Ecology and impacts of white-nose syndrome on bats

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Abstract | The recent introduction of *Pseudogymnoascus destructans* (the fungal pathogen that causes white-nose syndrome in bats) from Eurasia to North America has resulted in the collapse of North American bat populations and restructured species communities. The long evolutionary history between *P. destructans* and bats in Eurasia makes understanding host life history essential to uncovering the ecology of *P. destructans*. In this Review, we combine information on pathogen and host biology to understand the patterns of *P. destructans* spread, seasonal transmission ecology, the pathogenesis of white-nose syndrome and the cross-scale impact from individual hosts to ecosystems. Collectively, this research highlights how early pathogen detection and quantification of host impacts has accelerated the understanding of this newly emerging infectious disease.

White-nose syndrome (WNS) is a fungal disease in bats and one of the most devastating infectious disease outbreaks in wild mammals to emerge over the past century[1–15]. WNS was first detected in 2007 by biologists who discovered an abnormal mortality event at a cave in Albany County, New York (NY), USA, while conducting routine bat population monitoring surveys[16]. Bats that were still alive were covered in a white fungus, which was most noticeable on their muzzles, ears and wings, thus leading to the disease being named WNS[17,18]. Following this discovery, inspection of nearby hibernation sites (hibernacula) led to similar findings and further examination of photos collected from previous winter surveys revealed that bats at another nearby site had visible signs of infection with the fungus in the winter of 2005–2006. Thus, the earliest evidence of this disease in North America is on 16 February 2006 in Howes Cave, NY[17]. Histological examination of dead and dying bats later identified the likely causative agent as *Geomyces destructans*[19], a novel fungus that was unknown to science before its discovery in North America[17]. Based on DNA sequence data from other *Geomyces* spp. and related fungi, *G. destructans* was reclassified as *Pseudogymnoascus destructans*[16,17,20] in 2013.

P. destructans is a multi-host psychrophilic ascomycete[20] in the order Onygenales, which contains many other pathogenic and environmentally resilient fungi. Molecular evidence suggests that *P. destructans* has evolved with Eurasian bat communities, with which it has coexisted for millenia[21,22], to become a specialist pathogen that relies primarily on living bat tissue for growth and replication[22–24]. The investment in parasitic traits has led to physiological and ecological trade-offs[22–26], which make *P. destructans* both reliant on but also well adapted to infecting the epidermal tissue of hibernating bats during the winter[26,27]. While bat communities across Eurasia experience greatly reduced WNS disease severity with no evidence of mass mortality[28,29], naive host communities in North America experienced unprecedented population declines[1–15] on first exposure to this virulent pathogen[26,27].

Routine monitoring and retrospective photo documentation of bat populations enabled biologists to estimate the timing of *P. destructans*' introduction to North America with some certainty, making this disease emergence unique among other wildlife diseases. Early detection enabled the spread of *P. destructans* across North America to be tracked and the impacts of the pathogen on hosts to be accurately assessed. Building on this information, the first decade of WNS research has led to considerable advances in the understanding of the closely tied interactions between *P. destructans* and its hosts compared with other emerging wildlife diseases over similar timescales[30,31]. In this Review, we describe the origins, distribution, seasonal life history, pathogenesis, and the impacts and persistence of bats with *P. destructans* across the globe. Finally, we highlight conservation measures that have been taken to reduce the impacts of this pathogen and outline several areas of host and pathogen biology that require additional research.

Origins and introduction

Experimental[27], ecological[28,32] and molecular[20,21,33] evidence has shown that a single clonally spreading genotype of *P. destructans* was introduced into North America from Eurasia in the early-to-mid 2000s[21,33–36]. Photographic evidence, isolation from museum specimens and genomic

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data[21,37–40] indicate that *P. destructans* has likely been present in Europe and Asia for thousands of years or longer, with no evidence of host mass mortality in at least the past several decades[28,29]. Although the exact source of *P. destructans* and its mode of introduction into North America remain unknown[21], the introduction of this pathogen was most likely mediated by humans, either through direct or indirect transfer of infectious propagules. Proposed hypotheses include accidental transport of an infected bat or the transfer of infectious propagules on contaminated gear and equipment, on specialty European cave-aged food items, or by tourists. Currently, no data exist to distinguish among these modes of introduction, and further molecular epidemiological investigation of the source of the North American isolates could shed light on how this devastating pathogen was introduced.

The analysis of *P. destructans* isolates using microsatellites and single-nucleotide polymorphisms suggests that there are at least three distinct clades, representing geographic groupings of isolates from Far-east Asia (China), Central Asia (Mongolia) and Europe[21] (FIG. 1).

