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Sapronosis: a distinctive type of infectious agent

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Sapronotic disease agents have evolutionary and epidemiological properties unlike other infectious organisms. Their essential saprophagic existence prevents coevolution, and no host–parasite virulence trade-off can evolve. However, the host may evolve defenses. Models of pathogens show that sapronoses, lacking a threshold of transmission, cannot regulate host populations, although they can reduce host abundance and even extirpate their hosts. Immunocompromised hosts are relatively susceptible to sapronoses. Some particularly important sapronoses, such as cholera and anthrax, can sustain an epidemic in a host population. However, these microbes ultimately persist as saprophages. One-third of human infectious disease agents are sapronotic, including nearly all fungal diseases. Recognition that an infectious disease is sapronotic illuminates a need for effective environmental control strategies.

Distinctive pathogens in terms of ecology and evolution

Hercules' first Labor, killing the Nemean Lion, was difficult, but straightforward. His next Labor was more challenging, because the Lernean Hydra did not follow the rules of mortal beasts; its heads grew back after Hercules cut them off. Our modern-day Labors include combating infectious diseases, most of which play by a rule, the host-density threshold (see Glossary) for transmission, such that the number of new cases an original case generates, R_0, is one on average. R_0 is such a ubiquitous feature of host–parasite dynamics [1–3] that the host-density threshold is recognized as a theorem [4]. This theorem forms the basis of disease control programs that try to increase the threshold, by reducing transmission or by vaccination, so that the infectious disease will dissipate and then disappear from the system. Here, we recognize and describe a class of infectious diseases, sapronoses, that are primarily free-living organisms but can infect hosts opportunistically following contact. Thus, sapronoses do not abide by the host-density threshold theorem. A well-known example of a sapronosis is Legionnaires' disease, which is caused by the bacterium *Legionella pneumophila*, which lives in habitats as mundane as windshield-wiping fluid. Sapronotic agents, similar to the Hydra, do not follow conventional rules: we cannot control them by curing or removing infected hosts. In this review, we address the evolutionary and epidemiological attributes of sapronotic agents, suggesting some disease characteristics associated with them. We model their host–parasite dynamics, discuss relations with other types of infectious agents, and estimate the proportion of microbial human pathogens that are sapronotic. The general importance and relevance of sapronotic agents is also noted. We call for an explicit focus on sapronoses given that their relative incidence and importance is increasing.

What is a sapronosis?

Although you will not find the term 'sapronosis' in the current epidemiological lexicon, Terskikh [5] recognized that some infectious agents were saprophagic outside the host, only infecting humans under particular circumstances. Given that these organisms grow and reproduce well on nonliving nutrient sources, Hubálek [6] termed them sapronoses to emphasize their distinction from zoonoses (infectious diseases requiring a nonhuman host) and pointed out that, for sapronotic disease agents, evolutionary adaptation to a host was unlikely because their reproductive success was independent of host to host transmission. These infectious agents lacked a host-density threshold for transmission because their populations were dependent on habitats and nutrients apart from any host population [7]. Yet, when in a host, they presented a competent physiology, multiplying as a pathogen until either a host response reined them in or the host died. Unaware that a term for these infectious agents was already available, Lafferty and Kuris [7] termed the infectious agents 'pollutogens' because their infectious dynamic was akin to that of a particulate pollutant: both lack a host search or recognition strategy. However, unlike a pollutant, they have the ability to multiply within a host, as does a pathogen. Their coinage, being unneeded and also having etymological problems, should be abandoned. Here, we broaden the definition of sapronoses to include all infectious diseases, not just those of humans, caused by pathogens that are typically free living.

