The Palearctic view on a bat fungal disease

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Abstract

The fungal infection causing white-nose disease in hibernating bats in North America has resulted in dramatic population declines of affected species since it was first discovered in 2007. Shortly after, it was demonstrated that the causative agent, *Pseudogymnoascus destructans*, is native to the Palearctic, where it also infects several bat species. However, infection in the Palearctic rarely leads to severe pathology or the death of the host, suggestive of a lengthy coevolution between the host and pathogen. An understanding of the unique relationship between the host, the pathogen and the environment in the Palearctic can provide valuable insights into how the epizootic may continue to develop in the Nearctic, and how to effectively manage the disease. The local extirpation and changes in conservation status of affected species in North America has triggered a surge of research across a plethora of fields in bat and fungal biology, in both North America and Eurasia. Here, we summarise current knowledge on the fungal infection, from how *P. destructans* infects bats, to the delicate interplay between the pathogen, host and the environment, and to how individuals, species and populations respond to the fungal pathogen. We conclude on how tolerance is likely manifested in Palearctic bat species and whether there is potential for the development of tolerance in the Nearctic. We conclude with a systematic review of current literature on the management of the disease in North America and how it could best benefit from knowledge garnered from Eurasia. Our essay encourages policymakers and conservation managers to take a more holistic consideration of the epizootic.

A bat fungal disease

White-nose disease (WND) is a mycosis affecting hibernating bats (Blehert et al. 2009), currently considered to be one of the most detrimental wildlife diseases of modern times (Frick et al. 2016). Since the introduction of its causative agent, the cold-loving fungus *Pseudogymnoascus destructans* (=*Geomyces destructans* Blehert & Gargas 2009), to North America, WND has resulted in mass mortality of affected species and has caused unprecedented population collapses in many of the affected areas (Blehert et al. 2009; Frick et al. 2015). Endemic to the Palearctic, the fungus does not cause significant mortality in Eurasian bats, due to millennia of coevolution between the pathogen and the local bat hosts (Puechmaille et al. 2011a; Zukal et al. 2014; Leopardi et al. 2015; Fritze & Puechmaille 2018). Presently, after more than 15 years since the introduction of *P. destructans* to North America, some of the affected bat populations have begun showing signs of recovery (Frank et al. 2019), suggesting that the fungus and/or hosts are undergoing processes that can eventually lead to coexistence. The purpose of this essay is to form a synthesis of our current understanding on the relationship between host, pathogen and environment in WND dynamics, and provide considerations on conservation practices for North American bats affected by the disease. Understanding the dynamics of WND in the Palearctic and recognising the adaptive mechanisms that have allowed species to persist, can help predict the fate of Nearctic bat populations. We will therefore summarise research from the Palearctic and Nearctic to consider causality with regards to mortality, the definition of disease, how the interactions of the host, pathogen and environment contribute to disease, the concept of immunological tolerance, and how these could be considered in a holistic approach in viability assessments and planning of conservation measures.

How does a fungus kill a bat?

Ultimately, host mortality caused by WND in susceptible Nearctic bat species occurs via the disruption of the normal pattern of hibernation (Reeder et al. 2012; Warnecke et al. 2012). Hibernation consists of torpor bouts, where the bat is inactive and its body temperature is close to the ambient hibernacula temperature, and arousals, where body temperature rises and activity resumes (Thomas & Geiser 1997). During bouts of torpor, bodily functions including metabolism, breathing, blood flow and the immune system slow to conserve energy. Occasional arousal is used to rehydrate, defecate, mate, forage when prey are available, or to change hibernacula (Boyles et al. 2020; Blomberg et al. 2021). Each arousal is costly; they account for <1% of total hibernation time, but are responsible for over 80% of the energy expenditure (Thomas et al. 1990). Infected North American *Myotis lucifugus*, one of the best-studied affected species, arouse three times more frequently in the final third of the hibernation period compared to non-infected individuals (Warnecke et al. 2012), expending large amounts of the fat reserves.

One proposed explanatory cause for the increased arousal frequency seen in susceptible bats is related to fungal damage to patagium (tail- and wing membranes). The patagium has an important function during hibernation, acting as a diffusion membrane for gas exchange to retain homeostasis (Makanya & Mortola 2007). *Pseudogymnosascus destructans* releases enzymes that contribute to digesting this membrane (Chaturvedi et al. 2010; Reynolds & Barton 2014; O'Donoghue et al. 2015), and the build-up of a metabolite, riboflavin, causes further cell necrosis (Flieger et al. 2016). This process results in cupping erosions diagnostic of the disease (Meteyer et al. 2009) and the disruption of the diffusion process, which causes infected bats to accumulate significant quantities of dissolved carbon dioxide, leading to respiratory acidosis (Warnecke et al. 2013). This forces bats to arouse to hyperventilate, which is one of the proposed mechanisms for torpor disruption (Verant et al. 2014). Hyperventilation also increases water loss via exhalation, and further water loss is caused by the disturbance of fluid regulation in the damaged patagium (Cryan et al. 2010). Evaporative water loss (EWL) is a significant predictor of arousal frequency (Thomas & Cloutier 1992; Thomas & Geiser 1997; Ben-Hamo et al. 2013); susceptible bats may be induced to arouse to rehydrate as well as hyperventilate.

A parallel mechanism for increased arousal is triggered by cytokines, immunomodulatory proteins that are upregulated by the host in response to infection (Antachopoulos & Roilides 2005). *Pseudogymnoascus destructans* infection induces the production of inflammatory cytokines, such as IL-6 and IL-17, during the arousals that take place during hibernation (Field et al. 2015, 2018; Lilley et al. 2017). Irritation, such as pain and itchiness, associated with this inflammation, may stimulate the bats to arouse more frequently. With either underlying mechanism, or both working in tandem, the increased frequency of arousals leads to emaciation and eventual death in the more susceptible bat species.

What should we call it?

