tracking EBLV-1 seroprevalence in *Miniopterus schreibersii* and *Myotis myotis* across two sites in Catalonia. They reported a range of R_0 estimates across their field system (from 0.53 to 1.6) and emphasized the need for cross-species mixing and spatial metapopulation structure in maintaining the virus in their system – with a pronounced role for *M. schreibersii* in sourcing infections across the metapopulation due to its migratory behavior and high population density in the system. Despite fitting their SEIRS model to data, however, [43] did not explicitly compare fits of alternative transmission models allowing for infection-induced mortality. Thus, due to the absence of comparative hypotheses, we cannot be confident that EBLV-1 does not result in infection-induced mortality in bat hosts. Indeed, experimental infection with EBLV-1 in bats can cause mortality [44, 45], and pathological effects of infection have been posited in wild bat systems, as well [46].

Finally, the last two lyssavirus models uncovered in our search aimed to decipher the mechanisms underlying LBV persistence in Yinpterochiropteran bats, specifically *Eidolon helvum* bats on the African continent. Both [27,47] fit their models to field-derived data for *E. helvum*, the former using a cross-sectional serological dataset spanning six African countries and the latter using a longitudinal serological time series spanning four years of ~quarterly sampling (Table 2). [27] fit a maternally immune-susceptible-immune-recovered-susceptible (MSIRS) model to age-seroprevalence data, assuming the I class to correspond to seropositive status with no virus-induced mortality. They estimated an R_0 value of 1.6 for LBV in the pan-African *E. helvum* population and a duration of immunity of twelve years, which they posited to be lifelong. Deviating from [27,47] found support for LBV-induced mortality and lifelong immunity, with long incubation periods and low pathogen-induced mortality promoting low population-level persistence. Specifically, the authors fit an age-structured MSE[I]R model to longitudinal serological data grouped into broad (juvenile-adult) age classes. Like [40,47] model allowed for exposed bats to either seroconvert immediately and acquire lifelong immunity or progress to an infectious state that resulted in virus-induced mortality. [47] did not report a value for R_0 in their system, but we estimated it here to be between 0 and 1.90, depending on the seasonality of the birth rate (Table 2; Supplementary Appendix 2). In contrast to studies of RABV and EBLV-1 in wild bat hosts, LBV appears to be easily maintained – albeit at low levels – by the cross-Africa, panmictic *E. helvum* system [47]. Neither [27], nor [47] undertook any model comparison of their respective transmission structures, however, making it difficult to ascertain whether LBV more closes mimics the dynamics of RABV, with clear evidence of infection-induced host mortality, or EBLV-1, for which virus-induced mortality may be less widely reported.

Filoviruses

Like lyssaviruses, viruses of the family Filoviridae (filoviruses) are non-segmented, single-stranded, negative-sense RNA viruses in the order Mononegavirales [35]. Filoviruses include the infamous genera *Marburgvirus* and *Ebolavirus*, as well as the lesser known *Cuevavirus* and *Dianlovirus* (currently represented by only one species each hosted in wild bats) and *Striavirus* and *Thamnovirus* (thus far only described in fish) [79, 80]. To date, of the more prominent genera, two species of *Marburgvirus* and six species of *Ebolavirus* have been described globally [48], including several which cause case fatality rates ranging from 50% to 90% upon zoonotic emergence into human hosts [49]. Both *Marburgviruses* and *Ebolaviruses* are believed to be maintained in bat reservoirs, though to date, only the *Marburgviruses* have been isolated from wild bat hosts [10,50,51]; nonetheless, compelling serological and PCR-based evidence suggests that bats are also reservoirs for the *Ebolaviruses* [52]. Since 1967, Marburg virus and Ebola virus have caused over a dozen human outbreaks resulting from independent spillover events, most of which have been concentrated in west or central Africa [10,53].

