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CONCEPT

Synzootics

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Abstract

1. Ecologists increasingly recognise coinfection as an important component of emergent epidemiological patterns, connecting aspects of ecoimmunology, behaviour, ecosystem function and even extinction risk.
2. Building on syndemic theory in medical anthropology, we propose the term 'synzootics' to describe co-occurring enzootic or epizootic processes that produce worse health outcomes in wild animals. Using framing from syndemic theory, we describe how the synzootic concept offers new insights into the ecology and evolution of infectious diseases.
3. We then recommend a set of empirical criteria and lines of evidence that can be used to identify synzootics in nature. We conclude by exploring how synzootics could indirectly drive the emergence of novel pathogens in human populations.

KEYWORDS
coinfection, conservation medicine, ecoimmunology, host–parasite interactions, One Health, syndemics

1 | INTRODUCTION

Epidemics rarely happen in isolation, especially in an era when new outbreaks are occurring at an accelerating pace. In medical anthropology, the term **syndemics** (from 'synergistic epidemics') refers to the co-occurrence of two or more infectious or non-communicable epidemics with a greater than additive total health burden shaped and sustained by disease–social interactions (Singer et al., 2017). The idea of syndemics first gained traction as researchers grappled with the ways that the HIV pandemic intersected with other health crises: the *substance abuse*, *violence and AIDS* (SAVA) syndemic was the first in a series that have been identified since the 1990s (Singer, 1994). Developed to describe psychological and social dimensions and determinants of health, the syndemics concept has gained traction within infectious disease epidemiology, particularly as the COVID-19 pandemic has collided with dozens of pre-existing morbidities and socioeconomic factors to produce more severe clinical outcomes (Gravlee, 2020; Horton, 2020; Sanyaolu et al., 2020; Singer & Rylko-Bauer, 2021).

The syndemic concept offers a way to talk about complex population health problems as a system, and to identify their boundary conditions. While social determinants of health are widely

understood, the interactions among different morbidities are often harder to frame either as 'determinant' or 'outcome'. Syndemic theory places a priority on causal inference as a way of understanding correlated health outcomes, and on using causal methods to identify directionality within those systems. Often, these approaches focus on identifying the biological mechanisms (e.g. stress and epigenetic effects) that connect social determinants and lived experiences to worse medical outcomes. Rather than merely pinpointing the existence of syndemics, medical anthropologists aim to trace medical and social pathways of impacts, and use that knowledge to identify **syndemic interventions**: levers that improve health by targeting the right points in tangled causal pathways. Syndemic interventions are as multifaceted as the problems they aim to solve, seeking to improve health outcomes more effectively than by just targeting one morbidity at a time. Often, these interventions are clinical: For example, mass drug administration campaigns use 'rapid impact packages' as multipronged interventions against soil-transmitted helminthiases, schistosomiasis, lymphatic filariasis and sometimes non-parasitic comorbidities like HIV, tuberculosis and malaria. But syndemic interventions can also address the underlying determinants of health, including factors like disease ecology, education, culture, gender and race discrimination and healthcare access and affordability.

Looking forward, the syndemic concept will only become more important in a changing world. Due to factors like climate and land use change, novel pathogens are emerging at an accelerating pace (Smith et al., 2014; Woolhouse et al., 2008), and many will find a stronger footing in human populations thanks to both chronic health conditions and healthcare disparities (Carlson & Mendenhall, 2019). But these emergence events also represent the tip of a much deeper iceberg: Because of anthropogenic pressures, pathogen communities are being reassembled at a scale that encompasses the whole biosphere. Recent human experiences with pandemics are mirrored in wildlife by three recent panzootics (the global emergence of *Batrachochytrium dendrobatidis* and, subsequently, *B. salamandrivorans* in amphibians, Martel et al., 2014; Rosenblum et al., 2010; Scheele et al., 2019; Stegen et al., 2017 and the emergence of *Pseudogymnoascus destructans* in North American bats, Blehert et al., 2009) and additional catastrophic mass mortality events in wildlife (e.g. the mass die-off of saiga antelope apparently caused by *Pasteurella* bacteria, Fereidouni et al., 2019; Orynbayev et al., 2019). Events like these will only become more likely as the world changes (Carlson et al., 2020; Cunningham et al., 2017; Sanderson & Alexander, 2020) and require their own body of workable theory to help guide useful experimentation, insightful modelling and actionable policy recommendations for conservation efforts.