The term "White-nose syndrome" (WNS) was coined in the winter 2006–2007 to characterise the 'mysterious' die-off affecting hibernating bats in four hibernacula in eastern New York, USA, where abnormal behaviour was observed (Reeder & Turner 2008; Veilleux 2008). However, the use of the term for mycosis occurring in Europe has led to some confusion, because they are pathologically similar to those in North America but are not associated with symptoms used to characterise WNS (i.e., increased arousal frequency, emaciation) (Puechmaille et al., 2011; Pikula et al., 2012; Fritze & Puechmaille, 2018). Using the same terminology to characterise both a disease and a syndrome does not facilitate effective communication regarding the condition, nor does it promote advancements in comprehending the intricate complexities of a system. In medical terminology, a syndrome is "a group of signs and symptoms that occur together and characterise a particular abnormality", often with multiple or unknown causative agents, while a disease is "an impairment of the normal state of the living animal or plant body or one of its parts that interrupts or modifies the performance of the vital functions, is typically manifested by distinguishing signs and symptoms, and is a response to specific infective agents." With this in mind, and as advocated before (e.g., Frick et al. 2016), the community should refer to the unusual winter activity and mass mortality of bats as matching the signs and symptoms of white-nose syndrome and, on the other hand, the skin erosions observed as impairment of bat tissue, specifically caused by *P. destructans*, a diagnostic for white-nose disease. The presence of the fungus without any signs of the disease is also possible if mycosis is only superficial, a situation that should simply be qualified as "*P. destructans* infection" (Fig.1.; Casadevall & Pirofski 2000).

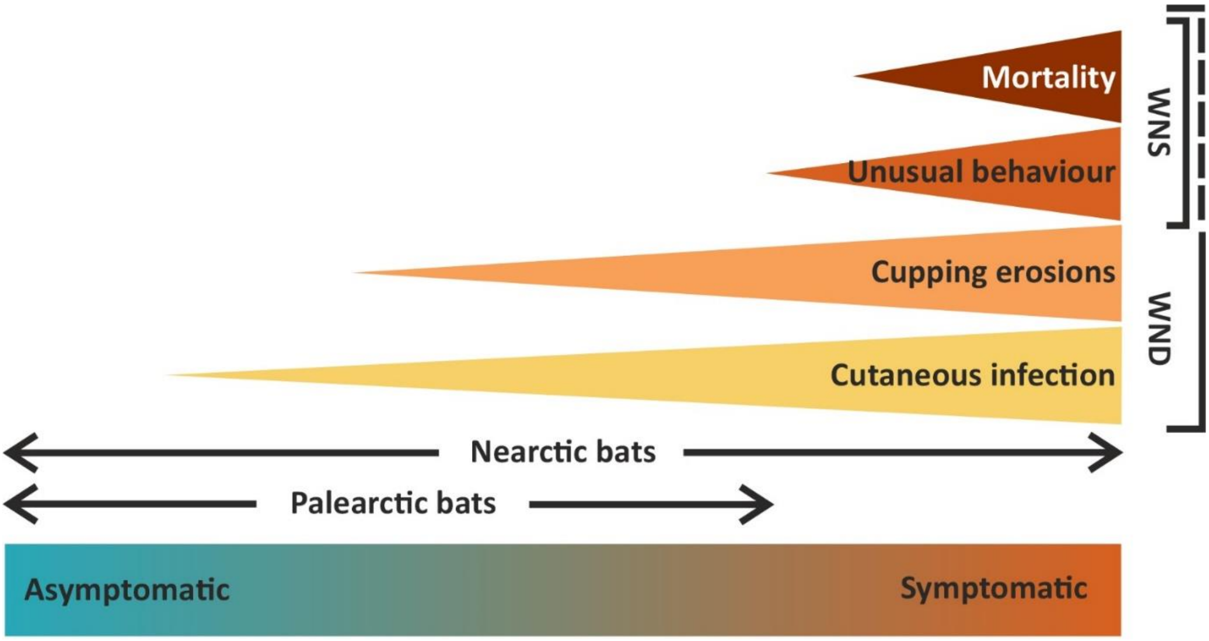

Fig.1. An illustration of the difference between white-nose syndrome and white-nose disease. Axis not proportional to incidence of a given symptom.

The disease triangle

Numerous factors, and their interactions, affect the outcome of a fungal infection, i.e., whether it is non-lethal or leads to pathology. To assist in categorising these factors, they have often been fitted within the disease triangle (Scholthof 2007), which illustrates how disease occurs at the intersection of factors related to the host, the pathogen and the environment. A shift in any of these factors may lead to manifestation of disease, depending on the direction of the shift (Fig. 2.). These factors can be abiotic, such as hibernacula environmental conditions, and biotic, such as the properties of fungal isolate, the microbiome of either the substrate or the host, hibernation behaviour of the hosts, and the inherent susceptibility and immune responses of the hosts to *P. destructans*. In the following paragraphs we summarise current knowledge on WND viewed through the perspective of the disease triangle.