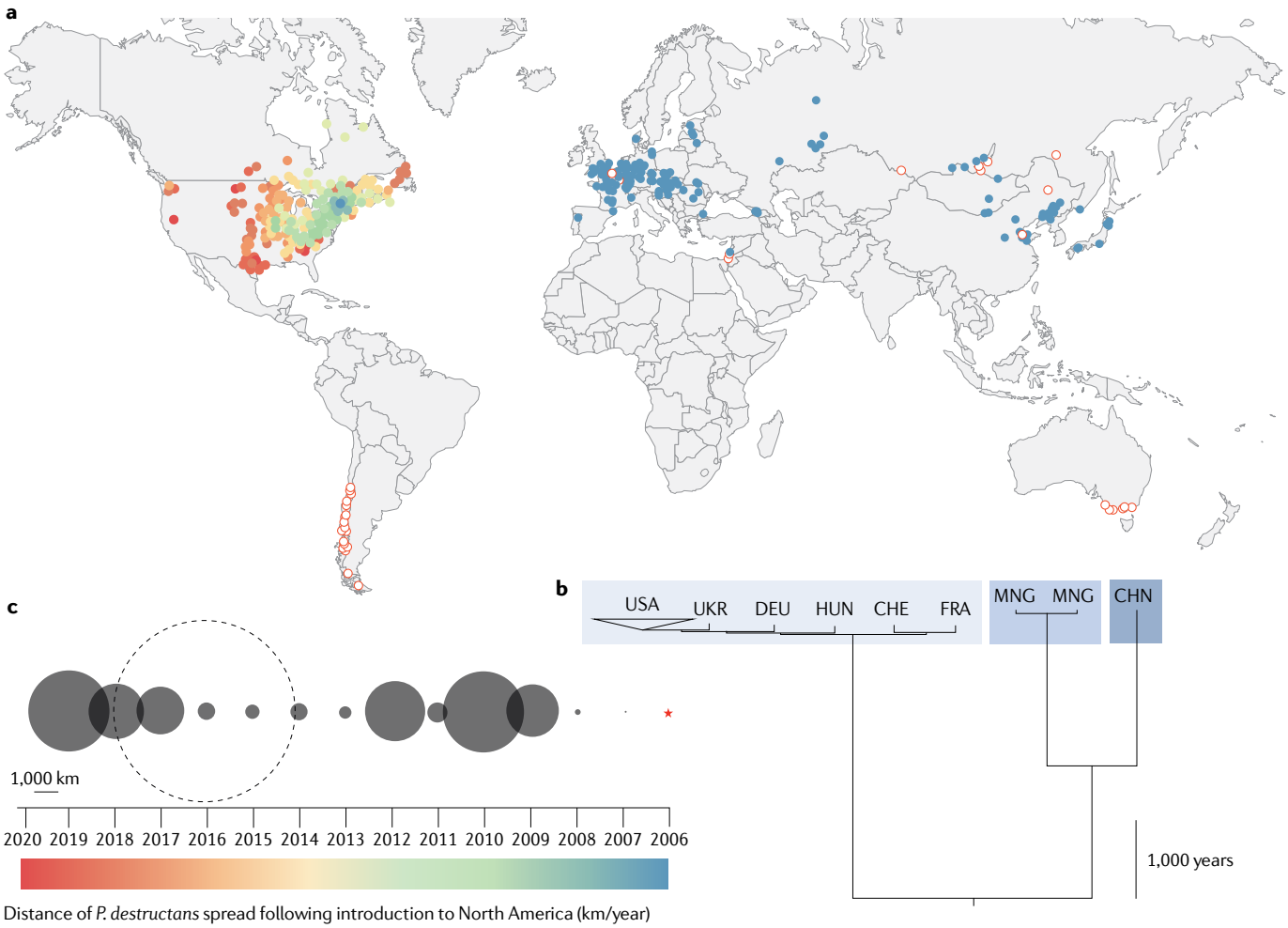


Fig. 1 | **Global distribution of *Pseudogymnoascus destructans*. a** | Points show locations that have been sampled for *P. destructans*[28,33,39,40,53–55,68,77,161–166]. Filled circles indicate sites where *P. destructans* was detected through qPCR, photographs and sampling of museum specimens and red open circles indicate sites where *P. destructans* was not detected (these sites in North America are not shown). This fungus has now been found in 23 countries/regions across Europe (including Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, France (FRA), Germany (DEU), Hungary (HUN), Italy, Latvia, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Switzerland (CHE), Turkey, Ukraine (UKR), the United Kingdom and over the entire span of Russia) and 5 countries/regions across Asia (China (CHN), Georgia, Israel, Japan and Mongolia (MNG)) and likely exists across this entire region where bats hibernate. In North America, the circle colour indicates the year of first detection in each administrative subdivision (such as a county or provincial district). **b** | A phylogeny adapted from REF.[21] shows a maximum clade credibility tree constructed from genomic single-nucleotide polymorphisms (SNPs) with branch length representing time. Isolates from North America are nearly indistinguishable at the SNP loci analysed, as indicated by the triangle. The three supported clades include Far-east Asia (dark blue), Central Asia (blue) and Europe (light blue). **c** | Timeline showing the distances of maximum *P. destructans* spread during consecutive winters in North America. Year labels show the second half of the winter period (for example, 2006 corresponds to the winter of 2005–2006). Distance (circle diameter) is measured as the distance (± 25 km) between the centroid of the farthest county or administrative division (as reported by whitenosesyndrome.org) detected in winter t + 1 from its nearest county in the previous winter (t) (for example, the size of the circle above 2009 is the distance *P. destructans* spread from the end of winter 2008–2009 to the end of winter 2009–2010). The jump from eastern North America to Washington state (dashed circle) represents an ~2,100 km movement; the black circle in the centre of the dashed circle indicates the distance spread excluding this jump. The initial introduction into New York, USA, in 2006, is indicated by a red star. Part **b** is adapted from REF.[21], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

The *P. destructans* genotype distributed across North America is a member of the European clade and is currently most closely related to an isolate collected from Ukraine (FIG. 1). However, sampling coverage in Eastern Europe and Central Asia is limited (FIG. 1), and a closer match to the North American isolate likely exists but is yet to be collected from this region. The greater diversity of isolates in East Asia in comparison to those in Europe, despite similar geographic distances, may suggest that the fungus first emerged in bats in Far-east Asia and then spread to Europe[21] (FIG. 1). However, more samples from across Asia are needed to fully examine the differences in diversity and their historic origins. Genetic evidence supports the idea that Eurasian bat species were present when *P. destructans* likely diverged from other closely related *Pseudogymnoascus* spp., indicating that *P. destructans* has had a long period of co-evolution with its bat hosts[21,41].

Patterns of spread

Over the past 15 years, *P. destructans* has spread across most of North America and, to date, it has been detected in 39 US states and 7 Canadian provinces (FIG. 1). The observed rate of spread of *P. destructans* in the first 8 years after the earliest North American record of the pathogen was gradual compared with that of other emerging pathogens that infect highly mobile hosts[42,43], with an expansion of 200–900 km per year. The rate of spread accelerated in the period 2008–2012 as the pathogen spread southwest along the dense karst region of the Appalachian Mountains and west into Missouri during the winter of 2009–2010 (FIG. 1c). In 2016, the North American genotype of *P. destructans* was detected in western Washington state, 2,100 km from the nearest known contaminated hibernacula in Nebraska[44] (FIG. 1). This long-distance dispersal likely represents a human-mediated movement and is not consistent with normal movement of bats. The fungus has subsequently been detected in other counties in Washington as well as in California, indicating a second expanding front in the western US (FIG. 1). Currently, the fungus has yet to be detected in Florida, despite being present in the nearby states of Georgia, South Carolina, Mississippi and Alabama for at least 7 years, suggesting that these states may represent the southern limit of the fungus' distribution (FIG. 1).

Studies examining patterns of spatial spread have estimated the probability of detecting the fungus as a function of distance from the first affected hibernacula in NY. WNS was more likely to be observed at sites with larger host colony sizes, a higher fraction of host species using high-humidity environments[45] and more densely aggregated host colonies with warmer temperatures[46]. Research based on patterns of *P. destructans* detection from 2007 to 2011 suggests that the density of karst habitat (a landscape underlain by soluble rocks, such as limestone, which is used as a surrogate for the number of natural caves) and longer winter duration increased the rate of spread[47]. Unfortunately, the fungus arrived in most US counties decades earlier than predicted[47], and the more rapid expansion across North America showed that the proposed barriers to fungal spread, such as large gaps between sites, were only temporary obstacles. Past patterns of spread indicate that *P. destructans* will reach all or nearly all hibernacula in the US and Canada over the next decade, if not much sooner.

The spatiotemporal pattern of *P. destructans* spread among hibernacula is not consistent with seasonal patterns of host movement between hibernacula. Bat movements are higher during autumn, when bats visit multiple sites for mating, than during winter, when their movements are restricted by cold temperatures, limited fat reserves and a lack of resources[48,49]. However, *P. destructans* was more likely to be first detected at a site in late winter than in early winter (~1–2 months from the start of hibernation)[50]. This observation suggests that the majority of spread occurs over winter, likely due to much higher levels of infection during this period, which increases the probability of successful introduction and establishment at a site[50].

The genetic population structure of one bat species, *Myotis lucifugus*, is similar to the broad patterns of spatial spread, which shows panmictic populations of this species east of the Rocky Mountains and more genetic structuring in western populations[51]. However, the spread of the fungus into Washington state in 2016 and the introduction of the fungus into North America in 2006 are inconsistent with normal movements by hibernating bats and suggest that human-mediated mechanisms, such as those described above, are necessary to explain these spreading events.

Genetic analyses to examine the patterns of spatial spread of *P. destructans* within North America have found no correlation between genetic and geographical distance, which suggests widespread mixing of *P. destructans* genotypes and frequent spread among infected hibernacula[21,35]. However, it is also possible that the lack of genetic diversity among clonal isolates has masked patterns of geographic spread. The analysis of mycoviruses that infect North American *P. destructans* has shown increased genetic clustering by distance[52], suggesting that more-rapidly changing fungal viruses may be a promising tool for examining finer scale spatial spread.

Although *P. destructans* has spread throughout much of North America (FIG. 1) and is present throughout Eurasia[28,32,39,53], there is no evidence that the fungus is present in the southern hemisphere in regions where bats hibernate (for example, South America and Australia[54,55]; FIG. 1). A risk assessment of the possibility of *P. destructans* introduction into Australian bat populations performed in 2019 suggests that introduction by a tourist, caver or researcher is likely in the next decade[56]. However, the impact of this pathogen on Australian bats is hypothesized to be lower than on North American bats owing to the shorter duration of the Australian winter[56].

Seasonal cycles of infection

Host and pathogen ecology drive strong seasonal patterns of *P. destructans* infections (FIG. 2). Given the cyclical nature of most fungi, which generally undergo periods of intense proliferation followed by dormancy or dispersal, their life histories are intimately tied to their primary nutrient sources. Like many other fungi with an

environmentally dormant stage, *P. destructans* produces conidia that are capable of surviving for long periods of time in underground hibernation sites[57,58], allowing the fungus to persist over summer when it is unable to replicate on and infect bats.