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Glossary

Accidental parasite: a free-living organism that might or might not multiply in or on an accidental host, but is not inherently parasitic. This includes 'pseudoparasites', which are organisms that are occasionally present in wounds or gut contents but do not eat host tissues. All sapronotic organisms are accidental infectious agents; examples include adult horsehair worms in humans and blowflies in wounds.
Allee effect: a positive effect of population density on fitness of the members of that population. A component effect refers to any measure of individual fitness.
Allee threshold: a critical density below which a population declines to extinction in response to an environmental variable, and above which it can increase.
Carrying capacity: the maximum population size of a species that can be indefinitely sustained in an environment.
Commensal: a species that lives in or on a host but does not derive nutrition from that host. Generally, commensals do not impact their host, but can do so if their numbers on a host reach high density. Some microbial commensals can cause sapronoses if they enter immunocompromised hosts; examples include whale barnacles (non-sapronotic) and trichosporon fungi (sapronotic).
Decay rate: the rate at which a variable in a model exponentially declines.
Density dependence: occurs when population parameters are regulated by the density of a population.
Detritivore: an organism that uses particulate dead organic matter for food.
Facultative parasite: a consumer that can complete its life cycle as a parasite, or as a free-living organism. This is not a common strategy, for example, *Parastrongyloides trichosuri*. Other parasites commonly termed 'facultative' must return to a host–parasite interaction after one or a few cycles of free-living generations, for example, *Strongyloides stercoralis*.
Infectious agent: a consumer that, for a given life-cycle stage, attacks and feeds on a single individual host or eats its partially digested gut contents, in contrast to predators and micropredators, which feed on multiple prey and/or hosts; these include parasites and pathogens.
Microparasite model: an epidemiological model for host–parasite dynamics for which the proportion of infected hosts, rather than the number of parasites per host, is the unit to be tracked. Typically, hosts are classed as susceptible, infected, or recovered; an example is *Hydramoeba hydroxena* on hydras [3].
Nosocomial infection: an infectious disease contracted while under medical care, usually acquired in a hospital.
Obligate parasite: a consumer that is infectious and must complete at least one stage of its life cycle as a parasite. Most infectious agents are obligate; an example is *Ascaris lumbricoides*.
Opportunistic infectious agents: infectious agents, usually pathogens, that are able to establish infections in particularly susceptible (immunocompromised) hosts, or through unusual routes, such as eyes, which are relatively poorly immunologically defended. These can include organisms that are obligate parasites or those that are sapronotic; for example, *Toxoplasma gondii* (obligate) and *Histoplasma capsulatum* (sapronotic).
Parasitic castrator: an infectious agent that, as result of a single infection, blocks or eliminates the reproduction of its host. The host continues to live on, producing only castrator offspring. Cessation for reproduction is not dependent on the number of parasites in the host; neither is it the mere cessation of reproduction before death of the host; for example, larval trematodes in first intermediate mollusk hosts.
Pathogen: an infectious agent that, in a given life-cycle stage, multiplies within that host. Its density depends on control by the immune capabilities of its host. If not controlled by host defenses, a pathogen will multiply until the host dies. These are appropriately modeled with microparasite models; for example, malaria in humans.
R_0: the basic reproductive rate of an infection, the number of new infections one case generates on average over the course of its infectious period, in a population not otherwise uninfected. When $R_0 < 1$, the infection will die out in the long run. However, if $R_0 > 1$, then the infection will be able to spread through a population.
Reservoir host: a host within which a parasite can complete its life cycle, but which is not the object of concern or study.
Sapronosis: an infectious disease caused by a free-living organism that can, under some circumstances, establish an infection and multiply within a host. When multiplying within a host, its progeny rarely if ever contribute to free-living population dynamics. Hence, there is no possible selection for attenuation or intensification of its virulence; for example, Buruli ulcer.
Sapronotic agent: a saprophage that can establish an infection, multiplying in or on a host, causing disease; for example, *Naegleria fowleri*.
Saprophage: a free-living organism that obtains its nutrition by consuming dissolved organic matter deriving from the decomposition of dead organisms or ejecta.
Target host: the host of concern. With respect to zoonotic diseases, it is obviously the human, but for all other diseases, it is the alternative to reservoir hosts, and is the host selected for concern by investigators.
Threshold density: the minimum population density of hosts at which transmission of an infectious agent can be sustained.
Type II functional response: a functional response is the consumption rate of food by a consumer, as a function of prey density. It is a key component of predator–prey theory that models the dynamical relation between predators and their prey. A type II response results from circumstances where food intake rate per consumer saturates with increasing prey density, for example, wolves preying on moose.