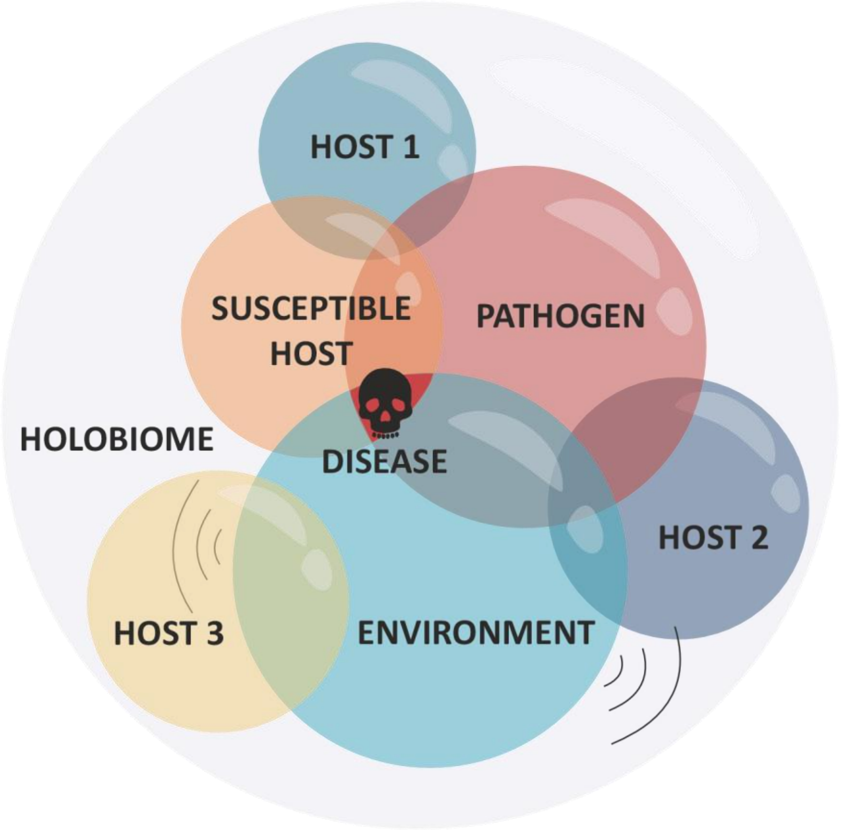

Fig 2. The disease triangle, in which disease (depicted by the skull symbol) occurs at the intersection of the properties of the host, the pathogen, and the environment (Scholthof 2007).

The pathogen

Pseudogymnoascus destructans is a specialised pathogen of hibernating bats (Minnis & Lindner 2013) with a now circumpolar distribution. The coevolution of this fungus with its hosts in the Palaearctic is evidenced by temporal fluctuations in the germination rate of *P. destructans* peaking during the hibernation period (Fischer et al. 2020), the unique enzymatic characteristics of the fungus with reduced saprotrophic enzyme activity and increased activity of enzyme associated with the invasion and digestion of bat skin tissue (Reynolds & Barton 2014; O'Donoghue et al. 2015; Flieger et al. 2016; Reynolds et al. 2016; Veselská et al. 2020), and the transcription of genes that facilitate the evasion of the host immune system (Reeder et al. 2017). Cave walls are the main environmental reservoir for this pathogen, from which the bat hosts can become infected (Fischer et al. 2022). Some evidence of density-dependent growth on the bats suggests that the fungus may be limited by intraspecific competition (Johnson et al. 2014), which may limit the successful settlement of dispersing *P. destructans* isolates into caves that are already occupied (Fischer et al. 2022). The invasive Nearctic *P. destructans* originated from Europe (Leopardi et al. 2015; Drees et al. 2017), and experimental inoculation suggested that the isolates found in North America are no more pathogenic than its European progenitors (Warnecke et al. 2012). The fungus, which is accumulating mutations, is spreading largely clonally across the Nearctic (Rajkumar et al. 2011; Ren et al. 2012; Khankhet et al. 2014), though signs of recombination have been detected and likely originate from mitotic recombination (Forsythe et al. 2021). While these mutations are associated with a change in optimal growth temperature (Forsythe et al. 2018), there is currently no evidence of an increase in pathogenicity being the cause of the disparity in disease outcomes between the Palaearctic and the Nearctic. Similarly, while *P. destructans* in the Palearctic shows substantially more diversity than in the Nearctic (Drees et al. 2017), with both heterothallic mating types present (Palmer et al. 2014; Dool et al. 2020), there is no evidence yet of differences in severity between isolates. Together, these studies on the pathogen suggest that differences in susceptibility to WND between Palearctic and Nearctic species are not primarily driven by changes in the pathogen.

The hosts

Currently, WND *sensu stricto* (Fig. 1) has been recorded on 12 Nearctic and 31 Palearctic bat species (Hoyt et al. 2021). The species most notably affected by the disease in North America are *Myotis septentrionalis*, *M. lucifugus*, and *Perimyotis subflavus*, which have experienced declines of over 90% in affected hibernacula (Cheng et al. 2021).

Up to 20 bat species in the Nearctic have been recorded with *P. destructans*, many sharing the same underground habitats with the pathogen, but remaining asymptomatic (Fig. 1.). One way that disease outcomes may be avoided is in a lack of prolonged exposure. For example, bats such as *Lasionycteris noctivagans* and *Lasiurus cinereus* may visit underground sites (Bernard et al. 2015) but they predominantly hibernate in trees (Perry et al. 2010) where the pathogen has not been reported. Therefore, they are less exposed to the pathogen compared to strictly cavernicolous species and their principal hibernation environment is seemingly not suitable for infection to progress and cause damage (Fig 2.). Other Nearctic species, such as *Eptesicus fuscus* and *Corynorhinus rafinesquii,* hibernate in underground sites that favour the proliferation of the fungus on the bats (Brack 2007), but, among other factors (Haase et al. 2021), their relatively high activity during winter or selection of colder microclimates within the hibernation sites keeps the fungal loads low (Johnson et al. 2012; Frank et al. 2014; Turner et al. 2022). Frequent arousals provide opportunities for the bats to groom off the fungus, inhibiting its proliferation and growth (Brownlee-Bouboulis & Reeder 2013). Notably, in these less-susceptible species, winter feeding facilitates increased arousal frequency and limits the infection (Dunbar et al. 2007; Johnson et al. 2012). In this regard, it appears that species most prone to infection are those that are not able to feed during the winter (Whitaker & Rissler 1993), and therefore exclusively rely on the fat reserves gathered prior to hibernation. For instance, the highly susceptible *M. lucifugus* employs increasingly long torpor bouts during late hibernation, which allows the fungus to proliferate and infiltrate the host tissue effectively (Reeder et al. 2012; Warnecke et al. 2012).