The temperature-dependence of *P. destructans* growth strongly dictates when infections associated with WNS can occur[59–61]. As a psychrophile, *P. destructans* can only grow at temperatures <20 °C (REF.[60]). Temperate bat species affected by WNS are heterothermic and have seasonal fluctuations in body temperature. When bats are euthermic and active on the landscape, their body temperatures are typically higher (37–41 °C (REF.[62])) than the 20 °C upper critical limit of fungal growth. However, the body temperature of bats drops to near ambient (1–16 °C (REFS[63,64])) at the start of hibernation in mid-to-late autumn, which is within the *P. destructans* growth range. This drop in body temperature coincides

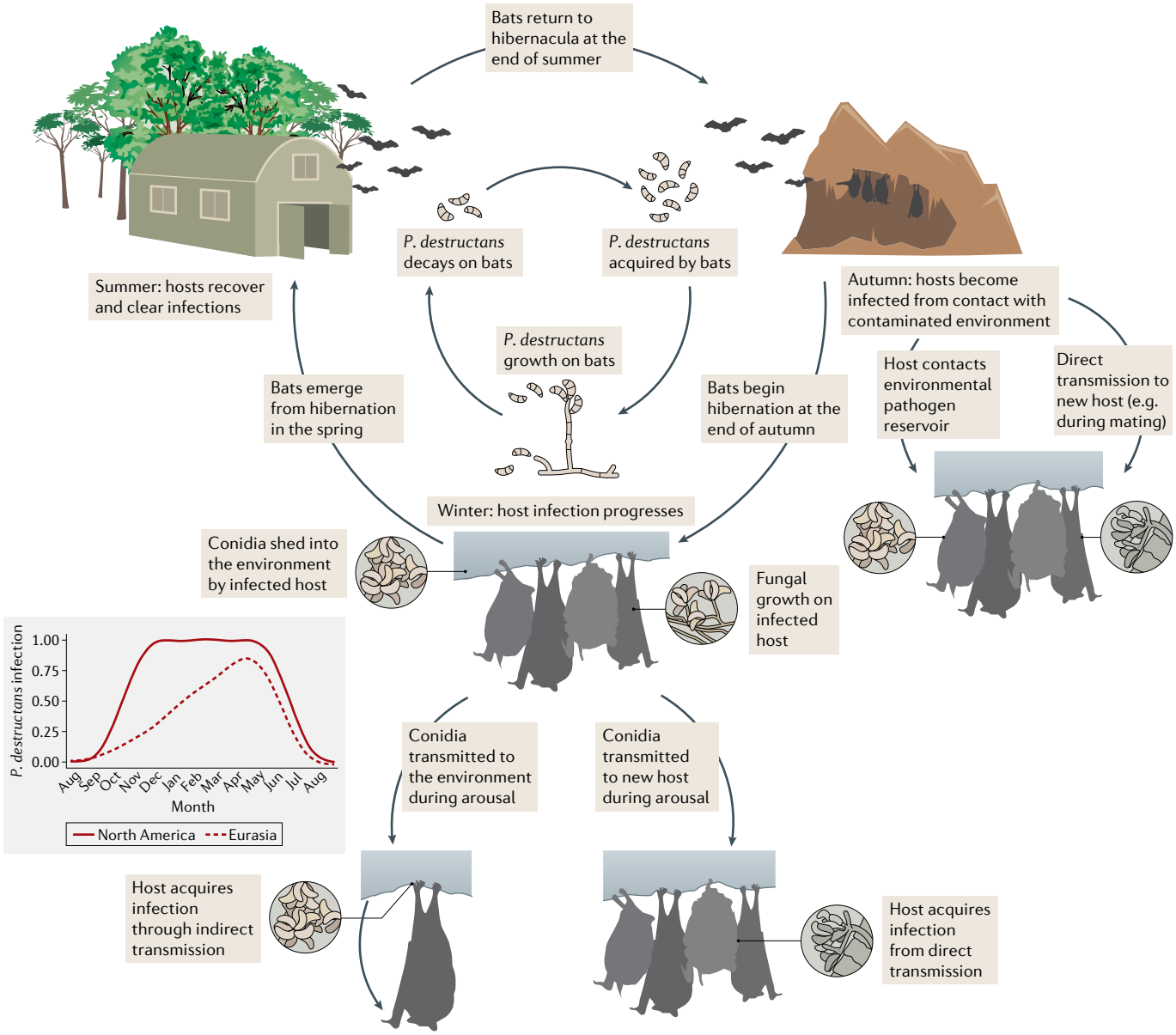


Fig. 2 | **Seasonality and within-site transmission of *Pseudogymnoascus destructans*.** The seasonal pattern of *P. destructans* and its bat hosts is depicted. The internal circle shows the abundance and growth phases of *P. destructans* during different stages in bat life history. The outer circle shows the seasonal life history of a typical temperate hibernating bat. *P. destructans* persists in subterranean environments when bats are absent from these sites or are active in the landscape. During autumn, bats return to hibernacula, begin to accumulate fat stores for the winter, mate and start hibernating. Bats become infected or reinfected during autumn from environment-to-host and host-to-host contact. These infections progress over the winter while bats are hibernating in subterranean sites (such as caves, mines and tunnels) from late autumn until early spring. If bats survive *P. destructans* infection, they then emerge onto the landscape in spring, when females will typically form maternity colonies and communally raise their young. Males disperse singly on the landscape, occasionally forming small bachelor colonies. Infections are cleared over this active period when the fungus cannot grow. Although this is a typical annual cycle, some species remain in caves and mines all year round but still appear to clear infections over the summer. The graph inset shows general trends of *P. destructans* on bats in North America and Eurasia. The reduced environmental reservoir in Eurasia results in delayed infection for bats across this region compared to North America[28].

with a reduction in host immune function, enabling the fungus to colonize their epidermal tissue[16] and grow[26,27].

Seasonal patterns of pathogen prevalence and intensity were similar for six bat species after *P. destructans* establishment in North America[26]. Most bats (~75%) in North America become infected over a short, ~2–3 week period between late autumn and early winter, whereas bats across Europe and Asia acquire new infections over a much longer time period (6–7 months) and have a lower average pathogen prevalence (~20%) in early winter[28] (FIG. 2). Across all regions, prevalence and fungal loads peak at the end of winter, which is when mortality occurs in North America[27,28,53,61,65–68]. Levels of *P. destructans* in the environment also increase over winter[28,66], which is likely due to the shedding of infectious propagules and the movement of bats within sites during arousal periods[27,69,70], intensifying the environmental contamination of *P. destructans*[28,66].

For bats that survive until spring, the return to euthermia can result in an intense inflammatory response in *P. destructans*-infected tissue, primarily in the wing and tail membranes[71,72]. This immune response can reduce fungal infection[73] but can also result in immune reconstitution inflammatory syndrome[71,74], which causes severe immune-mediated tissue damage and can result in death for already compromised individuals[75].

If bats survive through emergence from hibernation, they begin to clear infections within a few weeks[61,72,73,76]. Fungal loads drop significantly within 10 days following emergence and reach nearly undetectable levels (<1%) by mid summer[61,72,73]. Over this period, surviving individuals regenerate damaged tissue, and most lesions are healed between 25 and 40 days from the start of recovery[61,72,73]. *P. destructans* conidia can survive for only 5 days at 37 °C (the body temperature of active bats) on bat fur[59], which likely contributes to the clearance of *P. destructans* after the end of hibernation. Although no comprehensive study of *P. destructans* seasonality has been conducted across Europe or Asia, one study sampled over 200 individuals from 9 bat species in China during the summer months (June–July) and found a prevalence of *P. destructans* of ~1%[77], suggesting that seasonal patterns are likely similar across the entire distribution of this fungus.

The prevalence and fungal loads of *P. destructans* in Eurasian hibernacula environments have been found to decrease significantly during the summer[28], whereas the prevalence in North American hibernacula remains nearly constant at an average of ~45%[28,57,58]. These higher levels of environmental contamination result in the earlier timing of infection for bats in North America compared to bats across Eurasia[28]. *P. destructans* prevalence in North American summer roosts has been found to be far lower (~2–7%[78,79]) and probably represents contamination from bats rather than from a persistent pathogen reservoir, as this fungus has limited viability given the sustained temperatures of over 30 °C in these roosts[59]. During autumn, bats return to hibernacula and engage in the 'autumn swarm', a behaviour characterized by promiscuous mating, long-distance movements between hibernacula and contact with hibernacula surfaces[80–84], while also fattening in preparation for hibernation[83,85]. Bats become infected or reinfected from contact with the *P. destructans* environmental reservoir in hibernacula and subsequent contact with other bats during mating, which restarts the seasonal epizootic[28,58,61,78,86]. The autumn swarm is a phenomenon common to all temperate hibernating bat species[80–82]; however, the increased levels of *P. destructans* in the environment across North America leads to more transmission during this period than in Eurasia[28] (FIG. 2).