We propose that the application of syndemic theory to disease ecology can offer novel insights into complex infection outcomes in wildlife, aligning with existing disease ecology frameworks. To qualify as a syndemic, two or more diseases (potentially including either infectious or non-infectious conditions) must (a) cluster in a population (co-occur at a frequency greater than expected by chance) and (b) alter health outcomes as a result (Singer et al., 2017). Concurrently to developments in the syndemics field, for over two decades, ecologists have applied community ecology perspectives that view the host itself as an ecosystem, within which coinfecting pathogens can interact to affect host physiology and disease (Cox, 2001; Pedersen & Fenton, 2007; Petney & Andrews, 1998). It is well established that endemic parasites can exert strong directional forces on the burden of other pathogens present within a population (Knowles et al., 2013; Telfer et al., 2010) and that these interactions can influence population-scale epidemiological dynamics (Gorsich et al., 2018). But the hallmarks of syndemic theory—aspects like a focus on stress-as-mechanism, a toolkit for causal inference in complex systems or insights into syndemic intervention strategies—lack a cohesive and formal body of parallel theory for natural systems.

In this 'Concepts in Animal Ecology' piece, we propose that the idea of syndemics has a logical counterpart in the concept of **synzootics**: interactions among two or more **enzootic** or **epizootic** disease processes that increase health burdens in wild animals, facilitating disease emergence or other nonlinear emergent dynamics (Box 1: Glossary). We explore what synzootic theory could look like, how it might integrate existing threads in disease ecology and ecoimmunology research and where additional evidence would be beneficial.

2 | THE SYNZOOTIC CONCEPT

2.1 | What is a synzootic and are we missing them?

A syndemic is a population-level emergent property of clinical and cultural interactions that worsen morbidity of co-occurring epidemics. Sometimes, the term is misused simply to describe non-random comorbidities, but the defining feature of a syndemic is emergent dynamics at broad scales—features like worse clinical outcomes, positive feedbacks that accelerate transmission and unclear entry points for successful intervention. We suggest that synzootics will need a similarly precise definition broader than 'coinfection' to be maximally useful as an ecological concept. We propose the term **synzootic** (Box 1) to describe events in which some combination of **enzootic** and **epizootic** processes clusters to a degree that produces worse population-level health outcomes. Like syndemics, synzootics originate at the level of individual coinfection or comorbidity, but their key characteristic is a more than additive effect at both individual and aggregate levels to such a degree that meaningfully alters the epidemiological dynamics or distribution of the pathogens involved. Sometimes, these greater than random coinfections will be driven by shared behavioural and environmental factors, but within-host interactions can also be sufficient to create these patterns at population scales: One infection can entrench and exacerbate another, acting as both driver and outcome.

As with the HIV pandemic and the first known syndemics, some of the most obvious examples of synzootics are those that have formed around panzootics. For example, *Bd* has driven catastrophic declines in amphibian populations, particularly in the neotropics (Scheele et al., 2019). While coinfection with other pathogens is often not detected or reported, coinfections with *Ranavirus* do occur

BOX 1 Glossary

Countersynzootic: A negative synzootic interaction where infection with one disease acts as a buffer against another, or where the control of one pathogen facilitates the emergence of another.

Enzootic: Analogous to endemic in humans; describes disease persistently present at low levels in an animal population.

Epizootic: analogous to epidemic in humans; describes disease outbreaks which are temporary and widespread across an animal population.

Stress synchrony: multiple environmental and/or life-history (e.g. reproduction, migration) stressors that coincide in space and/or time to generate worsened health outcomes.

Syndemic: co-occurrence of two or more infectious or non-communicable epidemics with a greater than additive total health burden shaped and sustained by disease–social interactions.

Syndemic intervention: a clinical or ecosocial strategy to reduce disease burden that targets some combination of the shared drivers underlying a syndemic, the component diseases, and their clustered and connected outcomes, with the net effect of a greater degree of success than treating each condition in isolation.

Synzootic: The non-random clustering of two or more diseases within an animal population, with worse health outcomes at the population scale than expected from each condition in isolation.

Synzootic driver: A factor underlying the clustering of health outcomes in a syndemic, usually an ecosocial driver of multiple component diseases within a syndemic that drives their co-occurrence.

Synzootic interactions: within-host and population-level interactions between health conditions and pathogens that lead to differential health outcomes, relative to the expected pathogenesis and prognosis of each condition in isolation.

Synzootic vulnerability: within-host and population-level consequences of synzootic drivers which impact host exposure or susceptibility to facilitate one or both diseases involved in a synzootic.

and positive associations between the two pathogens have been identified (Warne et al., 2016; Whitfield et al., 2013). Another interaction with synzootic potential is that between *Bd* and *Bsal*, where experimental evidence indicates higher mortality in coinfected newts due to compromised immune responses, which suggests the potential for a synzootic in wildlife if environmental conditions facilitate clustering of the two pathogens (McDonald et al., 2020). Similarly, *Pd*, the fungus responsible for white-nose syndrome in bats, is linked to a number of environmental drivers (Hayman et al., 2016). In little brown bats, white-nose syndrome is associated with 60-fold increases in viral RNA of coinfecting *M. lucifugus coronavirus* (Myl-CoV), suggesting downregulation of antiviral responses and increased viral shedding potential (Davy et al., 2018). During the COVID-19 pandemic, the relevance of this kind of mechanism to spillback risk of SARS-CoV-2 into bats is still fairly uncertain, despite widespread concerns (Olival et al., 2020).