In Europe, the disease is largely associated with *M. myotis* (Puechmaille et al. 2011). *Myotis myotis* have higher pathogen loads, as well as higher prevalence and density of lesions on their patagium compared to individuals of other species sharing the same hibernacula (Zukal et al. 2014, 2016). Some *M. myotis* individuals have been observed in bouts of torpor lasting over eight weeks (Blažek et al. 2019), similarly to the Nearctic *M. lucifugus* (Jonasson & Willis 2012), which may exacerbate the fungal load on the host (Fritze et al. 2021). *Myotis myotis* has also been shown to have comparable fungal loads to susceptible Nearctic species, with contrasting studies placing this species with either higher (Zukal et al. 2016) or lower (Hoyt et al. 2020) fungal loads than their Nearctic cousins. However, infected *M. myotis* individuals are able to hibernate with marginal to negligible negative effects (Fritze & Puechmaille 2018). This ability to host similar pathogen loads, with comparable hibernation behaviours, may indicate an inherent tolerance in *M. myotis* and other infected Palearctic species.

There are several proposed, likely interconnected, mechanisms that promote tolerance to WND, limiting the fungal load or avoiding severe disease outcomes. A larger body size is likely protective, providing the host with the energy resources to survive the increased energy requirements of infection. *M. myotis*, having one of the highest fungal loads in Europe (Zukal et al. 2016; Hoyt et al. 2020), is also one of the largest species. However, as smaller species (e.g., *M. daubentonii, M. dasycneme, M. emarginatus)* have similar hibernation patterns as *M. myotis*, but also do not suffer from severe WND symptoms, additional energy reserves from a larger body size is not a central strategy for WND tolerance. A strongly supported mechanism is in the immune response of the host itself. Multiple studies point toward the susceptible *M. lucifugus* mounting a robust immune response to the infection, likely leading to immunopathology that contributes to mortality (Field, 2015, 2018; Lilley, 2017, 2019). In contrast, *M. myotis* shows no significant transcriptional response to infection (Lilley, 2019). Instead, this species appears to utilise the circulating innate immune effectors without initiating an immunological cascade (Fritze et al. 2021). This lack of a strong response may be a large contributor to survival in tolerant species (Whiting-Fawcett, 2021).

Falling on the border of the host and the environment, the skin microbiome is also very much a pathogen-limiting defence, as several microbes have been found with anti-*P. destructans* properties (Hoyt et al. 2015; Lemieux-Labonté et al. 2017, 2020; Grisnik et al. 2020; Li et al. 2022b, 2022a, 2023). A defensive microbiome can be viewed as part of a holobiont, or a single symbiotic entity in which the host and microbes are mutually dependent on each other for survival (Zilber-Rosenberg & Rosenberg 2008; Gilbert et al. 2012; Bordenstein & Theis 2015). Without the skin microbiome to act as a primary line of defence, a bat in torpor with a down-regulated immune system presents a prime opportunity for *P. destructans* to chronically infect the skin of the individual (Casadevall & Pirofski 2018). The holobiont can do so by competing with the pathogen for space/nutrients or by secreting antifungal agents, such as volatile organic compounds (VOCs) (Grice & Segre 2011), many of which have been shown to inhibit the growth of *P. destructans* (Cornelison et al. 2014; Padhi et al. 2018; Micalizzi & Smith 2020). Additionally, the mere presence of known antifungal taxa found on the skin of bats can inhibit the growth of *P. destructans* both *in vitro* (Cornelison et al. 2014; Hoyt et al. 2015; Hamm et al.

2017; Grisnik et al. 2020; Forsythe et al. 2022) and *in vivo* (Cheng et al. 2017; Hoyt et al. 2019). Unfortunately, no studies on the contribution of the microbiome have been conducted in the Nearctic so far, leaving a major part of the puzzle contributing to survival unaddressed (Troitsky et al. 2023).

In summary, factors contributing to the susceptibility of a bat species, or a specific entity within a species (e.g., sex; Kailing et al. 2023), to WND are most closely related with the hibernation behaviour and environmental condition favoured during hibernation. Bats that hibernate for long periods in proximity to *P. destructans*, and are inherently more susceptible, are more likely to develop severe disease outcomes.

The environment

For any disease to take hold, the host and the pathogen must coexist in a suitable environment. Many hibernating bat species and *P. destructans* share an environmental optimum in cool, humid hibernacula, creating appropriate conditions for disease manifestation. Environmental conditions contribute to the disease in a multitude of ways, both directly and indirectly, from the persistence of spores at hibernation sites to the proliferation rate of the fungus (Lorch et al. 2013; Vanderwolf et al. 2016; Fischer et al. 2020, 2022; Hoyt et al. 2020). Also, host infection intensity (Langwig et al. 2015b) and host identity (Laggan et al. 2023) contribute to the amount of spores shed, and therefore the persistence or decay of *P. destructans* in the environment. Environmental load contributes to whether host populations are stable or experience severe declines (Hoyt et al. 2020).

Environmental conditions largely determine the torpor patterns of bats occupying the hibernacula. Torpor bout duration, which correlates negatively with ambient temperature, is known to play an important role in WND dynamics. Under laboratory conditions, *P. destructans* grows optimally at temperatures between 12–16ºC (Verant et al. 2012) and in captivity, *M. lucifugus* hibernating at 10ºC show higher mortality than at 4ºC (Johnson et al. 2014). However, few bat species naturally hibernate at such high temperatures, and the highest fungal loads or probability of WND presence on wild hibernating bats in Europe are found at temperatures around 5–7ºC (Martínková et al. 2018; Blomberg et al. 2023). This disparity may be due to bats at temperatures closer to the laboratory optimum having too high of a metabolic rate (closely linked to immune system activity; (Hotamisligil 2017) to allow the fungus to proliferate freely. Shorter torpor bouts may also limit fungal growth, as result of the fungus being groomed off by more frequently arousing hosts (Puechmaille et al. 2011b). Given that the mean annual surface temperature of an area correlates with the temperature of hibernation sites, the comprehensive knowledge on the effect of temperature to disease severity has been used to identify high-risk areas for pathogen introduction and increased monitoring efforts (Blomberg et al. 2023).