Modes of transmission

P. destructans is primarily transmitted by direct contact between bats and through contact with contaminated environmental surfaces during autumn and winter[26,28,86] (FIG. 2). The fission–fusion and highly gregarious social structure of many bat species results in the efficient transmission of *P. destructans* (FIG. 2). While bat activity is greatly reduced during hibernation, bats cycle through periods of torpor with brief (~1–3 hours) intermittent arousals every ~2–3 weeks[69,87,88]. Activity during these arousal periods results in infected bats transmitting *P. destructans* to other individuals or an uninfected bat coming into contact with a contaminated environment. A study using a surrogate pathogen (a trackable ultraviolet (UV)-fluorescent dust)[86], revealed that, for two species (*M. lucifugus* and *Myotis septentrionalis*), a single individual bat transmitted the surrogate pathogen to a large fraction of the total population (~25%) at a site. However, a third species examined (*Perimyotis subflavus*) showed that spatial segregation within hibernacula reduced transmission to ~2%.

Examination of other potential transmission modes has found little evidence to suggest that aerosolized, vectored or vertical transmission are important in the dispersal of *P. destructans*[26,61,89]. For example, a study examined whether *P. destructans* conidia could be transmitted through the air by housing uninfected and infected bats in close proximity (~1.3 cm apart), though not in direct contact, for over 3 months[26]. None of the exposed bats became infected, suggesting that *P. destructans* conidia do not move freely through the air. A study examining the potential for vectored transmission found that spinturnicid mites collected from a colony of *Myotis myotis* tested positive for *P. destructans*[89]. However, this study did not explicitly examine whether these mites were responsible for initial infection or were simply contaminated as a consequence of the bats themselves becoming infected. Vertical transmission, the movement of a pathogen from parent to offspring, has also been explored in maternity colonies of several bat species. While a small fraction of offspring tested positive for *P. destructans*, the thermal requirements for the growth of this fungus and the timing of births (in summer) means that it is unlikely that *P. destructans* could survive the summer to infect bats the following winter[59,61,72,73].

Biology and pathogenesis

A specialist bat pathogen. Many fungi are saprophytes, meaning that they rely on decomposing matter that they break down into macromolecules, such as proteins, lipids and starch, which are absorbed through their cell walls to fuel growth[90]. Saprophytic fungi can range from

fully obligate to facultative saprophytes, as some species can also exploit nutrients from living organisms (for example, parasites)[91]. Studies comparing *P. destructans* to other closely related non-pathogenic *Pseudogymnoascus* spp. found that the *P. destructans* genome encoded ~65% fewer carbohydrate-activating enzymes (CAZymes) than other congeners[22]. CAZymes are involved in the breakdown and synthesis of carbon and are typically more abundant in decomposers than in parasitic fungi[92]. In conjunction with decreased enzyme potential, growth experiments revealed that *P. destructans* grows slower in vitro and utilizes a narrower range of carbon sources than its closely related species[22–24]. By contrast, enzymes that degrade collagen, the core structural protein in mammals, were the predominant hydrolytic enzymes in the *P. destructans* secretome and were not found in the secretomes of other *Pseudogymnoascus* spp.[25].

The examination of proteins associated with DNA repair pathways also showed that *P. destructans* lacks a gene (*UVE1*) that is important for the repair of UV-induced DNA damage[22]. Closely related *Pseudogymnoascus* spp. and most other microorganisms that are found in underground sites still harbour the *UVE1* gene, suggesting that loss of this gene is not a trait that is associated only with microorganisms that have evolved in the absence of UV light[22]. The reduced CAZyme production and inability to repair DNA damage may represent an evolutionary trade-off as *P. destructans* invested in mechanisms to exploit living animal tissue (for example, collagen-degrading enzymes) and evade the mammalian immune system[25].

Pathogenesis. *P. destructans* has been found on at least 62 species from 14 different genera of hibernating bats across all temperate regions of the northern hemisphere[28,32,39,40,53,93,94] (Supplementary Table 1) but has not been found to infect other mammalian taxa. In North America, epidermal skin lesions that are diagnostic of WNS have been confirmed in at least 12 bat species, and another 9 species have tested positive for *P. destructans* through a combination of DNA detection and pathogen culturing[17,95,96]. Across Eurasia, 41 bat species have tested positive for *P. destructans*, and >76% of these species have been confirmed with lesions diagnostic of WNS[28,32,39,40,53,93,94].

The lesions caused by *P. destructans* are found predominately on the ears, nose and muzzle of hibernating bats but are most severe in their wing and tail tissue (FIG. 3), which can serve vital regulatory functions,