Given that a sapronotic agent has an environmental reservoir, it shares some similarities with host–parasite relations that include a reservoir host. As for sapronoses, parasites with a reservoir become a problem when there is 'spillover' to other hosts of human concern, for instance, humans or husbanded species, owing to transmission from the reservoir. Control of such diseases implies control of the host–parasite dynamic in the reservoir host, or protection of the host of concern from the potential spillover of the parasite from its reservoir. An important distinction between a reservoir host and an environmental reservoir is that the latter is not alive; therefore, sapronotic agents lack host-density thresholds and adaptations to parasitic life styles.

Sapronoses are typically sustained by a nutritional source that is not another organism. They are free living but opportunistically infectious. Upon access to a host, they can be nourished by its tissues, reproduce in or on that host, and, if not checked by a host defensive response, cause morbidity or mortality. They need not be transmitted from an infected to an uninfected host, although there are some sapronoses, such as cholera, for which a transitory epiphenomenon of host-to-host transmission can occur. However, spillback of a sapronotic agent from an infected host to the free-living population of that saprophage is rare and, when it happens, it offers a negligible increment to the population. Some well-known human diseases meeting these conditions include histoplasmosis (*Histoplasma capsulatum*), valley fever (*Coccidioides immitis)*, melioidosis (*Burkholderia pseudomallei*), and granulomatous amebic infections (*Naegleria fowleri*) [8]. Although less studied, there are animal diseases that appear to satisfy the definition of a sapronosis, for example, white nose disease of bats, (*Pseudogymnoascus destructans*), sea fan aspergillosis (*Aspergillus sydowii*), *Fusarium* sp. fungal infections of sea turtles, and *Bacillus thuringiensis* of insects and nematodes, the last a commercial biocide and a rare human sapronosis [9–11].

Evolutionary considerations

The principle feature of a sapronotic agent is that it will persist, and might even thrive, without a host. Empirical evidence suggests that most sapronotic agents are free-living saprophages, absorbing and metabolizing dissolved decomposed organic matter [6]. Thus, the saprophages that enter a host do so upon happenstance. They then multiply within that host, which might be a sink in terms of the overall population of the saprophage. If so, there will be little or no positive selection for attributes that will sustain it in a host or promote transmission to another host. Consequently, a saprophage will not face trade-offs regarding ease of transmission and virulence, which is perhaps the principle driver of the evolution of virulence [12]. Hence, we can anticipate that sapronotic agents, even common ones, can be virulent because they bear little cost

in terms of harming their host. Virulent sapronoses include amebic meningitis and/or encephalitis and Buruli ulcer (*Mycobacterium ulcerans*) in humans, *Saprolegnia* spp. in fishes and *B. thuringiensis* in insects [11,13–15]. Although this virulence has been viewed as the initial condition on a path to the evolution of reduced virulence [6], there is no evidence that there can be selection for virulence in a sapronotic agent, and many have low virulence; for example, *Legionella longbeachae* causes a mild respiratory infection [16].

Detritivory, similar to saprophagy, but consuming particulate dead organic matter, may also be source of infectious agents [17]. There is evidence that plant detritivores have evolved pathogenic transmission to plant hosts [17].

A sapronotic agent is unlikely to be under selection pressure for adaptation to a host that is a sink. However, if the frequency of infection is high, then host defenses should evolve. Some sapronoses, such as valley fever [18], are prevalent enough that host adaptation could minimize their impacts [19]. Defensive adaptations will be localized among human populations experiencing such a threat.

Weather, soil, and other abiotic conditions vary from place to place, and sapronotic agents are likely adapted to the local environment. Strain and species-level differences may vary by location and elicit different symptoms from their hosts. Recent studies on *Coccidioides* spp. and *Legionella* spp. document this sort of variation [20,21]. For instance, host immunocompetence is associated with certain species or strains, whereas others can infect younger, healthy individuals.

There is much interest in emerging infectious diseases, and reproduction within a host might lead to the evolution of a host-dependent pathogen. These conditions might include high densities of stressed hosts, such as found in husbandry and hospitals.