Air moisture within hibernation sites is another environmental factor that is simultaneously important for bat hibernation and fungal growth. Environmental air moisture minimises evaporative water loss (EWL), reducing dehydration pressure on hibernating bats (Ehlman et al. 2013; Klüg-Baerwald &

Brigham 2017). Unfortunately for humidity-loving bat species, *P. destructans* also thrives in high air moisture (Marroquin et al. 2017). That being said, our knowledge on the relationship between air moisture levels, disease severity and bat behaviour is scarce. Indeed, most studies intending to investigate WND in relation to air moisture have used relative humidity to describe the dryness of the air (e.g., Langwig et al. 2012). Nevertheless, as already demonstrated by Kurta (Kurta 2014), unless measurement are made at the same temperature (i.e., Marroquin et al. 2017) such values alone do not reliably predict absolute levels of air moisture. Therefore, it is imperative to reassess the findings of these studies using absolute moisture data, which can be derived from raw (unaveraged) relative humidity and temperature data. Regrettably, such datasets are seldom provided by authors, hindering our ability to revisit the importance of air moisture on WND. Therefore, approaches incorporating absolute humidity have the potential to expand our understanding of both hibernation and WND.

If you tolerate this, then your children will be next

Hosts can respond to pathogens via three routes: through tolerance or resistance mechanisms, or by avoiding the infection altogether (Roy & Kirchner 2000). Tolerance strategies limit the impact of the pathogen on the host (Medzhitov et al. 2012), whereas resistance mechanisms aim to reduce the negative consequences of the pathogen by limiting the growth of the pathogen (Roy & Kirchner 2000; Schneider & Ayres 2008; Ayres & Schneider 2012). Established models have estimated that the maximum fitness of individuals suggest only extreme strategies should evolve: either total resistance or total tolerance (Fineblum & Rausher 1995; Boots & Bowers 1999; Boots et al. 2009). Given that tolerance strategies allow the free proliferation of the pathogen, without consequent loss in the fitness of the host, tolerance should be the evolutionarily favoured outcome of host-pathogen relationships (Roy & Kirchner 2000). Because of these estimates, resistance and tolerance are generally considered as alternate, independent strategies (Mazé-Guilmo et al. 2014). This paradigm could be taken apart by viewing these contending strategies as a continuum where a protective pathway operating through tolerance lies at the far end of host-pathogen-responses, with resistance forming the opposing extremity. This would allow a scenario in which mixed strategies are selected for in parallel or at different timepoints within the evolutionary history of a host-pathogen interaction (Fig. 3. Fornoni et al. 2004; Restif & Koella 2004). Successful resistance, most significantly operating via innate and adaptive immune responses, as well as frequent arousals from torpor, are effective at keeping pathogen loads low, but may come at a high fitness cost (Mandl et al. 2015). Balancing the fitness trade-offs between tolerance and resistance can lead both the host and pathogen to adapt to the novel interaction, and further, coevolve to a commensal relationship (Glass 2012).

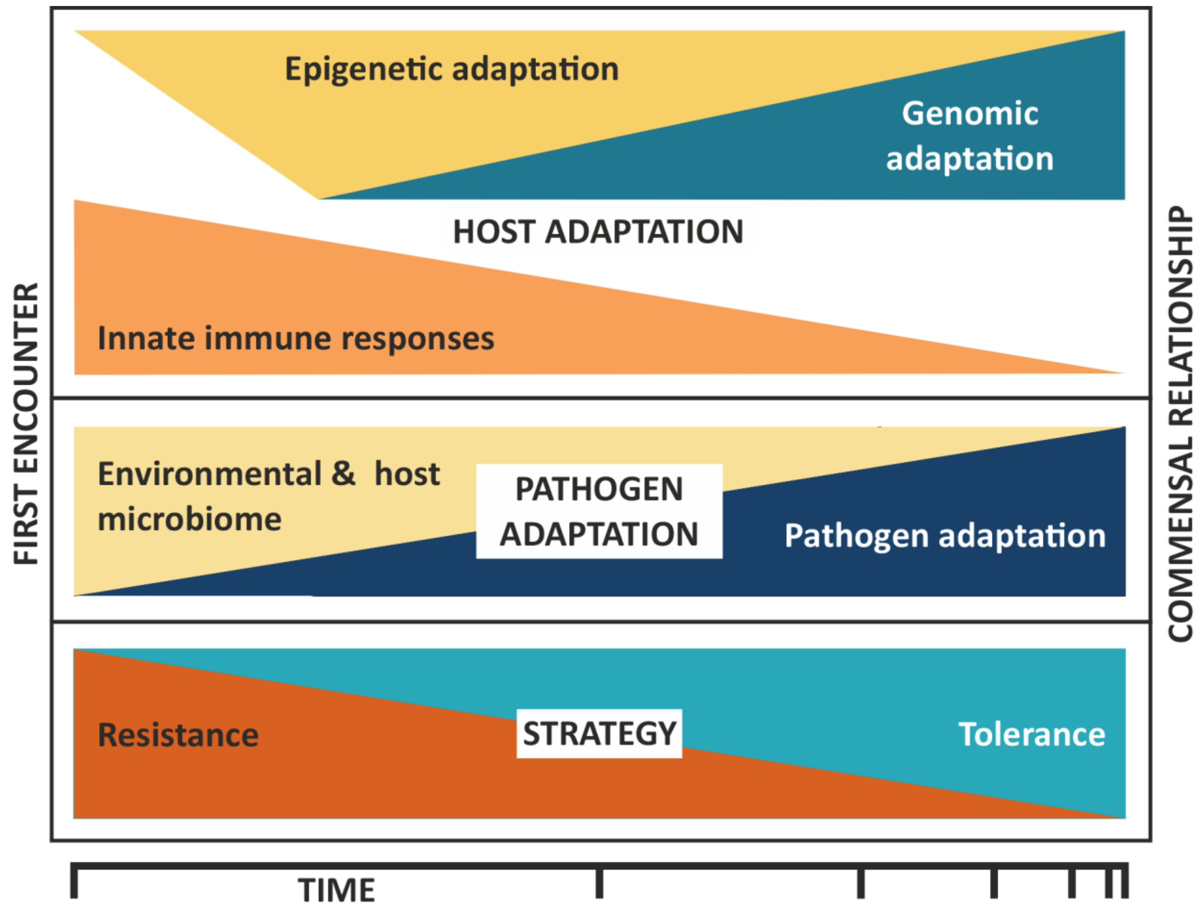

Fig. 3. Possible mechanisms contributing to resistance and tolerance and their shifting relevance through time. Figure is for depicting a possible scenario only and is not based on existing data.