In our review, we identified seven mechanistic, compartmental models focused on elucidating the dynamics of filoviruses in bat hosts (Table 1). One of these studies [31] presented a within-host model that explored the consequences of unique bat immune responses on within-host viral dynamics, using models fit to *in vitro* data derived from pseudotype filovirus infections in bat cell tissue culture. The remaining six were focused at the

population-level (Table 1). Of these six, four presented theoretical simulations of the reservoir dynamics underpinning the cross-species emergence of an unspecified *Ebolavirus* in a hypothetical African bat system [54–57]; results were largely too abstract to effectively advance efforts to understand the dynamics or persistence of filoviruses in wild bat hosts. By contrast, one other theoretical model, [58], used literature-derived parameter estimates for *Zaire ebolavirus* and *Marburg marburgvirus* infections in African fruit bats to investigate the probability of pathogen persistence in a panmictic host population, assuming a simple, age-structured SEIR framework. [58] concluded that, given published estimates from the literature for filovirus incubation and infectious periods, these viruses would be unlikely to persist in large, well-mixed bat host populations if host births were synchronous and occurred only once a year. Results suggested that biannual birth pulses in wild, fruit bat hosts might be needed to explain filovirus persistence at the population level. However, conclusions of this research effort rested completely on the assumption that SEIR dynamics were applicable to bat filovirus systems – an assumption with little empirical basis. As such, it is impossible to evaluate the accuracy of the study's conclusions.

In contrast to the lyssavirus studies, only one of the filovirus models identified in our review [25] fit a compartmental model to field data (Table 2). The authors fit a suite of discrete time matrix models to an eighteen-month time series of age-structured filovirus serology data in *Pteropus rufus* fruit bats in Madagascar, aiming to elucidate the mechanistic underpinnings of population-level filovirus persistence in this field system. They identified a best fit 'MSIRN' model structure, whereby bats progressed from maternally immune to susceptible, infectious, recovered, and finally, a non-antibody-mediated immune class. Since these authors represented seropositive individuals in the recovered class, this 'non-antibody mediated immune' class allowed them to model individuals who waned in antibody seropositivity but maintained lifelong immunity via some other immunological means, as has been suggested in the experimental literature for bat-borne filoviruses [59,60]. The authors reported a low force of infection and infectious class prevalence which, consistent with the findings of [58], suggested filovirus persistence to be unlikely in the population without some role for metapopulation structure or alternative pathway of viral pathogenesis, such as those explored for lyssavirus infections above. To elaborate on this finding, we refit a simplified, three age class version of the authors' twenty age class matrix model to the original data, from which we estimated a range of R_0 values (depending on the seasonality of the birth pulse) between 0 and 0.742 in this system – thus further supporting the need for spatial structure and/or unique within-host dynamics to explain bat filovirus maintenance. Notably, all models compared in [25] were fit to serological data for a bat-borne filovirus that has yet to be described genetically.

Henipaviruses

Henipavirus is a genus within the family Paramyxoviridae, which includes (yet again) non-segmented, single-stranded, negative-sense RNA viruses [61]. To date, only five species of henipavirus have been described globally, four of which find their reservoir hosts in Yinpterochiropteran fruit bats of the Pteropodidae family: Hendra (HeV) [62], Nipah (NiV) [63], Cedar (CedV) [64], and Ghanaian henipavirus (GhV) [65]. By contrast, the fifth described henipavirus, Mojiang (MojV), is derived from rats in China [66]. HeV and NiV are known zoonoses that cause severe respiratory disease in humans [67], CedV is thought to infect only bats [64], and the host ranges for GhV and MojV have yet to be well-elucidated – though serological evidence suggestive of GhV spillover to humans has been demonstrated in Cameroon [68], and MojV was first isolated in concert with suspected human fatalities to pneumonia [66].

In our review, we identified five studies focused on modeling the dynamics of henipaviruses in bat reservoirs. Two of these studies, [69,70], presented theoretical, simulation-based models of the dynamics of Hendra virus in Australian fruit bat populations, using parameters derived from the literature. [69] developed a simple SEIR model within a metapopulation framework to explore the impact of population-level connectivity on infection dynamics, with the aim of explaining the spatial-temporal dynamics of Hendra virus spillover events in eastern Australia. The authors concluded that anthropogenic fragmentation of habitat and urban habituation reduced fruit bat migration, disaggregating bat metapopulations and decreasing population-level immunity to promote less frequent but more intense viral epidemics. Since the model was not fit to data, it is not possible to evaluate its effectiveness in recovering patterns observed in the field. Using a similar approach, [70] simulated an individual-based MSEIR model of Hendra virus dynamics to explore the impacts of viral latency and recrudescent infection in 'recovered' individuals on virus persistence at the population level. Unsurprisingly, the authors found that faster rates of recrudescence corresponded to an increased probability of virus persistence. As with the [69] model, however, the [70] model was purely simulation-based, making it impossible to assess the validity of viral recrudescence as a mechanism of virus persistence.