Epidemiological considerations

The epidemiology of sapronoses has some peculiarities that differ from other types of infectious agent. Sapronotic pathogens cannot be said to have a transmission 'strategy'. They infect hosts by opportunity on contact or ingestion of passive stages, such as cysts or spores. Sometimes, a wound or an injury can enable entry into a host. Sapronotic agents lack transmission strategies used by other infectious agents, including direct contact between hosts, vectors, or through trophic transmission from prey to predator hosts. Active searching stages seem improbable because, if such stages existed, saprophages would not be seeking a host. Given that extant populations of free-living saprophages often have specific habitats, such as caves for *H. capsulatum*, or soils of arid regions for *Coccidioides* spp. [20,22], transmission rates are proportional to contact rates of potential hosts within those habitats. Potential hosts infrequently encounter some of these habitats. Hence, infection events might be uncommon and sporadic.

Immunocompromised hosts are more susceptible to infection by sapronoses. Sapronotic pathogens, such as the *Mycobacterium avium–intracellulare* complex, *Coccidioides* spp., and amebic meningitis, appear among the list of opportunistic diseases of HIV-infected humans [23–25]. Older humans, with diminished natural immunity, are also more susceptible to sapronoses, such as Legionnaires' disease [26]. This pattern of susceptibility implies that, at some level, there has been evolution by hosts to defend against these opportunistic infections. If multiple hosts contact the infectious saprophage within its habitat, there can be a cluster of cases, as often reported for Legionnaires' disease. The index case cluster occurred at an American Legion convention hotel in Philadelphia [27]. These bacteria live in stagnant bodies of water such as plumbing systems, sometimes associated as symbionts within amebae that are also present in those habitats [28]. Dissemination through sprays or fountains can induce contact with multiple individuals over a short period of time. This clustering can be deceptive, mimicking transmission among those hosts. The high frequency of older, immunocompromised individuals, or of those with prior pulmonary diseases, becoming infected with Legionnaires' disease, suggests that reduced immune defenses facilitate entry.

Sapronoses with transmission among hosts

Some important human infectious diseases appear to be sapronotic in origin but with a substantial epiphenomenon of transmission among hosts. The two most striking examples are cholera and anthrax. *Vibrio cholerae* persists in aquatic soft-bottom habitats [29]. However, when poor sanitation enables ingestion of large quantities of bacterial spores by humans, transmission among humans can lead to epidemics with conventional pathogen dynamics. However, once transmission among humans has been stopped, cholera can reemerge from its normal saprophagic existence.

Anthrax, caused by *Bacillus anthracis*, is a more perplexing example of a sapronosis with host-to-host transmission. Its free-living strains reproduce slowly, perhaps under limited conditions, and its spores are persistent, an adaptation to the arid environments where the disease is often endemic. Nonetheless, anthrax does reproduce in soil [30,31]. Notably, it thrives on nutrients near animal carcasses, giving it an association with animal hosts even without host-to-host transmission [32,33]. As for *Legionella*, a symbiotic association with amebae might promote the disease potential of anthrax [34].

Modeling sapronoses

For insight into the differences between sapronoses and conventional infectious diseases, such as how they can affect host populations, we developed a mathematical model with a set of differential equations of population growth rate based on a pathogen with an infective stage that, depending on parameter values, could either be transmitted from host to host or disseminated as a sapronotic agent (Box 1). Sapronotic agents are assumed to be present in the environment, but dynamics there are not tracked and assumed constant. We compared criteria for pathogen invasion, coexistence with the host, and extirpation of the host, as well as the case of pathogen spillover, for these two pathogen types. Most of the results are deducible with basic logic, so we provide a verbal summary and provide the math in Box 1.

Box 1. Pathogen model with or without transmission among hosts

Here, we assume a system in which host births are local, but infectious stages can enter or exit the system at a rate that is independent of the dynamics of the target host. The model assumes that the host is regulated through density-dependent declines in birth rates. The full system of equations is:

$$dX/dt = b(X + gY)/[1 + d(X + Y)] - mX - \beta X(W_O + W_L)$$

$$dY/dt = \beta X(W_O + W_L) - Y(m + \alpha)$$

$$dW_L/dt = qY - \beta(X + Y)W_L - \mu W_L - \lambda W_L$$

$$dW_O/dt = \theta - \beta(X + Y)W_O - \mu W_O - \lambda W_O,$$

where the state variables are X for uninfected hosts, Y for infected hosts, W_L for locally produced infectious stages, and W_O for externally produced infectious stages (such as a sapronotic agent). The model assumes that infectious stages are absorbed when they contact a host, that they do not distinguish between infected and uninfected hosts, and that contact with more than one infectious stage does not alter the effect of infection on the host (i.e., this is a modified microparasite model). In addition, there are several parameters: q is the production of infectious stages by infected individuals, β is the contact and transmission rate from an infectious stage to a host, μ is the decay rate of infectious stages, g is the effect of infection on birth rate (g = 0 is a parasitic castrator), m is background mortality, d is density dependence, λ is the loss rate of locally produced infective stages (emigration due to diffusion or advection), and α is disease induced mortality. Finally, the sapronotic agent term θ represents the arrival rate of infectious stages at a particular location as determined by either production by a local source, or production at a distant source and subsequent diffusion, advection, and decay. We assume that all parameters are independent of each other.

The above system of equations can be condensed into infected and uninfected hosts by assuming that the density of infective stages, W, reaches equilibrium faster than the birth and death rates of the host. Also, if $W = W_O + W_L$.

$$W = (qY + \theta)/[\mu + \lambda + \beta(X + Y)]$$

Substituting this equality into the equations for X and Y leads to:

$$dX/dt = b(X + gY)/[1 + d(X + Y) - mX - \beta X(qY + \theta)/\mu + \lambda + \beta(X + Y)]$$

$$dY/dt = \beta X(qY + \theta)/[\mu + \lambda + \beta(X + Y)] - Y(m + \alpha)$$

The carrying capacity of the host is K = (b − m)/(dm). The host threshold density for transmission (critical community size) of a conventional pathogen ($\theta = 0$) is $N_T = (\lambda + \mu)(\alpha + m)/\beta(q - \alpha - m)$. Equilibrium values can be solved analytically with a program such as Mathematica (our approach) or simulated with inputted parameter values (as was done to produce Figure I). Figure I shows equilibrium solutions for the prevalence (% infected) of a similar pathogen (local transmission) and a sapronotic agent as a function of host carrying capacity (X-axis). For a pathogen, there is a host threshold density that the carrying capacity must exceed for the pathogen to invade. For host populations above this threshold, prevalence increases with host carrying capacity. By contrast, the sapronotic agent extirpates the host when host carrying capacity is low. Its prevalence declines because the number of hosts infected with the sapronosis asymptotes as host density increases. There is an Allee effect at intermediate host carrying capacity where the host can persist at carrying capacity, but cannot invade when rare if the sapronosis is present.

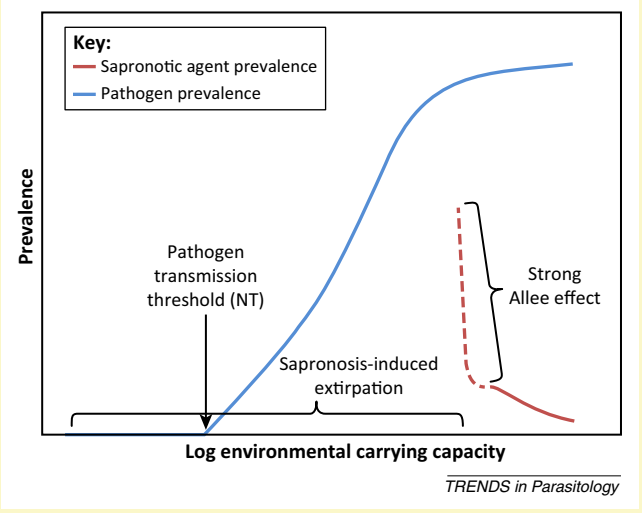

Figure I. Equilibrium solutions for transmissible pathogens and sapronotic agents. Equilibrium solutions for similar pathogen (local transmission) and sapronotic agents as a function of environmental conditions. The X-axis represents variation in host birth rate (log scale), which is meant to correspond with habitat quality. The Y-axis plots prevalence (% hosts infected). For a pathogen, there is a host threshold density that is too low at poor habitat quality, otherwise, prevalence increases with habitat quality. The sapronotic agent extirpates the host under low habitat quality conditions. Its prevalence declines with habitat quality because the number of hosts infected with the sapronosis asymptotes as host