Although we propose synzootic framing as part of a novel approach to understanding the drivers and consequences of coinfection, we note that **synzootic interactions** (Box 1) should already be widespread, if undetected, in nature. For example, helminths (endoparasitic worms) are ubiquitous pathogens of wildlife and are known to interact with a wide range of secondary pathogens (Graham, 2008). In wild bovine populations, the presence of helminths increases mortality from coinfecting *Mycobacterium bovis* (Ezenwa & Jolles, 2015), and coinfection with helminths increases severity of noncerebral malaria in mouse models (Graham et al., 2005). Interactions such as these are rife in wildlife disease ecology and highlight the potential for synzootics to develop given conducive environmental conditions. However, studies in wild animals, while they may elucidate some aspects of synzootic interactions, rarely provide full-fledged evidence for synzootics. Practical sampling constraints often limit researchers' ability to monitor individuals and eliminate confounding factors determining outcomes of parasite interactions. Synzootics are undoubtedly being missed in the wild, and their frequency will only increase as global change accelerates. How, then, can we identify a synzootic in the wild? What lines of evidence are most salient? Below we discuss the mechanisms by which a synzootic might occur and offer a framework for the minimum criteria defining synzootic events in wildlife.

3 | SYNZOOTIC INTERACTIONS AND DRIVERS

3.1 | How would a synzootic form?

The contextual environmental factors that lay the foundation for an interaction between two diseases to result in adverse health outcomes are a key component of syndemic theory (Singer et al., 2017). Likewise, the suite of environmental factors that shape parasite community assemblages is of enduring interest in disease ecology but often difficult to investigate in practice (Johnson et al., 2015). A synzootic itself will be a discrete event involving a synergistic relationship between two or more pathogens (Figure 1, shaded) and the outcome for the hosts. Such interactions may be unidirectional (where one condition worsens another) or bidirectional (where both diseases are worsened by the interaction). Underlying this interaction, there may be large-scale **synzootic drivers** in the environment that result in **synzootic vulnerabilities** within the population. For example, habitat degradation increases host vulnerability and