The remaining three henipavirus models all fit mechanistic, compartmental transmission models to population-level henipavirus data in an effort to explain virus persistence (Table 2). Two of the studies, [27,71], investigated the persistence of Ghanaian henipavirus (GhV) in *Eidolon helvum* bats, using, respectively, pan-

African cross-sectional, age-structured serological data and a nine-year serological time series from a captive colony in Ghana. The third study, [25], fits a suite of discrete time compartmental matrix models to an eighteen-month age-structured serological time series tracking infection of an undescribed African henipavirus species in *Eidolon dupreanum* bats in Madagascar. Both [25,27] fit their henipavirus models to data from the same field system that they used to model the dynamics of other bat infections – respectively, LBV for [27], and an undescribed filovirus for [25] (though the latter found henipaviruses and filoviruses to be hosted by different species within their dataset]. Both author groups reported that best fit model structures were consistent across pathogen systems – the same modeling frameworks used to explain persistence for LBV and filoviruses also effectively recapitulated the dynamics of henipaviruses in these systems (Table 2 and Figure 3). In Australia, the dynamics of several disparate bat paramyxoviruses have been shown to exhibit synchronicity in space and time [72], suggesting that mechanistic models of bat-virus interactions may be applicable across multiple bat hosts and viruses – though more pronounced differences in bat and virus systems may be more difficult to generalize. Nonetheless, both [25,27] demonstrated support for similar mechanisms of waning antibody-mediated immunity post-initial seroconversion as explanations for patterns observed in their henipavirus data. [27] fit data with an MSIRS model, identifying an important role for return to susceptible status and eventual reinfection in promoting viral persistence in a stochastic framework. [25] did not explicitly investigate viral persistence in their system but rather focused on recovering the mechanisms driving age-seroprevalence patterns in the data. The authors found the strongest support for a model form [MSIRN) which allowed bats to wane from seropositive to seronegative status but nonetheless maintain lifelong non-antibody-mediated immunity to reinfection. The authors noted, however, that troughs in the proportion infected in between annual birth pulses would be difficult to maintain if stochastic fadeout had been permitted in their model. Thus, both [25,27] concluded that henipavirus dynamics would be difficult to explain without some role for viral recrudescence or loss of immunity and reinfection to preserve transmission in the absence of an influx of susceptible births across the year. Notably, however, [27] assumed seropositivity to correspond to infectious epidemic status [the I class], reporting an R_0 value of 2.13 for *E. helvum* henipavirus across Africa, while [25] modeled seropositivity as an indicator of antibody-mediated immunity [the R class]. As with the Madagascar filovirus, we here refit a simplified three age class version of the [25] model to the original data to allow for estimation of R_0 in this system [Supplementary Appendix 3]. We calculated a seasonal R_0 that ranged between 0 and 0.585 for this system and was unable to support viral persistence.

Finally, [71] recovered similar results to [25,27], through fitting models to captive colony data for *E. helvum*. The authors compared all biologically possible combinations of compartments within an SEIR framework and ultimately, found the strongest support for models that permitted waning immunity post-seroconversion. As commonly demonstrated by lyssavirus models, the authors recovered considerable support for multiple pathways of viral pathogenesis in different individuals, with some bats permitted to return immediately to susceptibility following initial exposure (SES) while others oscillated between infectious (I) and latent (E) stages in cycles of viral recrudescence. The use of captive colony data makes this system somewhat less comparable to the population-level studies discussed above, though the authors benefitted from the opportunity to fit their model to repeatedly resampled individuals across the time series. Notably, [71] fit models to captive colony data under varied assumptions of the epidemic phenotype indicated by seropositivity – recomputing analyses under assumptions of seropositivity corresponding to exposed, infectious, and recovered states (EIR+), as well as under assumptions of seropositivity corresponding to a recovered state only (R+). The resulting dynamics were largely comparable under both EIR+ and R+ assumptions, though modeling of seropositivity corresponding to only recovered status required an extremely high estimate for R_0 (66.7 under R+ assumptions vs. 2 under EIR+ assumptions) to recover the high population-level seroprevalence witnessed in the data. Across all fitted models, authors universally modeled a standard mortality rate across all epidemic classes, though [25] hypothesized in their discussion that elevated henipavirus-induced mortality could drive the observed decline in seroprevalence at late age classes witnessed in their dataset.