In accordance with these hypotheses, there is indeed wide support for tolerance as the survival mechanism of *M. myotis*, a species with an extended evolutionary history with *P. destructans* (Fritze et al. 2019; Hecht-Höger et al. 2020). In fact, it appears that *M. myotis* does not elicit a transcriptional response to infection at all during hibernation (Lilley et al. 2019), responding only with the already circulating immune effectors (Fritze et al. 2021). In contrast, the Nearctic *M. lucifugus*, only recently exposed to the pathogen, attempts to control pathogen loads through an immunological resistance strategy, leading to harmful immunopathology (Langwig et al. 2017; Lilley et al. 2017; Field et al. 2018; Hecht-Höger et al. 2020). More importantly, it appears that bats in the Palearctic have evolved a commensal relationship with *P. destructans* as a result of shared evolutionary history (Zukal et al. 2016; Davy et al. 2017; Lilley et al. 2019). Commensalism can result either via lowered virulence of the pathogen (Jansen et al. 2015), or development of tolerance in the host, or both. Although well-studied examples of fungal pathogens contributing to dampening host responses are known from other study systems (de Jonge et al. 2012), there is evidence of *P. destructans* attempting to avoid detection by the host immune system in the WND-susceptible *M. lucifugus* (Reeder et al. 2017). Therefore, although it does not appear to be fully commensal (Casadevall & Pirofski 2000), the relationship in the Palearctic is an end result of coevolution to which both the host and pathogen contribute.

However, while evolution should favour the development of tolerance in host-pathogen relationships, not all Palearctic species that successfully cope with *P. destructans* infection have adopted these strategies. For instance, alongside behavioural defences, there is some evidence that *Rhinolophus ferrumequinum* may employ resistance towards *P. destructans* (Hoyt et al. 2016; although see Blomberg et al. 2023), with enhanced immune function at the latter stages of hibernation (Li et al. 2023). In addition to resistance, bats may indirectly completely limit *P. destructans* growth by either selecting microclimates that are outside the environmental optimum of the pathogen (Turner et al. 2022) or by switching to entirely different habitats, as was hypothesised to be the case for *Myotis bechsteinii* (Martínková et al. 2010). These different host behaviours add to the complexity of potential host responses as a part of WND dynamics. However, behavioural responses to the mycosis, i.e., infection status, have been difficult to prove in bats similar to infection-induced changes in mice (Lopes et al. 2016).

WND of change in the Nearctic

The first-infected populations of Nearctic bats have begun stabilising (Reichard et al. 2014; Frick et al. 2017; Dobony & Johnson 2018; Frank et al. 2019), but the mechanisms facilitating persistence are not well understood. Although tolerance should be ultimately favoured (Roy & Kirchner 2000), the Nearctic bat populations may not have had enough time to evolve this strategy. However, several changes have been observed in surviving populations. For instance, surviving bat populations appear to be fatter ahead of the hibernation season compared to bats prior to WND (Cheng et al. 2019). This would allow infected bats a higher frequency of arousal from torpor without emaciation. It also appears that highly affected bat species in the Nearctic (*M. lucifugus*, *M. septentrionalis* and *P. subflavus*) are found at hibernation sites with lower temperatures than were favoured by the majority of the populations prior to the epizootic (Johnson et al. 2016; Turner et al. 2022). Lower temperatures correlate negatively with the growth rate of the fungus (Verant et al. 2012) and facilitate longer torpor bouts for decreased energy expenditure (Thomas et al. 1990). Furthermore, where the disease is occurring, a higher fraction of bats seem to be hibernating individually when compared to pre-epizootic (Langwig et al. 2012), but whether this is a behavioural response or purely due to the decline of population size overall is not yet known.

Infected *M. lucifugus* from surviving populations also show dampened immune responses compared to populations just coming into contact with the pathogen (Lilley et al. 2019). However, at the genomic level, studies show mixed evidence with regards to selection on standing genetic variation that would explain dampening of immune responses (Lilley et al. 2020; Auteri & Knowles 2020; Gignoux-Wolfsohn et al. 2021). Epigenetic processes provide a plausible avenue for rapid response after the introduction of a novel pathogen. Epigenetic actions that can modulate the host defence against microbial pathogens include DNA methylation, histone modification and the activity of non-coding RNAs (Jones 2012). Ultimately, alterations of, for example, DNA methylation and the resulting changes in gene expression may generate heritable population-level phenotypic variation, which can be acted upon by natural selection and drive population adaptation to novel pathogens (Garcia et al. 2019). Whether epigenetic processes could be contributing to the dampening of responses, acting either on the transcription of the host or pathogen genes, has not been investigated yet in the context of WND, but could yield an explanation to the apparent dampening of responses (Morandini et al. 2016; Garcia et al. 2019).