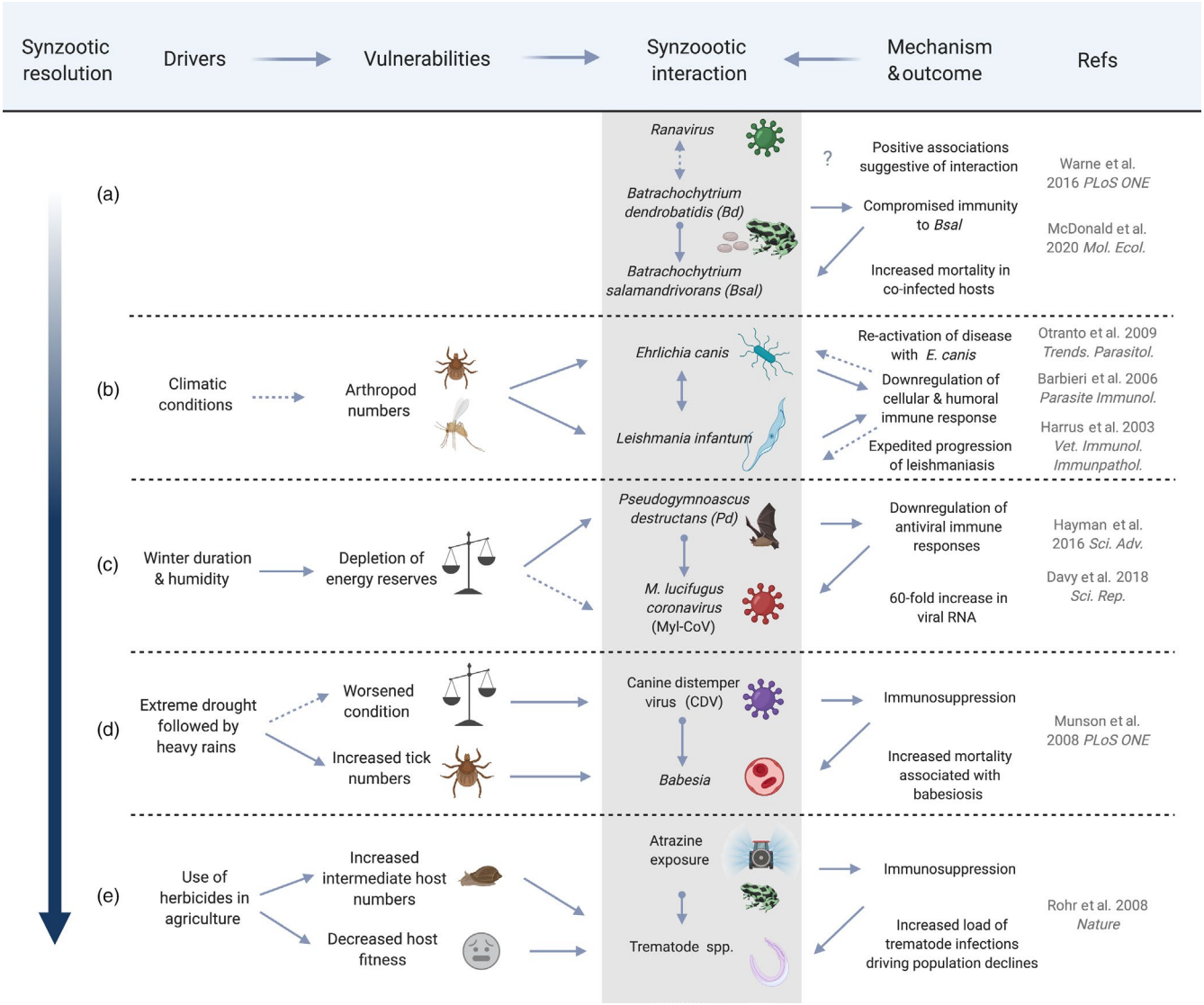

FIGURE 1 Illustrative examples of synzootic interactions with varying degrees of the full synzootic process resolved. With increasing resolution (left), links between drivers, vulnerabilities, and outcomes of synzootic interactions are more concrete. Solid arrows indicate evidence of indicated link; dashed arrows indicate hypothesised relationship

subsequent prevalence of *Plasmodium* and *Haemoproteus* among bird species (Reis et al., 2020). Similarly, habitat fragmentation alters vampire bat diet composition and gut microbiota heterogeneity, which may render them more susceptible to some bacterial pathogens (Ingala et al., 2019). These types of events describe *how* a synzootic might form, but they cannot inherently describe *whether* it will occur, nor do they predict the nature of the synzootic (i.e. events in the first two columns of Figure 1 do not guarantee anything will follow in the second two columns, but they can inform predictions).

In syndemic theory, the pathway by which a syndemic occurs is of fundamental importance, but inference regarding such pathways is often complicated by the involvement of non-communicable diseases, which often are shaped by a complex interplay of physical, social and mental stress (Singer et al., 2017). In the integration of syndemic theory and disease ecology, the former brings a more holistic view of drivers of disease vulnerability, while the latter can offer specific insight into the mechanisms by which synzootics may occur given the relative lack of confounding with mental distress in wild animals. Broadly, the field of ecoimmunology views immune responses as highly context-dependent and costly processes (Schoenle et al., 2018; Sheldon & Verhulst, 1996). Ecoimmunologists have worked to move away from 'black box' views of physiological stress and health (MacDougall-Shackleton et al., 2019), instead trying to unpack how environmental stressors coincide with often seasonal energetically demanding activities such as reproduction or migration to drive variation in immunity and disease dynamics within populations (i.e. **stress synchrony**; Becker, et al., 2020; Plowright et al., 2011). Decomposition of a mediator like 'stress' into its component parts in this way will often be more feasible for animal systems due to a combination of complementary perspectives from disease ecology and experimental work in captive and domestic populations. For example, the integration of community ecology into ecoimmunology

has yielded multiple well-defined hypotheses governing the net effect of the interactions between immune responses and coinfecting pathogens (Graham, 2008; Pedersen & Fenton, 2007). These frameworks, alongside experimental laboratory coinfection studies, allow for formulation of a priori hypotheses regarding synzootic interactions. Likewise, the intersection of spatial ecology and macroecology with ecoimmunology has recently provided key advances highlighting the relationships between environmental conditions and disease dynamics (Albery et al., 2019; Becker, Albery, et al., 2020), in turn strengthening insights into links between drivers, vulnerabilities and synzootic interactions (Figure 1).