Coronaviruses

Only two of the twenty-five bat virus models identified in our review concerned bat infections with coronaviruses, the viral family that includes SARS-CoV-2, the causative agent in COVID-19 (Table 1). Distinct from the three bat virus taxa highlighted above, coronaviruses are positive sense, single-stranded RNA viruses, which can be classed into four genera – *Alphacoronavirus* and *Betacoronavirus*, which originate in bats, as well as *Gammacoronavirus* and *Deltacoronavirus*, which originate in birds [73]. A combination of factors, including large genomes, positive sense genetic material, and a high propensity for viral recombination makes coronaviruses particularly prone to cross-species emergence [74] – including zoonotic emergence into human hosts. Prior to the emergence of SARS-CoV-2, six zoonotic coronaviruses have been previously described, four of which (HCoV-299E, HCoV-NL63, SARS-CoV, and MERS-CoV) are believed to be originally derived from bats [75]. Bats host a staggering diversity of

Alphacoronavirus and *Betacoronavirus* lineages [76]; however, there is a notable lack of modeling and field studies targeted toward understanding the circulation of these viruses in their wild reservoirs.

Of the two coronavirus studies recovered in our review, one [77] was primarily a human model aimed at simulating conditions favoring SARS-CoV-2 spillover from bats to intermediate hosts to humans, in which the bat dynamics were delineated but not explicitly modeled. The other study, [78], fit compartmental models to a ten-week mark-recapture field dataset of PCR-detections of a novel *Alphacoronavirus* in Australian *Myotis macropus* bats, comparing the classic SIRS framework with a derivative that allowed bats to become either persistently or transiently infected (Table 2). The authors found support for the model with two infectious classes that permitted some individuals to remain infectious for a more protracted ('persistent') period, and estimated a best fit R_0 value of 1.5903 for the system. Consistent with models of filovirus and henipavirus infections in bats, the authors found no support for elevated mortality in infectious individuals, though the dataset from which inferences were made was notably small.

Discussion

Interest in understanding the dynamics of potentially zoonotic viruses in their wild bat reservoirs has increased across the past decade, and the trend in research effort over time reflects this (Figure 2). In this review, we identified twenty-five mechanistic, compartmental models published in twenty-three peer-reviewed publications that investigated the dynamics of viruses in bat hosts (Table 1). Models were focused on four key bat virus taxa of known zoonotic potential [20] – lyssaviruses, filoviruses, henipaviruses, and coronaviruses – with lyssaviruses (in particular rabies, RABV) most represented, followed by filoviruses and henipaviruses, and very little research effort devoted to coronaviruses. A particularly informative subset of ten population-level models were explicitly fitted to field-derived data from different bat virus systems – with the aim of elucidating the viral dynamics underpinning persistence in each system (Table 2). We here summarize findings regarding the persistence mechanisms inferred for each of these four viral clades.

In general, the bat virus modeling literature largely agrees that rabies is maintained in wild bat hosts by heterogeneous outcomes following virus exposure, where some bats die while others seroconvert – though the extent to which bats are able to recover from a clinically infectious state is debated [40,41]. Consistent with these findings, protective immunity from repeated RABV exposure has also been demonstrated experimentally [81]. In addition to immunity, host population dynamics driven by hibernation in temperate regions and spatial structuring in the tropics also appear to play a critical role in RABV maintenance at the population level [40,41]. Given that these results vary across systems, however, the lack of rabies modeling in migratory bats from temperate regions or more solitary species globally, points to gaps in our complete understanding of the generalizable dynamics of the viral genus as a whole. Broadly, the dynamics of EBLV-1, another phylogroup 1 lyssavirus [43], and LBV, a phylogroup-2 lyssavirus [27,47], appear to largely mimic those of RABV, though consensus on the mortality effects of infection with non-RABV lyssaviruses has yet to be achieved. Previous studies supported mechanisms by which at least a subset of bats recover from non-RABV lyssavirus infection to obtain immunity – especially in the case of LBV, for which protective antibodies may persist for life [27,47].