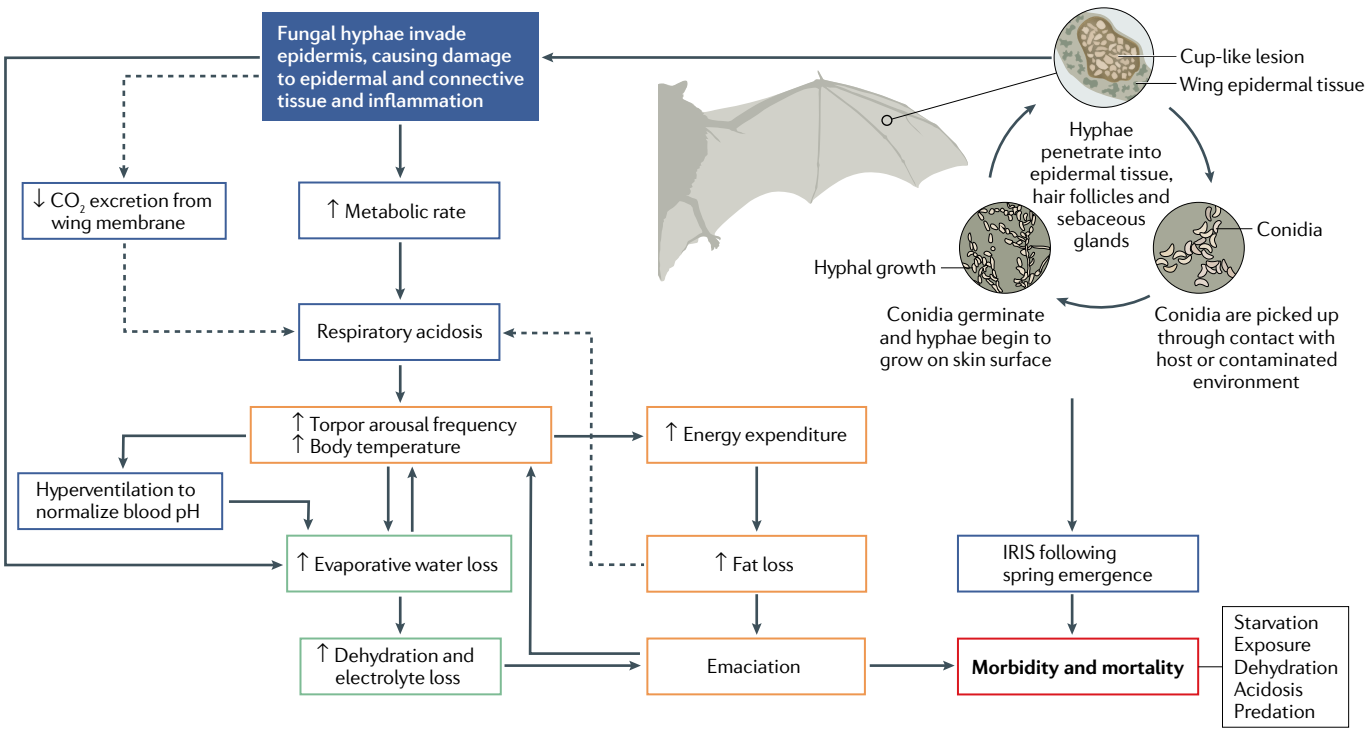
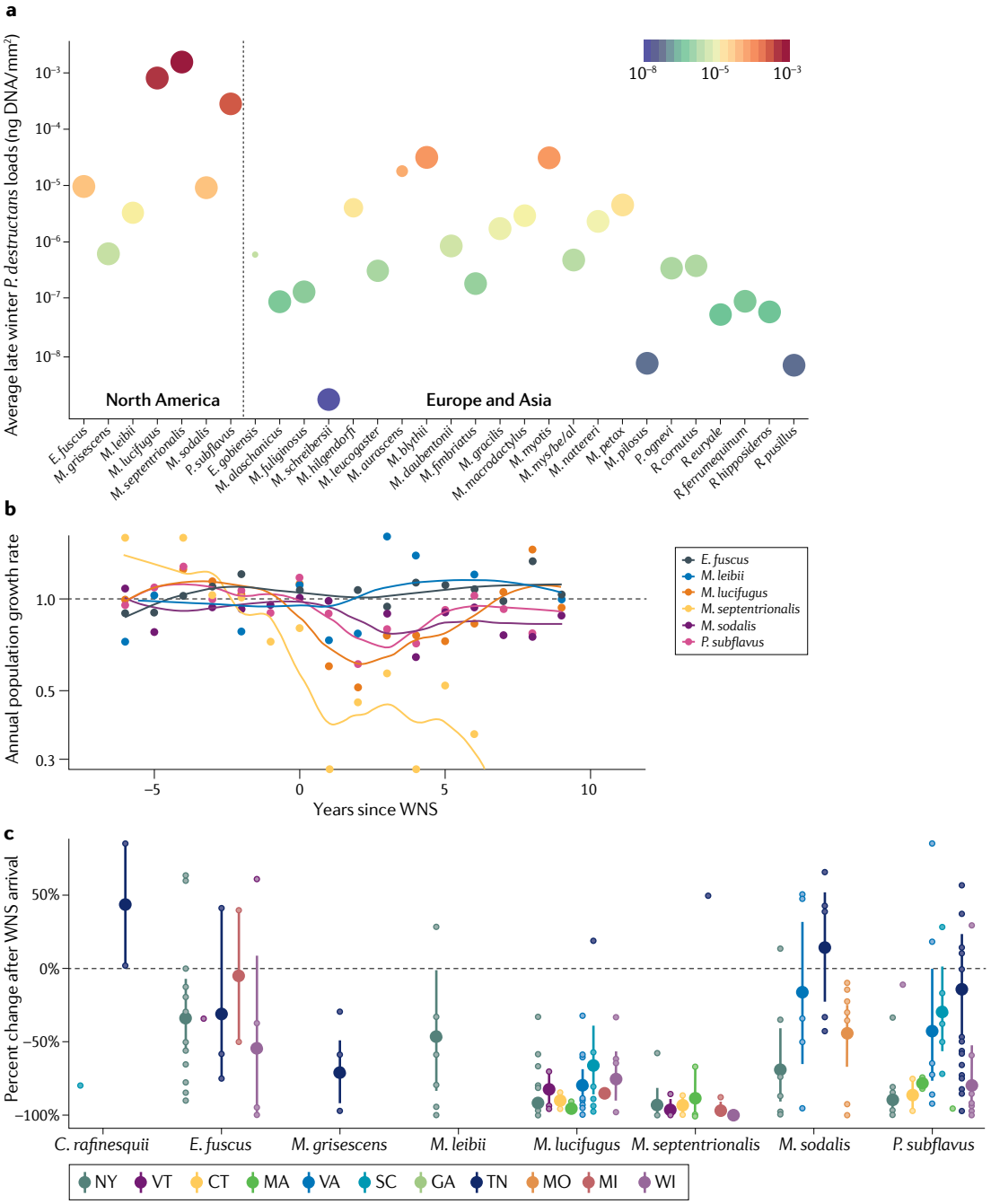


Fig. 3 | **Effects of *Pseudogymnoascus destructans* infection on bat hosts.** Under the right conditions, a *P. destructans* conidium germinates, producing a germ tube[156] that develops into hyphae, which eventually form hyphal mats termed mycelia that comprise the vegetative fungal growth on and in bat epidermal tissue[16,167,168]. The fungus initially grows on the surface of the skin but progresses to invasion of the epidermal tissue. These infections alter the skin lipid profile and eventually form cup-like epidermal lesions and ulcerations of the wing membrane, which can extend into the connective tissue and result in necrosis[16,76,129]. The hyphae also invade hair follicles and sebaceous glands, filling the epidermal sheath and invading nearby connective tissue[16,97]. Growth on the surface of the skin produces non-motile, unicellular arthroconidia or conidia through septation and fragmentation of existing hyphae[19,167,168]. *P. destructans* possesses the genetic machinery for sexual recombination (not shown in diagram) in some regions (Europe and Asia)[169]. However, the fungus introduced and circulating in North America seems to only be capable of asexual reproduction[21,68,169]. The introduction of additional mating types to North America could increase the rate of *P. destructans* evolution in North America, allowing it to further adapt to bats across this region and potentially escape the accumulation of deleterious mutations. The flow chart shows the physiological cascade initiated by *P. destructans* infections[99,101,102,104,107,126]. Dashed arrows indicate hypothetical relationships. Immune reconstitution inflammatory syndrome (IRIS) may lead directly to mortality during spring emergence when an intense immune response is initiated in reponse to *P. destrcutans* infection that has accumulated over winter in epidermal and connective tissues.



including thermoregulation, gas exchange, water balance and immune function[16,97–101]. These infections lead to a cascade of physiological effects[99,101–104] that eventually result in increased arousal frequency[27,70,87,105,106], loss of fat stores and starvation[87] and, in many cases, death. In captive *M. lucifugus*, death occurred 88–114 days after experimental infection[27]. Evaporative water loss and increased frequency of arousals likely create a feedback loop that can exacerbate the physiological effects of the disease[99,101,104]. Dehydration (for example, electrolyte depletion and hypovolaemia) caused by excess evaporative water loss in infected bats is a key contributor to WNS mortality[99,101,104], and there are multiple hypotheses about the pathways by which *P. destructans* infection may result in dehydration[102,107] (FIG. 3). Other physiological markers of early infection that precede increased arousals include a higher metabolic rate, acidosis (elevated blood partial pressure of carbon dioxide and bicarbonate) and elevated blood potassium levels[99,101,104].

WNS-induced mortality in bats seems to be partly related to an ineffective and possibly damaging immune reaction to infection, which does not limit fungal growth[108] and is not exhibited in species that suffer lower disease impacts[109–113]. The transcription of genes associated with inflammation, the immune response and metabolism was upregulated only during arousals from torpor in infected *M. lucifugus*[114]. While localized inflammation in response to infections does occur, hosts typically show a lack of leukocyte recruitment to sites of infection[74]. Torpor seems to limit the

Fig. 4 | **Impacts of *Pseudogymnoascus destructans* on bat populations. a** | Fungal loads on North America and Eurasian bat species. Circles show the predicted fungal loads (log_{10} ng of DNA) on different bat species (indicated on the X axis) standardized to March 1; data from REFS[28,61,65,67]. Loads are corrected for bat size by dividing predicted loads by the average forearm length to give log_{10} ng of DNA/mm^2. The diameter of the circle is the inverse of the standard error, with larger circles having smaller standard error. Circle colour indicates the intensity of fungal infection. **b** | Annual population growth rates of bats affected by white-nose syndrome (WNS) across all regions. These data are from published accounts[1,9,25] and federal and state government reports[1,9,28,96,170–176]. The dashed line indicates stability and solid lines show Loess curve fits to annual population growth rates for each species. *Myotis lucifugus* is the only species with an increasing population growth rate ~6 years after the arrival of WNS, and *Myotis septentrionalis* shows a trajectory towards extinction. **c** | Percent change in bat populations 2–3 years after *P. destructans* arrival in different US states (shown by two-letter state codes; data sources as in part **b**). Bold points show mean and 95% CIs. In some species, such as *Eptesicus fuscus* and *Myotis sodalis*, declines were highly variable among regions. In Wisconsin, *E. fuscus*, which can hibernate outside of conventional bat hibernacula, declined by 78%. Observed declines were not just due to emigration during mild winters, as pathogen arrival to sites occurred over 5 years with differing winter severity.

ability of bats to mount a full immunological response to *P. destructans* infection and the titres of antibodies to *P. destructans* could not explain the differences in WNS-related mortality among North American bat species and between North American and European bats[115]. More generally, bat species that suffer lower mortality from WNS exhibited fewer changes in gene expression in response to infection[116] and less alteration of arousal frequencies[113] than did species with a higher WNS-related mortality.