The lack of host-to-host transmission creates distinct epidemiological dynamics for sapronoses. Given that infective stages from the environment are finite in number, transmission of a sapronotic agent to the host population saturates with host density. For instance, if there are ten infective stages and five hosts, all hosts can be infected, but if there are 500 hosts, only a few of them can be infected. This saturating transmission is akin to the well-known type II functional response from predator–prey theory, with similar implications for how sapronotic agents affect their host, for instance, the inability to regulate the host population [35]. For this reason, when we suggest that a sapronosis reduces host abundance, we do not mean to imply that it 'regulates' its hosts. Saturating transmission also means that infectious saprophages can cause what is called a component (partial) Allee effect, which is when an aspect contributing to population growth rate increases with host density. If the infection rate is high and the sapronotic agent impacts host fitness, then the component Allee effect can outweigh the benefit of increased resources when rare, leading to a demographic (overall) Allee effect for the host. As we discuss below, this Allee effect can prevent the host from invading the system when the host is rare.

A system with a self-regulated host and a host-specific, locally transmitted pathogen has three possible equilibria. A trivial equilibrium is when no hosts are present. A second equilibrium is when the host carrying capacity is above the transmission-threshold density. Here, the host and pathogen can coexist. In the third equilibrium, the host carrying capacity is below the threshold density for pathogen transmission. Hence, the pathogen cannot invade the system. For this reason, the pathogen cannot drive the host extinct. No matter how pathogenic it is, a conventional pathogen always burns out when the host becomes rare. To extirpate the host requires a host reservoir of some kind.

A system with a self-regulated host and an infectious saprophage also has three possible host–pathogen equilibria. The first two equilibria above (no host or host and pathogen coexist) are possible. However, because a sapronotic pathogen has its source outside the system, there is no host threshold density below which the pathogen goes extinct [37,36]. Instead, the third equilibrium for a host–sapronosis system is unstable, creating a critical host density called the Allee threshold, below which the host population declines to extinction in the presence of the pathogen and above which it can increase until it reaches the stable equilibrium for host–sapronotic agent coexistence. Under these conditions, hosts would be prevented from invading a region having a sapronotic agent in the environment. In other words, at low initial host density, an uninfected host population should grow to the carrying capacity, but in the presence of a sapronotic disease, most hosts will become infected and, if the saprophage is pathogenic, this can prevent hosts from establishing. However, once above the critical host density, transmission saturates, and a lower proportion of hosts are infected by the sapronotic agent, allowing the host population to grow. However, if the sapronosis is too common and pathogenic, a sapronotic-induced extinction always results. Given that the relative position of the unstable equilibrium declines with the environmental carrying capacity for the host, sapronoses should have their greatest impact in conditions where hosts are already struggling to survive.

There are important similarities between sapronotic agents and pathogens that spill over from a reservoir host to a target host. If the target host is susceptible and intolerant and the reservoir is tolerant, the pathogen can impact the target host and even extirpate it, similar to a sapronosis. However, if the target host does not produce enough transmission stages in return, spillover is a sink for the pathogen (the dilution effect) and could eradicate it [38]. In theory, hosts could also be sinks for sapronotic agents through a dilution effect, although the extent to which this is important would depend on the details of the biology of the saprophage in the environment.

Recognizing a sapronosis

What sort of landscape epidemiology patterns would we expect to see from sapronoses versus transmitted pathogens? At first glance, the patterns might well be similar with fine-scale variation in prevalence and associations with host characteristics, such as size or age. However, (i) the spatial pattern of sapronoses will be consistent with dilution, advection, and decay from a source without further spread across metapopulations, whereas conventional pathogens will spread with time through connected host populations; (ii) sapronoses will often be most prevalent under conditions where host stress increases susceptibility to infection (poor environmental conditions) with consequent decreased host abundance. By contrast, conventional pathogens will be most prevalent where environmental conditions lead to high host density, facilitating host-to-host transmission; and (iii) most importantly, sapronoses can cause local host extinction and do so repeatedly, whereas host-specific pathogens transmitted among hosts rarely do.

An interesting animal example of a sapronosis is sea fan aspergillosis [39,40]. The inability of the fungus to reproduce when developing on sea fans prevents local transmission. Its disease ecology exhibits localized patterns in space and time and among host size classes. It might not be a coincidence that this fungus occurs in the Caribbean, where coral reef ecosystems are under environmental stress. Aspergillosis has substantially reduced sea fan abundance at many locations, and there is some evidence that selection for resistance among the hosts has already occurred [40].