In contrast with lyssaviruses, data-fitted models of filovirus dynamics in bats remain rare. Our review recovered only one such example (Table 2), likely reflecting the known difficulty in identifying infections with these viruses in wild bat hosts [25]. The one data-fitted filovirus model identified in our review demonstrated support for filovirus-recovered bats waning in antibody signature but maintaining lifelong immunity via some other immunological means, consistent with results from the experimental laboratory infection literature [25,59,60]. The authors of this study suggested a declining seroprevalence in older age bats, which could reflect heightened mortality in infected individuals, though further research will be needed to elaborate these trends in other systems.

Following lyssaviruses, understanding of henipavirus dynamics in bat reservoirs shows the most promise to date – in part a reflection of the feasibility of noninvasive viral surveillance through under-roost urine collection in these systems [82]. Our analysis identified only five studies focused on bat-henipaviruses, but three of these five studies presented mechanistic models fitted to field-derived data [25,27,71]. All three studies reported that waning antibodies post-seroconversion contributes to observed henipavirus dynamics, consistent with findings for bat filoviruses. Collectively, these studies also suggested a possible role for recrudescent infection or loss of immunity and reinfection in recovering henipavirus persistence. Broadly, data-fitted henipavirus models assumed no elevated mortality in infectious individuals; however, [25,suggested this as a possible mechanism for observed declines in seroprevalence in older bats, as also posited for filoviruses. Generalizable trends for bat henipaviruses remain somewhat muddled largely due to the idiosyncratic nature of the datasets modeled – including one purely cross-sectional study [27], one eighteen-month time series [25], and one time series derived from a captive colony [71]. Notably, no existing study has yet to

fit a compartmental transmission model to the Australian bat reservoirs for Hendra virus, despite claims that this system is a model system for understanding bat virus spillover [83].

Finally, our review identified a notable dearth of studies investigating coronavirus dynamics in wild bat hosts, highlighting a critical future research priority, particularly given the COVID-19 pandemic. Notably, the one fitted coronavirus model recovered in our analyses was the only mechanistic model identified which was fitted to PCR-based data, instead of serology, allowing for effective testing of a hypothesis of persistent infection and periodic shedding – as has been posited to drive bat virus dynamics more broadly [11]. Since bat-borne coronaviruses are typically localized in the gastrointestinal tract and shed in feces, these viruses may be amenable to under-roost noninvasive surveillance in a manner similar to that previously adopted for henipaviruses [82], offering one potential future avenue to make rapid gains in our understanding of the ecology of these pathogens in their bat reservoir systems.

Collectively, the vast majority of fitted bat virus models were targeted toward deciphering the dynamics of lyssaviruses in New World or European Yangochiropterans or henipaviruses in African Yinpteropchiropterans (Figure 1). One notable research gap identified was the absence of *any* data-fitted models from Asia – the site of emergence for both the SARS-CoV and SARS-CoV-2 pandemic viruses [2] – and the presence of only one data-fitted model from Australia (Figure 1, Table 1). To date, mechanistic models in bat virus systems have been largely limited to attempts to decipher the transmission mechanisms governing persistence of potentially zoonotic bat lyssaviruses, filoviruses, henipaviruses, and coronaviruses, though ultimately, the field aims to use these tools to do much more: mechanistic models offer a powerful means of describing causal relationships, predicting future trends, and exploring the efficacy of potential interventions. These models' capacity for meeting more complex challenges rests, however, on the accuracy of the parameter choices and assumptions upon which they are based. The field of bat virus modeling has been limited by a lack of basic understanding of the pathogenesis of these four key viral taxa within an individual bat host, forcing researchers to adopt expansive model comparison approaches to deciphering transmission dynamics that likely only approximate a still-undiscovered reality [e.g. 25, 41, 71]. To date, the most progress has been made in deciphering the dynamics of rabies virus, largely because this system stems from a long history predicated on within-host experimental infections in live bats [84]. Challenges in cost and containment have limited the progress of similar approaches for filo- or henipaviruses of known zoonotic capacity [e.g. 59,60,85–87] and been largely unexplored for coronaviruses. Isolation and experimental infections of bat-derived henipaviruses, filoviruses, and coronaviruses without known capacity for human spillover may offer an opportunity for within-host insights to be gleaned with fewer restrictions. Ultimately, studies linking pathogenesis of a particular virus in a particular bat host with data collected for that same host and virus in the field are greatly needed to expand mechanistic inference.