Impact on the host

P. destructans has caused widespread declines in multiple bat species across eastern North America[1–15] (FIG. 4). Prior to the arrival of WNS, populations of six bat species in the Northeastern US (defined here as including NY, Vermont (VT) and Connecticut (CT)[1]) and the Midwestern US (defined here as including Michigan (MI) and Wisconsin (WI)[28]) were growing (average growth of 11% in the Northeastern US[1] and 10% in the Midwestern US[28]). Following the arrival of WNS, millions of bats died from the disease, with declines in some species exceeding 95% and entire populations of several species extirpated[3]. Steep declines in counts of wintering bat colonies were corroborated by declines in estimates of bat abundance during the summer[7,8,11]. However, in some areas, observed summer declines were delayed by a year, potentially due to the movement of bats from unaffected areas into optimal summer habitats[6].

Variability in host declines. Declines caused by WNS have varied among host species, over time and across space (FIG. 4). Across several species, the impacts of WNS are load dependent, with the highest mortality observed in species experiencing the highest fungal loads[65] (FIG. 4). *M. septentrionalis* is at serious risk of extinction as multiple studies showed similar drastic declines in both the Northeastern US[1,3] and Midwestern US[28,66], with complete extirpation occurring in nearly 70% of sites where WNS had been present for at least 4 years[3]. *M. lucifugus* populations experienced cumulative declines of 96% in the Northeastern US and 97% in the Midwestern US[1,2] and also declined in the Southern US (defined here as including Virginia (VA), South Carolina (SC), Georgia (GA) and Tennessee (TN)) (FIG. 4), suggesting that shorter hibernation periods in the Southern US were not entirely protective. *P. subflavus* experienced similar population declines to *M. lucifugus* (95% and 99% cumulative decline in the Northeastern US and Midwestern US, respectively), although non-hibernating populations of this species in the Southern US and Central America may protect *P. subflavus* from global extinction. For several species, including *Eptesicus fuscus* and *Myotis leibii*, average population growth rates after the arrival of WNS were nearly stable but populations were no longer growing. This change in population growth rate likely represents some mortality in these species, not just emigration during mild winters, as pathogen arrival to sites occurred over multiple years with differing winter severity. *Myotis sodalis*, an endangered species, experienced serious (70% cumulative) population declines in the Northeastern US but some populations were less affected[117].

Population declines have not yet been quantified for several other bat species that are infected by *P. destructans*. Lower fungal loads in some of these less-studied species, such as the endangered species *Myotis grisescens*, may indicate a lower impact[67]. Regardless, sustained hibernation seems to be critical in determining whether a species will be affected by this pathogen, as the non-obligate hibernator *Tadarida brasiliensis* was not highly susceptible to mortality in an experimental infection study[118]. Impacts of WNS in the more diverse bat communities of the Western US, where *P. destructans* recently arrived, remain largely unexplored (but see REF.[119]).

Drivers of variation in host impacts. Temperature and humidity are strong modifiers of *P. destructans* growth[60,120] and have been shown to be important factors influencing the impacts of WNS at the individual[121–123], species[65] and population level[1]. Within the range of temperatures at which bats hibernate (generally 1–16 °C)[28,63–65], *P. destructans* growth is higher at warmer hibernation temperatures[60,65,124]. Increased fungal growth on bats leads to more severe disease pathology, which in turn decreases survival[125]. As a result, bats that select warmer roosts have higher fungal loads and experience more severe disease impacts[65]. Higher humidity also increases fungal growth[120] and was positively correlated with population impacts of *P. destructans* in *M. sodalis*[1]. However, lower humidity increases bat evaporative water loss, which is exacerbated by WNS[99,101,102,104,126], making the link between humidity and WNS survival less clear[127].

Numerous other factors may influence the variation in survival among bat species and populations. For some species, smaller populations suffered less severe declines, suggesting that lower bat densities might reduce transmission[1,86]. Bat populations across all temperate regions roosting in areas where *P. destructans* is more abundant in the environmental reservoir have lower population growth rates, suggesting a dose-dependent effect of the *P. destructans* environmental reservoir[28,66,124].

Other host factors are probably important in determining the variation in outcomes among species, including differences in torpor physiology[104,113], skin lipids[128,129], the skin microbiota[130–133], immune response[74,108,109,134–136] and co-infection with viruses[137], although more detailed studies and experiments are needed to identify the importance of each of these factors. Climate is also likely to be an important contributor to variability among populations[123,138] due to its effects on hibernation length, but the joint effects of hibernacula temperature and winter severity have not yet been comprehensively analysed.

Host persistence

Following severe declines in several formally abundant bat species, growth rates of some populations across North America began to stabilize[1,2,5,139,140] (FIG. 4b). In particular, colonies of *M. lucifugus* in the Northeastern US are now stable or growing. To date, there is little evidence to suggest that the populations of other affected species in North America are increasing (FIG. 4b). For example, growth rates are still negative for many affected *M. sodalis* populations[117,141]. Coastal refugia have been implicated in the persistence of a few remnant *M. septentrionalis*[142], although more research is needed to understand whether bats are actually surviving *P. destructans* infections in these habitats. Multiple studies have investigated the drivers of bat survival with WNS, mainly focusing on *M. lucifugus* or Eurasian bat species, spanning general (FIG. 5) to specific explanations of bat persistence and often reporting conflicting results. Broadly, the general mechanisms of bat persistence that have been investigated include resistance[32,65,116,139], tolerance[67,68,139], infection avoidance through reduced transmission[1,28,139], and pathogen evolution[21,27].

In North America, there is widespread agreement among studies that most individuals continue to be infected at very high rates during early hibernation[28,67,139,143] and therefore pathogen avoidance or reduced transmission owing to lower host density are less important in enabling the survival of *M. lucifugus*. This mechanism, and more generally a reduction in transmission due to reduced bat densities, was one of the original hypotheses to explain differences in the effects of WNS among host populations[1]. However, subsequent studies showed that spatial separation of individuals at the onset of WNS is likely a sickness response that occurs after *P. destructans* has already been transmitted to most of the colony[70,144].

Several studies have examined other general mechanisms of host persistence. A study using an epidemiological model fit to infection data[139] found that fungal growth was lower in persisting *M. lucifugus* populations in the Northeastern US than in epidemic populations where *P. destructans* had recently invaded. This finding is consistent with higher host resistance in persisting populations than in more recently exposed populations (FIG. 5a), which supports more anecdotal evidence of less visible fungal infections in surviving bat populations over time. By contrast, another study examining infection dynamics[67] found that fungal loads in some persisting colonies were fairly stable over time and suggested that bat persistence might also be mediated by tolerance. Factors that could explain these discrepancies include a lack of dynamic pathogen data during the epidemic phase in the Northeastern US and a lack of individual-level data in both studies as well as an inability to account for transmission differences or to link fungal growth and bat health in the second study[67]. As neither study collected individual-level health data, it is unclear whether population-level data showing colony persistence could mask reduced individual survival probabilities, particularly if there is compensatory reproduction or immigration from other persisting colonies. Northeastern US populations may also be behaviourally resistant if they are using colder microclimates than epidemic Midwestern US populations. Therefore, while populations in the Northeastern US are unequivocally more resistant than Midwestern US populations during the WNS epizootic, whether population survival is mediated by resistance (either innate or behavioural), tolerance or a combination of both remains unknown. Comprehensively investigating each factor requires accounting for initial transmission and pathogen dose while following individual hosts within multiple populations over time in order to disentangle the mechanisms producing similar patterns (FIG. 5). For example, the mechanisms conferring tolerance or increases in general vigour appear similar and are only disentangled by comparing two populations to determine if differences still exist when hosts are uninfected[145]. In all cases, pathogen dynamics must be measured in conjunction with bat health.