Biodiversity of human sapronoses

To evaluate the biodiversity and systematic affiliations of human sapronoses, we randomly selected 150 pathogens from the list of 1415 human pathogens in the Appendix to [41] (Box 2). For each pathogen, its life cycle, mode of transmission, pathology, and environmental or animal reservoirs were investigated through a search of the primary literature. An assignment of sapronosis or non-sapronosis was based on the criteria defined above.

A full third of the 150 pathogens assessed were found to be sapronotic agents (Table 1). Fungi represented approximately two-thirds of these, despite accounting for only 240 (17%) of the 1415 human diseases [41]. One of the pathogens listed as a fungus has been reclassified as an alga [42], also sapronotic. Fungi were dominated by sapronotic agents, and all but one of the fungi assessed was evaluated as sapronotic. Given that many detritivores are fungi [17], this may account for fungal prominence among sapronoses.

Bacteria were also common among the sapronotic diseases, with almost one-third causing sapronoses. None of the viruses or helminthes caused sapronotic diseases. Viruses all have an obligate reliance on host cells for replication. The lack of any human metazoan sapronotic agents was confirmed by a similar evaluation for all 354 metazoan parasites in the comprehensive checklist of [43]. The 12% of the protozoans recognized as sapronotic disease agents in our randomized survey was similar to a complete evaluation of the 83 protists in [43] where eight (10%) were identified as sapronotic. Seven of these were amebae: six species of *Acanthamoeba* and *Naegleria fowleri*. The dinoflagellate, *Pfeisteria piscicida*, under some circumstances, can transmit among fish hosts. Its nutritional source appears to be necrotic tissue [43]. To the extent it is transmitted among hosts, it might be included among the sapronotic diseases with a sporadic host-to-host epidemiology.

Table 1. Proportion of human infectious diseases that are sapronotic[a]

Clade	No. (%) sapronoses	No. of non-sapronoses	Total assessed	% of all sapronoses
Bacteria	18 (28.6%)	45	63	36.0%
Fungi	30 (96.8%)	1	31	60.0%
Alga	1 (100%)	0	1	2.0%
Protozoa	1 (12.5%)	7	8	2.0%
Helminthes	0	23	23	0.0%
Viruses	0	24	24	0.0%
Total	50 (33.3%)	100	150	100%

[a]Randomly selected from the comprehensive list of human parasites and pathogens in [41].

Box 2. Human pathogens and parasites that are sapronotic

We randomly selected 150 human pathogens from among 1415 pathogens and parasites in the Appendix to [41], which are detailed below. The list is divided into bacteria, fungi (and an alga), helminthes, protozoans, and viruses. Sapronotic agents are shown with an asterisk, and zoonotic species are underlined.

Bacteria

*Achromobacter piechaudii**
*Acinetobacter junii**
Acinetobacter lwoffii
Actinobacillus equuli
Actinomyces meyeri
Arcanobacterium pyogenes
*Bacillus sphaericus**
*Bacillus thuringiensis**
Bordetella bronchiseptica
Borrellia caucasica
Brucella melitensis
Capnocytophaga ochracea
*Chryseobacterium meningo septicum**
Citrobacter koseri
Citrobacter sediakii
Clostridium bifermentans
Clostridium chauvoei
Clostridium novyi
Clostridium sordellii
Corynebacterium minutissimum
*Delftia acidovorans**
Ehrlichia chaffeensis
Ehrlichia equi
Enterobacter amnigenus
Enterococcus avium
Enterococcus durans
Enterococcus faecium
Eubacterium brachy
Eubacterium combesii
Eubacterium contortum
Fibrobacter intestinalis
*Fluoribacter bozemanae** (*Legionella bozemanii*)
*Fluoribacter dumoffi** (*Legionella dumoffi*)
Fusobacterium mortiferum
*Gordonia terrae**
Klebsiella oxytoca
*Legionella cincinnatiensis**
*Legionella lansingensis**
*Listeria weishimeri**
Mycobacterium gordonae
Mycobacterium marinum
*Mycobacterium mucogenicum**
*Mycobacterium senegalense**
Neisseria meningitidis
Neisseria sicca
*Nocardia brasiliensis**
Pasteurella canis (may be *syn: P multocida*)
Pasteurella dagmatis
Prevotella tannerae
*Pseudomonas stutzeri**
Rhodococcus fascians
Selenomonas noxia
Staphylococcus warneri
*Stenotrophomonas maltophilia**
Streptobacillus moniliformis
Streptococcus agalactiae
Streptococcus constellatus
Streptococcus equi
Streptococcus gordonii
Tatumella ptyseos
*Yersinia frederiksenii**
*Yersinia intermedia**
*Yersinia ruckeri**