Genomic adaptation to a new host-pathogen interaction through evolutionary processes, such as selection from standing variation, occurs over several generations, with adaptation through *de novo* mutations taking even longer (Booker et al. 2017). Therefore, other factors may initially contribute to making the interaction less harmful to the host. For instance, the mammalian skin possesses commensal bacteria that participate in a variety of protective functions (Nakatsuji et al. 2021); some selected species or strains of bacteria appear to have a mutualistic and beneficial relationship with the host, by directly killing pathogens (Cogen et al. 2010; O'Neill et al. 2020) or even contributing to wound-healing (Di Domizio et al. 2020). Indeed, differences in the skin microbial communities have also been documented between bat populations exposed or not exposed to the pathogen (Lemieux-Labonté et al. 2017), and some microbes have been found to inhibit the growth of the fungus (Fritze et al. 2012; Hoyt et al. 2015; Singh et al. 2018; Grisnik et al. 2020; Li et al. 2022a). These properties contribute to the hologenome theory of evolution, where a functional biological unit, a holobiont, operates through the genetic material of both the host and its microbiome (Zilber-Rosenberg & Rosenberg 2008). With an ability to inhibit the growth of a novel pathogen and potential for rapid adaptation, the microbiome can provide a buffer allowing populations to persist until an appropriate evolutionary genomic response has been selected for (i.e., genetic assimilation [Robinson & Pfennig 2013]). Furthermore, the environment also has a microbiome, which in the case of the environmentally transmissible pathogen, such as *P. destructans*, can have a large influence.

Adaptation to the novel interspecific interaction may be occurring at varying temporal time scales via several different routes in the host, the pathogen and the holobiont. Because of the plethora of factors at play, the intersections of these properties should be considered in a multidimensional space for one to be able to perceive which scenarios, or combinations of factors, result in disease.

In the Nearctic, large die-offs have only been reported in three species (*M. lucifugus*, M. *septentrionalis*, *P. subflavus*) (Cheng et al. 2021). It is important to comprehend that the overlap in distribution of the host and the pathogen is likely greater than the distribution range for the incidence of the disease causing mortality (Xu et al. 2023). Furthermore, high incidence of mortality appears to be restricted to a proportion of the overlapping distribution range, where factors contributing to disease intercede favourably. For instance, although the distribution range of *M. lucifugus* and *P. destructans* spans longitudinally across the entire continent of North America, large-scale mortality has only been observed in the intensively mined karst regions on the eastern portion of the continent, whereas western populations appear at least less affected (Udell et al. 2022). Host behaviour and environmental conditions favour the generation of an epizootic in these regions affecting much of the population, although disease can occur sporadically elsewhere too, when conditions are met.

While it is difficult to tease apart the relative importance of these factors, examining the properties that Palearctic bats have acquired to avoid mortality from WND during their evolutionary history may give us some insight into what are possible outcomes after extended coexistence, i.e., apparent commensalism (Fritze et al. 2019; Lilley et al. 2019). Here, infection history and coevolution is similarly moderated by variability in the factors present in the disease triangle, leading to varying outcomes even after apparently lengthy exposure times (Zukal et al. 2014; Hoyt et al. 2016a).

Let it be?

Despite populations showing signs of stabilisation or recovery, managing the spread and effects of the epizootic is very much an active effort in North America. In fact, action is required by governmental mandate in the U.S. when threatened or endangered species are involved (U.S. Fish & Wildlife Service 2022). Therefore, several management strategies have been suggested and trialed to counter WND (please see Table 1). To assist in quantifying the management methods tested so far, we performed a Web of Science (WoS) search using the following search terms: ALL=("bats" AND "management") AND ALL=("white-nose syndrome" OR "WNS" OR "white-nose disease" OR "WND"). The search was conducted on 8 August 2023.

Table 1. Table summarising publications with tested management methods with total number of papers per management class, how it was tested (Model, Field, Lab), and what the effect was (NA, No effect, Negative, Positive).

	No. of papers	**No. of method used**			**Total of outcomes**			
Management method		**Model**	**Lab**	**Field**	**NA**	**NE**	**Neg**	**Pos**
Antifungal compounds	9	16	4	3	0	6	7	10
Culling	3	3	0	0	0	0	2	1
Host health	8	7	4	0	1	1	3	6
Host health, antifungal compounds	3	4	0	0	1	0	1	2
Improving host summer habitat	2	1	1	1	1	0	0	2
Improving host winter habitat	3	1	0	2	1	1	0	1
Modifying hibernation sites	8	7	2	2	3	3	3	2
No management	1	1	0	0	1	0	0	0

The WoS-search resulted in 195 published papers, out of which two were discarded based on the title. The resulting 193 published peer-reviewed papers (supplementary Table 1) were reviewed, and data was collected on whether a treatment was tested, the type of treatment tested, whether it was tested in a lab, in the wild, modelled, or a combination of these, and whether the practice had an effect (positive/negative/none). It is important to note that a positive result does not mean that the treatment cured the disease but rather that the treatment had a significant positive effect on the simulated/measured parameter (e.g., survival, fungal load, use of hibernation site, etc.). Besides, some positive effects are long-lasting (e.g., improving habitat) while others are rather short-lasting (e.g., antifungal compounds). We further excluded two methods that came up in the literature search: monitoring (7 papers) and education/attitudes towards bats (5 papers) as they do not have an effect that can be measured. Out of the remaining 181 papers, 37 tested one or multiple treatments or management practices (see Table 1 for treatments). Most management methods considered were model based (67.8%) followed by lab based (18.6%) and field based (13.6%). Positive results were reported for 7 treatment classes: the use of antifungal compounds (10/23 tests), culling (1/3 tests), improving host health (6/11 tests), a combination of antifungal compounds and improving host health (2/4 tests), improving summer (2/3 tests) or winter foraging habitats (1/3 tests) and modifying hibernation sites (2/11 tests). In contrast, negative effects were reported for 5 treatment types, including the use of antifungal compounds (7/23 tests), culling (2/3 tests), improving host health (3/11 tests), the combination of antifungal compounds and health improvement (1/4 tests), and modifying hibernation sites (3/11 tests). In the case of other tests, the paper reported the management strategy to have no effect, or effect on WND could not be concluded. To conclude, the only management methods with only positive or no effect were the improvement of summer and winter habitats.

The efforts so far highlight the importance of pinpointing research gaps to help identify suitable timing of action (Langwig et al. 2015a; Grider et al. 2022), management priorities (Bernard et al. 2020) and feasible methods that provide a long-term solution (Verant & Bernard 2023). For instance, any individual treatment, e.g., vaccinations and administration of antifungal compounds, will be logistically difficult to administer to an effective number of bats on a regular basis, not least because a lot of hibernation sites are yet unknown (Weller et al. 2018). A treatment or management action also appears to facilitate the recovery of affected populations only if the disease is mild (Fletcher et al. 2020).