The causes and consequences of coinfection have been extensively investigated in wildlife disease ecology (Bordes & Morand, 2011; Vaumourin et al., 2015). Making use of such existing perspectives can complement classifications used in traditional syndemic theory and help describe the procession of a synzootic from driver to outcome (Figure 1). Within this framework, a synzootic can be viewed as more fully 'resolved' the more the process of clustering and outcome of infection is understood (Figure 1). For example, environmental factors shaping arthropod presence can have similar effects on the prevalence of both *Ehrlichia canis* and *Leishmania infantum* in canines, resulting in frequent coinfections in Mediterranean regions (Otranto et al., 2009; Trotz-William & Trees, 2003). In coinfection contexts, *L. infantum* drives downregulation of host cellular and humoral responses and can therefore predispose hosts to reactivation of *E. canis*; simultaneously, *E. canis* downregulates major histocompatibility complex class II receptors, which may expedite clinical progression of canine leishmaniasis for a bidirectional effect (Barbiéri, 2006; Harrus et al., 2003; Otranto et al., 2009). However, in this case, potential worsened health outcomes are largely hypothesised based on immunological mechanism (Figure 1b). In a more resolved example, climatic extremes of drought can bring about epidemics of canine distemper virus (CDV), while heavy rainfall following droughts increases tick abundance and subsequent transmission of *Babesia* (Munson et al., 2008). Immunosuppression induced by CDV magnifies levels of babesiosis within populations and results in unprecedented mortality compared to isolated CDV epidemics within the same populations, which cause no measurable mortality (Munson et al., 2008; Figure 1d). Strong synergistic effects can also occur between infectious and non-communicable conditions. For example, northern leopard frogs *Rana pipiens* are negatively affected by atrazine (an herbicide) through multiple, intersecting pathways that contribute to amphibian population decline: Atrazine application both favours increased abundance of gastropods, which serve as intermediate hosts of endemic trematode parasites, and has an immunosuppressive effect on frogs, which worsens individual outcomes of trematode infections (Rohr et al., 2008; Figure 1e). Synzootic interactions such as these which may contribute to population declines highlight the need for considering these interactions in disease management. In marine mammals of the Pacific Northwest, for example, increasing frequency of coinfection with *Sarcocystis neurona* alongside *Toxoplasma gondii* increases protozoal encephalitis and mortality events (Gibson et al., 2011). For critically endangered species such as Hawaiian monk seals in which disease due to *T. gondii* already poses significant problems, such a synzootic interaction would prove a devastating risk of increased mortality (Barbieri et al., 2016).

Just as much of the utility of syndemic theory lies in addressing complex health issues rather than simply understanding synergistic disease clustering, a synzootic perspective may be valuable for disease management. By using the knowledge of the full synzootic process (Figure 1), **synzootic interventions** can target synzootic vulnerabilities to more effectively address disease morbidity. For example, combining nutrition supplementation with anthelmintic treatment increases the efficacy of anthelmintics in wild wood mice since undernutrition exacerbates negative effects of infection (Sweeny et al., 2021). Additionally, in classic syndemic frameworks, an iatrogenic interaction occurs when treatment of one condition inadvertently results in adverse effects due to some interaction with a coinfecting pathogen (Singer et al., 2017). Although evidence is sparse and these types of interactions are likely to be much rarer in wildlife, they are still possible. For example, treating canids with steroids for a fungal or bacterial infection can inadvertently worsen the metabolic disorders—Cushing's and Addison's diseases (Ferasin, 2001; Murphy et al., 1990). Furthermore, parasite interactions can in some cases result in a better outcome for hosts when they are antagonistic to each other or immunologically cross-protective (Bordes & Morand, 2011). Where these **countersynzootics** are present, removing one of a set of interacting pathogens as a focal pathogen can result in competitive release. For example, removal of helminths in a wild *Peromyscus* population increased the prevalence of Sin Nombre virus (Sweeny et al., 2020). As synzootics become increasingly common in wildlife populations in a changing world, it is therefore likely that the management of pathogens of concern will need to carefully address underlying determinants of vulnerability without inadvertently worsening net disease burden through unintended side effects of control efforts (Hopkins et al., 2020; Sokolow et al., 2019).

4 | IDENTIFYING SYNZOOTICS IN PRACTICE

Despite rigorous frameworks for mechanistic and causal inference, the coinfection literature is riddled with necessary caveats for interpreting results. Results detailing coinfection interactions from laboratory studies are not easily transferable to more complex environments, and most sampling and statistical methods from wildlife studies primarily report only associations rather than true directional interactions among parasites. This represents an important challenge for applying syndemic theory to synzootics, because identification of a true syndemic requires showing a synergistic outcome as well as non-random clustering of pathogens rather than simple pathogen co-occurrence. In other words, co-occurrence of two pathogens is *necessary* but not *sufficient* to diagnose a synzootic. Working from different types of data available to disease ecologists,

what can we consider sufficient with regard to synzootic identification? Laboratory models and empirical co-occurrence data are valuable lines of evidence, but they are unlikely to provide sufficient evidence in their own right. Here, we detail how inference from several data types along the spectrum of helpful, necessary or sufficient as a guide to identifying synzootics.