Other more specific factors underlying the survival of bats with WNS in North America continue to be investigated and potentially include differences in arousal frequencies[106] and fat deposition[143], although it is unknown whether these factors are the cause of stable populations or the consequence of some other mechanism (FIG. 5). Differences in pathogen virulence are unlikely to be the most important factor currently determining host stabilization in North America, as experimental studies indicate that the virulence of European and North American *P. destructans* isolates are comparable[27] and that there is little genetic spatial or temporal structure in *P. destructans* populations across North America[21,33,35].

Studies investigating changes in *M. lucifugus* population genetic structure before and after WNS declines also found conflicting patterns. Three studies reported evidence of genetic changes between declining and persisting *M. lucifugus*[136,146,147]. However, another study[148] found no such differences in *M. lucifugus* populations before and after WNS-induced declines but did find increased differentiation between bat populations in NY and Pennsylvania after WNS declines. Differences among these studies may be due to differences in sampling design and methodology or could reflect biological differences in selection among populations.

In Eurasia, a key factor allowing host coexistence with *P. destructans* is the delayed timing of infection. Across this region, the decay of the environmental reservoir of *P. destructans* during summer results in a slower transmission and reduced early winter infection

in Eurasian bat colonies, resulting in delayed exposure, a form of pathogen avoidance[28] (FIG. 5c). Eurasian bats return each autumn to hibernacula that are far less contaminated with *P. destructans* than North American hibernacula, resulting in lower fungal loads and reduced mortality by the end of winter[28]. Comparisons using identical sampling and testing procedures to measure fungal burdens in both Eurasia and North America have

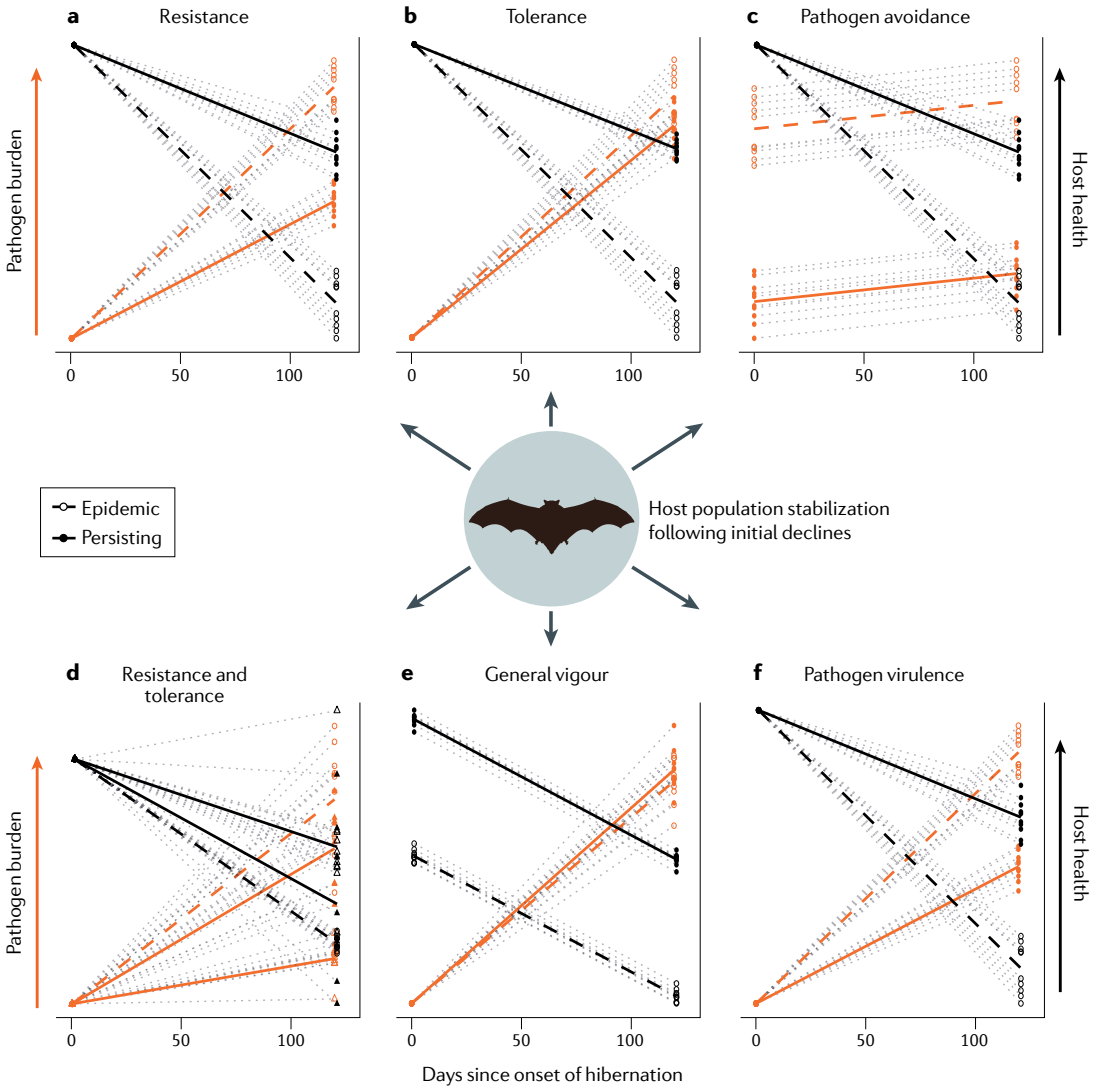
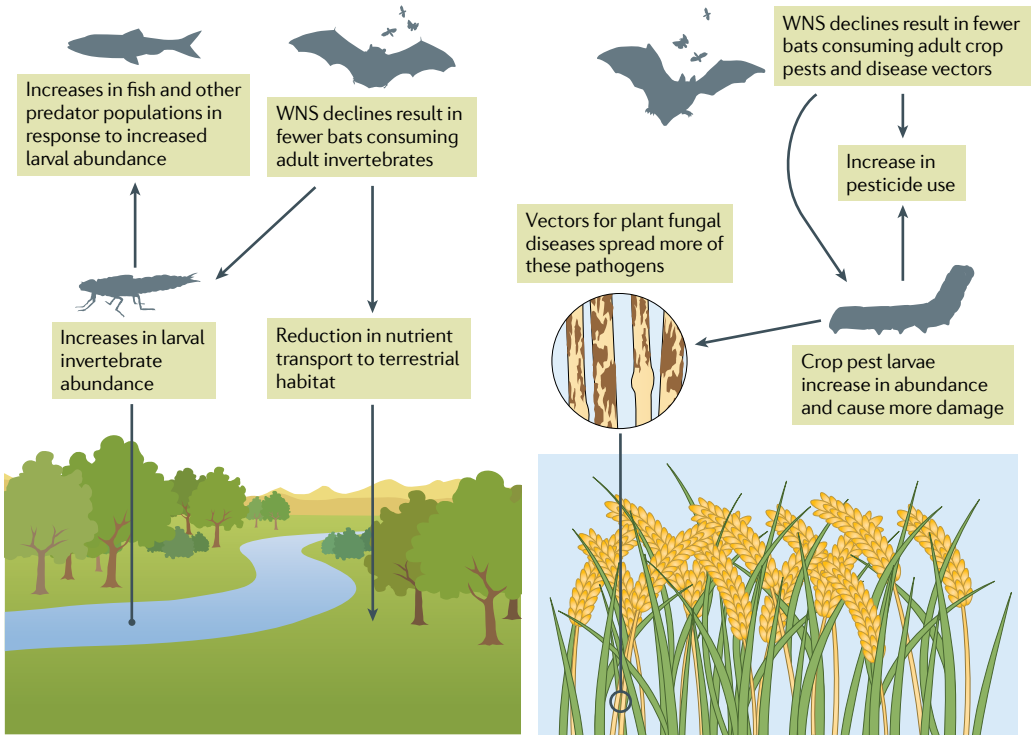