While some management methods, such as the use of probiotics to enhance the protective microbiome against WND, have shown promising results for a single bat species under controlled laboratory settings (Hoyt et al. 2015; Cheng et al. 2017), it is unlikely to decrease the spread of the pathogen and associated disease. Additionally, the effects of probiotic use as a defensive measure can be unpredictable, because the topic remains vastly understudied, especially under the large range of natural conditions encountered by hibernating bats. For example, diversity within the cutaneous microbiome is associated with bat species resistant to WND (Vanderwolf et al. 2021), suggesting a consortium of antifungal microbes, instead of just one species/strain, could potentially be an optimal mitigation strategy for WND in the future. However, each microbial taxa introduced to an ecosystem poses a risk because it could potentially act as a pathogen to the other organisms living in the environment, like the often cited *Pseudomonas fluorescens* (Barker et al. 1991; Sadd & Schmid-Hempel 2006; Pompini et al. 2013). In some cases, probiotics may even worsen disease severity (Cheng et al. 2017). This is particularly the case when the treatment is occurring pre-pathogen exposure. However, the exact timing of bats being exposed to *P. destructans* has not yet been precisely identified (Fischer et al. 2022): timing that likely exhibits variation across different species, geographical regions, sexes, age groups, and other factors. Consequently, while modelling outcomes and laboratory experiments may yield encouraging results, achieving scalability in implementing them adequately in the field, perhaps on an annual basis, across extensive areas like North America does not appear achievable in practice.

As research on WND continues, we can confidently say that we have enough knowledge to suggest less-individualistic management methods that alleviate bat stressors, as this not only promotes the health of the bat fauna in entirety, but also promotes adaptations allowing the host to persist with the pathogen (McCallum 2012; Bernard et al. 2020). In other words, rather than targeting a single stressor (*P. destructans*), we advocate for management actions that act on key parameters that are generally important for bat (and ecosystem) health (Verant & Bernard 2023). These would include the protection and improvement of available hibernacula (Turner et al. 2022; but see Boyles et al. 2023), minimising bat disturbance (Thomas 1995), increasing prey availability (Cheng et al. 2018), limiting wind turbine-related mortality (Erickson et al. 2016), and raising public awareness (Salleh et al. 2020; Shapiro et al. 2021). Not all positive effects are intuitive: for instance, some species only increase in number when there are enough alternative hibernacula in the vicinity (Turner et al. 2022). Increasing fat stores is vital for overwinter survival (for WND and in general), so management strategies that increase prey availability are particularly pertinent, such as controlling pesticide use, and restoring aquatic habitats (Cheng et al. 2018), especially because it is known that enhanced fat storing are an important adaptation for some populations of *M. lucifugus* (Cheng et al. 2019). Given that limited resources are available, management strategies with a more holistic approach than an individualistic approach may be easier to enact, and, crucially, benefit the entire ecosystem rather than potentially harming it (Meierhofer et al. 2022). Implementing these measures will not only yield immediate benefits, but also lead to long-lasting positive consequences for bats and many other organisms. Moreover, contrary to the application of anti-fungal compounds or vaccines, these initiatives have the potential to be self-sustaining over time. Additionally, species that are more susceptible to WND should be favoured in conservation planning: those utilising extended torpor bouts, preferring higher humidity, hibernating in large aggregations, and those expressing immunopathology.

Management actions also have the potential to keep individuals alive that would not be able to survive in the presence of *P. destructans*, and hence diluting adaptive genetic variation, slowing down the evolution of resistance/tolerance. Considering this, the concept of "doing nothing" (Ashley-Smith 2018) presents an alternative angle to disease management, whereby populations left to their own devices are expected to survive as a consequence of natural processes, without human intervention. Of course, not performing management actions is context-specific (Bernard et al. 2019; Verant & Bernard 2023), as it is also important that research on the topic does not come to a standstill (Reeder et al. 2016). Nevertheless, in accordance with the philosophy of "doing nothing", the Nearctic species would follow the same pattern as the Palearctic leading to coexistence through evolution. However, there are some important differences to consider. First, the current epizootic is occurring during the Anthropocene, in which organisms are facing additional threats from rapid environmental change (Pereira et al. 2010), climate change (Blois et al. 2013), energy production (Gaultier et al. 2020), and a cocktail of environnemental pollutants (Cable et al. 2022). We are evidencing the largest number of extinctions since the last mass extinction (IBPES 2019): a very different scenario to what bat populations in the Palearctic may have faced during the early stages of their infection history (Leopardi et al. 2015). These additional threats to populations contribute to the formation of extinction vortices, multiplying the probability of eradication (Palomares et al. 2012), and therefore, "doing nothing" cannot be applied as such. However, it can be agreed upon that action without sufficient knowledge is more detrimental.

White-nose disease is a devastating disease that will continue to spread to new bat populations across the North America continents, most severely affecting gregarious, cave-dwelling bats. However, more recent data has shown that species can adapt tolerance or resistance mechanisms to survive this disease. Management strategies require an overall understanding on the intersection of factors contributing to disease to help understand why certain species are more prone to be severely affected. This helps predict the impact on bat populations as WND spreads into uninfected areas and assists in planning and implementation of effective conservation measures. Furthermore, planning should consider the rapidly changing environment of the Anthropocene. Climate change will have an effect on the distributions of hosts, disease manifestation, and on how populations can recover (Blomberg et al. 2023). With time and carefully planned conservation measures, bats in currently infected populations will continue to recover, and newly infected populations on the American continents will persist long enough to evolve mechanisms that allow them to recover and thrive. The goal should be to ameliorate the evolutionary process taking place during host-pathogen coexistence and allowing *P. destructans* to coevolve with its host from a deadly pathogen into an innocuous endemic.

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