4.1 | Helpful: Laboratory coinfection studies

Experimental infection with multiple pathogens and subsequent monitoring of host outcomes is a powerful approach for establishing mechanisms underlying coinfection, facilitated by the high degree of control that researchers can exercise over timing of infection and sampling. Laboratory mouse models have, for example, shown greater anaemia and loss of body weight due to *Plasmodium chabaudi* infection in individuals coinfected with the filarial nematode *Litomosoides sigmodontis* (Graham et al., 2005). However, a meta-analysis of 42 mouse models demonstrated both antagonistic and synergistic relationships during malaria and helminth coinfection dependent on whether the *Plasmodium* infection is resolving or lethal malaria, which may not be apparent in field data (Knowles, 2011). These divergent outcomes highlight a limitation of laboratory studies in fully translating to natural scenarios. Some tractable laboratory systems can account for diverse coinfection contexts; for example, experimental investigation of how infection order shapes pathogen interactions and outcomes has been conducted with *Daphnia magna* (Clay et al., 2019). However, for many wild species, it is not feasible to maintain captive populations and experimentally induce infections due to ethical or biological safety limitations. Systems which are amenable to captivity are tractable at the expense of translation, with natural conditions difficult to approximate. Evidence from laboratory populations in most cases will therefore be **helpful, but neither necessary nor sufficient,** to identify a synzootic (Figure 2).

4.2 | Necessary: Empirical co-occurrence data

Despite great interest in interspecific pathogen interactions and their consequences in wild populations, their detection remains an ongoing challenge. Presence and absence data of pathogen community members are commonly documented in wild host populations, which can be used to infer co-occurrence of pairs of pathogens. However, although co-occurrence may be accompanied by ecological interaction, this is not guaranteed (Barner et al., 2018; Blanchet et al., 2020). Environmental conditions might drive abundances of multiple species similarly in the absence of interactions. Indeed, comparing methods for inferring ecological interactions has shown that reliance on pairwise co-occurrence detection can generate a higher than expected rate of false positives (Barner et al., 2018). In many instances, this can even result in inferring the wrong direction of an interaction (Barner et al., 2018). For example, positive correlations reported in the field between two pathogenic trematodes (*Ribeiroia ondatrae* and *Echinostoma trivolvis*) in amphibian hosts mask the negative influence exerted on one by the other (Johnson & Buller, 2011). Furthermore, interactions with pathogen species outside of the focal pair can minimise the probability of detecting a true interaction via co-occurrence metrics. Such interactions produce causal noise that may require more advanced statistical approaches such as partial correlations to interpret properly (Blanchet et al., 2020). Clustering of pathogens within a population is therefore **necessary** but, due to a number of complicating factors, unlikely to

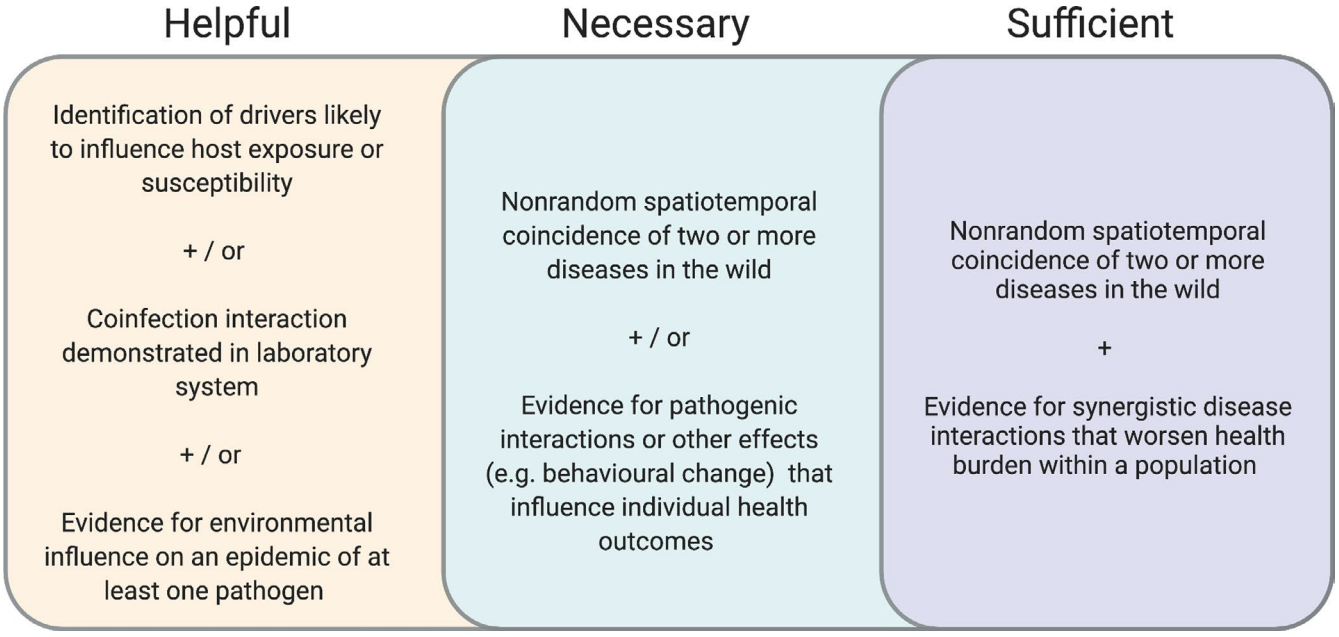

FIGURE 2 To make "synzootic" a sufficiently distinct concept from coinfection, we propose a set of criteria for evidence from field and laboratory studies

be **sufficient** to demonstrate a synzootic. In other words, all synzootics involve coinfection, but all coinfections do not constitute a synzootic. However, information from occurrence data is highly valuable in that environmental conditions influencing occurrence of two species simultaneously have the potential to be implicated within synzootic relationships.