In the face of current limitations surrounding our understanding of the within-host pathogenesis of several clades of bat-borne virus, we propose a few key opportunities for research advances. Firstly, mechanistic modeling of heterogenous field data need not rely so exclusively on classic compartmental approaches; most of the studies highlighted in our Table 2 subset fit models to pathogens with transmission dynamics that operate on timescales far more rapid than the interval of data collection – such that model fitting attempts to infer mechanism at a scale finer than the data can offer. The vast range of R_0 estimates recovered across similar bat-virus systems suggests that research to date has failed to account for critical features of many bat virus infections; for example, [71] estimate a 30-fold higher value for R_0 when assuming seropositivity to represent *E. helvum* bats recovered from vs. actively infected with Ghanaian henipavirus. Such massively different estimates for equally plausible transmission scenarios suggest that the field is reaching for mechanism well beyond that which the data can currently supply. Added insight could instead be derived from more statistically based approaches, such as Bayesian state-space modeling, which can be used to back-infer exposure timing from serological data or discriminate source hosts from recipient hosts in multi-species settings [88,89] – rather than attempting to reconstruct entire time-series. Similarly, more relaxed approaches to dynamical modeling, which allow for time-varying transmission rates without specifying a mechanism [e.g. 90], could help overcome uncertainties and gaps in existing field data.

Ultimately, however, if we are serious about preventing the next major pandemic of a bat-borne zoonotic virus, we will need to greatly expand model-guided field studies to reflect the global extent of bat hosts and their pathogens [91]. We recognize that there are considerable barriers to data collection that may slow progress in this field, but advances are needed in order to reduce future public health threats. In particular, more studies incorporating PCR-based viral shedding data, in concert with serology, would greatly enhance our capacity for mechanistic inference from field data by allowing for both a snapshot of immediate infections paired with infection history derived from serology. Nonetheless, active bat virus infections can be notoriously difficult to detect: though a number of bat species have been found to be

positive for filovirus antibodies, PCR-positivity for these pathogens is rare and more often detected invasively in organ tissue samples rather than excreta [10]. Additionally, age-structured serological data (documentation of numerical age information paired with serological status) offer another means by which to heighten the mechanistic insight that can be gleaned from field data, by allowing for the fitting of catalytic models to age-seroprevalence curves [92]. Historically, age data have been difficult to obtain from wild bats, requiring invasive chemical and morphological analysis of bat bones or dentition, or long-term tracking of tagged individuals [93]. Recent progress in the bat aging field – in particular the development of epigenetic clocks for bats [94,95] – offers an exciting opportunity to make collection of age-structured serological information more widespread.

Inference from fitted mechanistic models can also be strengthened via longitudinal data collection in repeatedly resampled populations, in particular those which track individuals through capture-mark-recapture processes. The recapture of longitudinally tracked individuals, as modeled in [71] for example, allows for investigation of changes in within-host serological status and its influence on population-level fluctuations in transmission. Captive colony studies like those used in [71] offer the advantage of facilitating access to individuals for recapture, as well as safeguarding the boundaries of closed population assumptions for modeling. Nonetheless, captive environments lack the ecological complexities of metapopulation and interspecies mixing that likely play critical roles in driving bat virus dynamics in the wild [41,43]. Longitudinal field data collection may, however, be infeasible, given difficult-to-access bat roosting sites, which bats sometimes abandon in response to researcher visitation [96].

In this review, we summarize our current understanding of the mechanisms underpinning viral persistence in bat-virus systems and highlight several areas in which future approaches could be prioritized and improved. Both techniques and insights have diversified and developed in the thirteen years since the first dynamical model of a bat-virus system was published; nonetheless, there remains much to still discover.

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