Fig. 5 | **General mechanisms of host persistence.** Following the introduction of novel pathogens, several general mechanisms could allow hosts to persist with disease. All graphs show hypothetical realizations of simulated data based on the relationships between pathogen burden (orange) and host health (blue), extrapolated from Raberg et al.[145]. For white-nose syndrome, burden measurements are typically fungal loads, whereas health measurements might include survival or tissue invasion. Simulations assume hosts become infected with identical pathogen doses at identical times, with the exception of part **c**, where healthier host populations initially acquire lower pathogen burdens (dose-dependence) or are infected later, as might happen if transmission decreases as populations decline. Epidemic declining populations (dashed lines) and persisting populations (solid lines) are compared. Grey dotted lines connect individual hosts from epidemic (open circles) or persisting (filled circles) populations. Resistance (part **a**): persisting hosts experience slower pathogen growth resulting in lower average burdens at the end of hibernation and higher health. Tolerance (part **b**): persisting hosts have similar pathogen growth rates to the epidemic population but have higher health. Pathogen avoidance (part **c**): Persisting hosts have lower pathogen burdens because they have lower or delayed pathogen exposure enabling higher health, despite similar pathogen growth rates. Resistance and tolerance (part **d**): two persisting populations with identical health differ in their resistance and tolerance. Both persisting populations (A and B) are more resistant (for example, have lower fungal growth rates) than the epidemic population but all individuals in population A (open triangles) are resistant, with low fungal burdens. Hosts in population B (closed triangles) are overall more resistant than epidemic hosts but also more tolerant, with higher health at the same fungal burdens. General vigour (part **e**): the persisting population does not differ in pathogen growth and thus average burden but differs in health (different health intercepts) due to innate differences that would be present in uninfected hosts. Pathogen virulence (part **f**): persisting populations have lower growth in this example, as would be predicted by trade-off theory[177]; however, actual patterns depend on evolutionary changes and could thus mimic parts **b**–**d**.

Box 1 | **Ecosystem impacts of white-nose syndrome**



Pseudogymnoascus destructans has caused severe declines in several species of insectivorous bats, and the magnitude of host community decline could have cascading effects on agricultural pests, pathogen vectors, and other aquatic and terrestrial insects that bats consume. An explicit quantification of the impact of white-nose syndrome (WNS)-caused declines in bat populations on insect communities has yet to be conducted. However, numerous studies have highlighted the importance of *P. destructans*-affected bat species for ecosystems. Many of the *P. destructans*-affected bats are known to forage primarily along rivers, streams and in forested corridors[178]. As a result, some of the most significant impacts to ecosystems may be among terrestrial and freshwater systems (see the figure, left panel). For example, small increases in benthic macroinvertebrate abundance have been observed after WNS-induced bat declines[179]. However, fish abundance also increased following bat population impacts possibly due to the increase in benthic macroinvertebrates, which could mask the effects of WNS on this ecosystem[179]. Several studies have also noted that, as some WNS-affected bat species declined, less affected bat species moved into their preferred habitat, suggesting that relaxation of niche partitioning[179–181] could also reduce trophic effects. However, some constraints on foraging habitat, such as total canopy cover, likely still limit the potential for less affected bat species to fully compensate for population declines[179].

In agricultural systems, bats are known predators of numerous crop pests[182], and the exclusion of bats from corn fields resulted in a higher abundance of insect larvae and increased the number of arthropod vectors that could spread plant fungal pathogens[183] (see the figure, right panel). These data suggest that bats benefit agricultural systems in myriad ways, including by consuming agricultural pests directly and by reducing the pathogens they transmit. Further support for the importance of bats in suppressing agricultural pests is provided by preliminary data suggesting apparent increases in baseline fungicide and insecticide applications as WNS arrived in new counties, which could have cascading effects on ecosystem health[184].

Declines of bat populations could also impact human health if consumption of disease vectors, including mosquitoes, by bats decreases. One study found that *Myotis lucifugus* consumed up to 12 different mosquito species, including *Culex restuans*, a vector of West Nile virus and St. Louis encephalitis[185]. In addition, the presence of *Myotis septentrionalis* reduced oviposition by *Culex* spp. mosquitoes through direct predation of adult females[186]. However, mosquito consumption likely varies among regions, and studies have noted that mosquitoes may be eaten opportunistically[187]. Therefore, while WNS impacts could influence vector abundance, insect time-series data accompanied by bat abundance and use is needed to understand the impact of bats on arthropod vectors.

found consistently lower fungal loads on European and Asian bat species than on bat species in North America (FIG. 4), which is consistent with reduced fungal lesions and visible infections across Eurasia[28,32,53]. One study reported high fungal loads on European bats and suggested that they might be surviving by a higher tolerance to *P. destructans*[68]. However, this study used a qPCR assay with different quantification standards[149] than that used to analyse samples collected from North American bats[150] and was unable to account for the timing of transmission or initial exposure; therefore, the persistence of European species with WNS cannot be attributed to pathogen tolerance. In addition, experimental infections of Eurasian *M. myotis* bats found very limited fungal growth, which is consistent with resistance rather than tolerance[151]. It remains unknown whether other Eurasian species would experience similar disease severity to their North American counterparts if challenged with pathogen doses comparable to those that North American species experience.

Conclusions

The introduction of *P. destructans* has had devastating consequences for North American bat communities[1–15]. Some impacts of WNS are likely to last for many decades, while others may be permanent (BOX 1). The slow population growth rates of heavily affected bat species, which usually give birth to only one young per year, means that it will take decades or longer for populations to recover to their original densities, even if they could return to pre-WNS growth rates[140,141,152,153].

As *P. destructans* can establish long-term environmental reservoirs, it is unlikely that this pathogen could ever be eradicated from North America, which has resulted in research being focused on preventing spread and mitigating impacts[30]. Mitigation efforts have

included both topical, oral and implanted treatments for hosts as well as attempts to reduce the environmental pathogen reservoir and delay transmission. Several treatments have now been tested in vitro, in vivo or in situ[133,135,154–158], including antifungal chemicals, volatile organic compounds, probiotic microbes, biopolymers and vaccines (reviewed elsewhere[153,155]). Currently, only one probiotic treatment and a vaccine have been shown to reduce mortality in a single species, *M. lucifugus*[135,155]; however, no treatment has been deployed on a landscape scale. Other actions taken to minimize the impacts of WNS include limiting recreational activities in caves to reduce the disturbance of bat populations, restricting habitat alteration near hibernacula, and an early and unsuccessful effort at captive breeding[30]. The development of effective tools is still urgently needed to help reduce impacts in bat species that have shown no sign of stabilization and are most at risk of extinction.

There has been a rigorous surveillance effort to track the spread of *P. destructans* across the US and Canada, using a combination of passive and active measures, with confirmation through qPCR detection and histology in new counties, states/provinces or species. Concern about research-related disturbance to bats has occasionally resulted in reduced surveillance in some regions and in an inability to comprehensively assess population trajectories and species persistence. However, recent research suggests that visits related to population monitoring and research have no detectable effect on population growth rates[159]. Continued monitoring will be critical in assessing the impacts of WNS on bat populations as *P. destructans* spreads, just as it was for the initial discovery of this disease[160].

There are multiple areas of uncertainty where additional research could help to advance WNS epidemiology and ecology. WNS research has been constrained by the limited ability to perform host experimental infection studies relative to other emerging diseases and much of our knowledge comes from a single North American species, *M. lucifugus*. Thus, additional work in other affected bat species or the development of a model organism system would greatly expand our knowledge about the impacts of WNS. Experimental work that needs to be undertaken includes analysing differences in pathogen virulence and understanding the susceptibility to mortality in multiple North American and Eurasian species. While substantial effort has been made to understand how some bat populations are now persisting with WNS, additional attention is needed to achieve a comprehensive understanding of the complexity of multi-host community persistence. To truly appreciate the contribution of different persistence mechanisms will likely require the use of experimental infections and the integration of epidemiological models with field and laboratory data. Enhanced knowledge of *P. destructans* biology across Eurasia and North America will also provide additional insights into the factors contributing to regional differences in pathology and help to elucidate the risks of introducing other novel strains of *P. destructans*. Finally, the ecosystem consequences of WNS-induced bat population declines have only been superficially explored (BOX 1) and a more detailed analysis of the effects on agricultural, terrestrial and aquatic systems is needed. Collectively, this information could promote conservation and policy considerations that can help to prevent and mitigate the consequences of novel pathogen emergence in the future.

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