4.3 | Sufficient: Longitudinal data and/or experimental perturbation studies

Where data are observational by necessity, there are means of better informing inference about pathogen interactions. For example, using parasite load (number of parasites per infected host) commonly provides more information than simple presence–absence data (Knowles et al., 2009) and can capture a more detailed view of the relationship among pathogens. Pathogen intensity data coupled with longitudinal monitoring can determine how one parasite at time t influences the population of a second parasite at time $t + 1$. These methods have shown, for example, that coinfection can exert stronger influence on infection dynamics than host factors (Telfer et al., 2010) and that priority effects shape the outcome of coinfection (Clay et al., 2019).

However, longitudinal observational data are rarely available at a sufficiently high resolution to determine the order of infection and the host consequences of coinfection within individuals and populations. As an alternative, the removal of target parasites and monitoring downstream effects on non-target parasites and host immunity or fitness is a powerful approach that allows for experimental assessment of parasite community dynamics in the wild (Pedersen & Fenton, 2015). For example, helminth removal in wild wood mice revealed a negative interaction with the gastrointestinal protozoan *Eimeria hungaryensis* (Knowles et al., 2013). In tractable systems, antiparasite experiments might also involve manipulations of additional environmental variables that offer insights into coinfection responses given expected **synzootic drivers** such as changing resource landscapes (Lange et al., 2014). The ability to identify worsened individual health outcomes is therefore **necessary;** however, it is possible, if unlikely, that individual-level effects may contrast with those at the population level. For example, increased individual-level mortality caused by coinfection with helminths and *Mycobacterium tuberculosis* has been observed in a wild buffalo system, yet helminth removal results in higher transmission and prevalence of *M. tuberculosis* in the population (Gorsich et al., 2018). Longitudinal time series of infection as well as experimental approaches demonstrating individual- and population-level outcomes can therefore provide both **necessary** and **sufficient** evidence for the conditions and interactions that define a synzootic.

5 | CONCLUSION

Syndemic theory finds an analogue in the synzootic concept and, more broadly, the rich detailed study of coinfection and within-host interactions that characterises modern disease ecology. We suggest that synzootics may become increasingly relevant to conservation medicine as emerging wildlife diseases present a significant threat to species' survival, and as veterinarians and conservation managers are forced to weigh the compound impacts of potential disease interventions. We also anticipate that understanding synzootics may have relevance to the study of emerging zoonotic diseases. Ecosystem changes are often several degrees removed from impacts on human health but may act as important drivers nonetheless. Previous work has highlighted the relevance of ecosyndemics—whereby extreme weather alters hosts or pathogens to favour syndemics—to zoonotic disease, and these links are likely to exist from synzootic perspectives as well. For example, the invasion of Burmese pythons in south Florida has led to declines in some mammal populations, causing mosquitoes to feed more on small rodent reservoirs of a rare mosquito-borne zoonosis (Everglades virus), potentially altering disease risk for humans (Hoyer et al., 2017). Dynamics like these might only become more complex—and harder to anticipate—when compound drivers, multi-pathogen communities and within-host interactions come into play. How might we anticipate the synzootics of the future?

Known synergies between different anthropogenic stressors offer a first clue that synzootics may become more likely. Every ecosystem is experiencing a different combination of warming, pollution, land conversion, fragmentation and invasive species, among other pressures (Loarie et al., 2009). Often, these correlate positively over space, and coincide in ways that might have synergistic effects, altering host–pathogen relationships and accelerating their turnover through time (Halliday et al., 2020; Morand, 2020; Walsh et al., 2020). In addition, anthropogenic stressors can contribute to **stress synchrony** between energetically demanding activities, both environmental and intrinsic, to generate worsened infection outcomes (Plowright et al., 2008). However, this clustering mostly operates at macroecological scales and tells us little about the specific nature of disease impacts. For more mechanistic insights, disease ecologists often reduce complex patterns down to two main dimensions of transmission: susceptibility and exposure. Both will change in coarsely predictable ways with anthropogenic stressors, potentially offering some indication of how tomorrow's synzootics will look different from today's.

Although more nuanced perspectives have largely replaced the 'warmer, sicker world' hypothesis (Lafferty & Mordecai, 2016), global change is widely understood to have damaging effects on the baseline health and condition of wild animals, increasing their susceptibility to disease. Extreme heat, habitat loss, extractive pressure (e.g. wildlife trade) and direct interactions with humans can all lead to higher stress, lower immune function and probably greater susceptibility to pathogens (Becker, Albery, et al., 2020; Messina et al., 2018; Murray et al., 2019). Adverse impacts of global change on parasites may also have inadvertent synzootic impacts on susceptibility. Evidence increasingly suggests that parasites may be particularly vulnerable to climate-induced extinction, given the 'double jeopardy' of direct vulnerability and coextinction risk (Carlson

et al., 2017; Cizauskas et al., 2017). Although some parasite extinctions are likely beneficial for their hosts' health, others may have a countersynzootic effect that increases vulnerability to environmental stressors (Selbach et al., 2020) or to other pathogens. For example, within-host competition among helminth parasites reduces the transmission and virulence of *Ribeiroia* trematodes in frogs (Johnson & Buller, 2011; Johnson & Hoverman, 2012), and the loss of that buffer might facilitate trematode emergence (Carlson et al., 2013). In other ecosystems, anecdotal evidence suggests that the collapse of host-helminth networks may already be underway (Sitko & Heneberg, 2020). More broadly, when parasites go extinct, they leave behind a void that other parasites and pathogens may fill, ultimately facilitating disease emergence—not just in wildlife but also in humans. Given the challenges of causal inference, examples of this pattern are unsurprisingly limited at best, and largely anecdotal (Esser et al., 2019). Nevertheless, we might more broadly expect that species could become more vulnerable to virulent infections in a rapidly changing world due to dysbiosis or the extinction of their native parasite fauna.

While global change is expected to generally increase susceptibility of wildlife, shifts in climate and land use are also projected to expose most species to more pathogens. At the macroecological scale, this pattern is usually discussed through the lens of biotic homogenisation: wild animals, vectors, parasites and pathogens are all undergoing rapid geographic range shifts, and a few species are expected to become globally cosmopolitan (Carlson et al., 2017, 2020; Poisot et al., 2014). However, homogenisation hides several layers of clustering at finer scales. For example, increasing prevalence of parasitic infections is largely projected in the Arctic or more broadly the northern hemisphere (Cohen et al., 2020; Dobson et al., 2015); In contrast, there is evidence that cross-species exchange of novel pathogens is likely to be clustered at the edge of biodiversity hotspots and at higher elevations, where range-shifting mammal species may co-occur for the first time (Carlson et al., 2020). The spatial and ecological clustering of these phenomena is likely to be further determined at fine scales by pathogen transmission mode. For example, just as the global invasion of urban-adapted *Aedes aegypti* mosquitoes has generated arbovirus syndemics in Latin American cities (Carlson & Mendenhall, 2019; Singer, 2017), common mosquito or tick vectors are likely to structure multipathogen synzootics in nature, especially as these vectors invade pristine ecosystems and become a dominant force in human-altered landscapes.

Together, projected changes in host susceptibility and exposure—and the likely interactions between them—point to the possibility that synzootics will become a dominant feature of the Anthropocene. For example, when species bring pathogens into immunologically naive host communities (Chalkowski et al., 2018; Goedknegt et al., 2017), the resulting epizootics may be more suitable to synzootics due to faster and higher disease-induced mortality. Moreover, the future hotspots of cross-species transmission driven by geographic range shifts are expected to fall disproportionately in human-settled and agricultural land (Carlson et al., 2020), increasing the likelihood that animals involved may have poorer baseline health, and a greater probability of acting as zoonotic reservoirs (Gibb et al., 2020; Murray et al., 2019). Together, these kinds of changes point to the possibility that severe, high-mortality epizootics and panzootics of novel pathogens will become increasingly common due to global change. Furthermore, the trajectory of these outbreaks will be heavily interconnected across different host–pathogen systems. This may have relevance not only for conservation medicine (e.g. if these future synzootics pose a higher risk of disease-induced extinction, as observed with recent fungal panzootics) but also for food and health security. Increasingly, ecologists understand that pathogens most readily traverse the interface of natural ecosystems, agricultural systems and human populations in places where anthropogenic stressors on ecosystems are most severe. Using synzootic theory to focus on systems-level understanding and causal inference could help identify cases where increasingly entrenched wildlife diseases might be connected to human health, especially when synzootic pathogens can cross the wildlife–human interface. If any of the 10,000 potentially zoonotic viruses lurking in wildlife are involved (Carlson et al., 2019), the line between synzootics and syndemics may even become blurred, as suggested by a recent case where *Bd*-related amphibian declines were shown to increase malaria risk in human populations by virtue of vector population release (Springborn et al., 2020). Such potential remains contingent on a strong evidence base about the existence, characteristics and frequency of synzootics, which will require substantial future research.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors contributed to writing this manuscript.

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No data were used for this manuscript.

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