Fungi (and an alga)

*Absidia corymbifera**
*Acremonium strictum**
*Aspergillus clavatus**
*Aspergillus terreus group**
*Bipolaris australiensis**
*Bipolaris hawaiiensis**
*Bipolaris spicifera**
*Candida lusitaniae**
*Chlamydoabsidia padenii**
*Chlorella protothecoides** (alga)
*Cladorrhinum bulbillosum**
*Curvularia geniculate**
*Doratomyces stemonitis**
*Emmonsia parva**
*Leptospaeria senegalensis**
*Microascus cinereus**
*Microascus cirrosus**
*Mucor hiemalis**
*Myceliophthora thermophile**
*Mycocentrospora acerina**
Nannizzia cajetani
*Penicillium decumbens**
*Penicillium marneffei**
*Phaeoaneliomyces elegans**
*Phialemonium obovatum**
*Scytalidium infestans**
*Taeniolella exilis**
*Tetraploa aristata**
*Trichoderma viride**
*Trichosporon asahii**
*Tritirachium oryzae**
*Volutella cinerescens**

Protozoa

*Acanthamoeba hatchetti**
Cyclospora cayetanensis
Cystoisospora belli (formerly *Isospora belli*)
Enterocytozoon bieneusi
Leishmania aethiopica
Leishmania naiffi
Plasmodium simium
Trichomonas vaginalis

Helminths

Alaria marcianae
Ancylostoma caninum
Artyfechinostomum mehrai
Australobilharzia terrigalensis
Brugia guyanensis
Dirofilaria tenuis
Echinoparyphium recurvatum
Echinostoma ilocanum
Echinostoma jassyense
Gastrodiscoides hominis
Haplorchis vanissima
Heterophyopsis continua
Metagonimus yokogawai
Metorchis conjunctus
Micronema deletrix
Moniezia expansa
Opisthorchis felineus
Paragonimus bankokensis
Paragonimus kellicotti
Schistosomatium douthitti
Schistosoma mattheei
Strongyloides ransomi
Toxocara canis

Viruses

Andes virus
Borna disease virus
Bunyamwera virus
Chikungunya virus
Everglades virus
Eyach virus
Far eastern Tick-borne encephalitis virus
Gan gan virus
Hepatitis G virus
Human Herpesvirus 2
Influenza A virus
Kyasanur forest disease virus
Lechiguanas virus
Marituba virus
Measles virus
Mokola virus
Molluscum contagiosum virus
New York virus
Ockelbo virus
Rotavirus C
Rotavirus F
Tamdy virus
Tanapox virus
Zinga virus

In past infectious disease summaries, many sapronotic agents have been misclassified as zoonoses. For instance, most (60%) human pathogens were considered zoonoses [41]. This included 113 fungi and 269 bacteria. Extrapolation from our random sample removes almost all the fungi from consideration as zoonoses, along with many bacteria and some protozoa. This is important for two reasons. First, it challenges the hypothesis that most infectious diseases of humans are transmitted from animals, as does an analysis of the parasitic diseases that are prevalent morbidity sources for humans [44]. Second, recognizing the difference between sapronoses and zoonoses is important because we can now direct attention to the environmental sources for sapronoses.

Our tabulation of sapronoses allows us to generalize about their pathology. Most of the randomly selected sapronotic agents cause rare, opportunistic infections, targeting immunocompromised hosts. Some are so rare and mild that they are nonpathogenic, such as *Chlamydoabsinia padenii* and *Listeria weishimeri* [45,46]. However, a few of the sapronotic agents can infect immunocompetent hosts, albeit rarely, leading to severe disease. These include *Nocardia brasiliensis*, [47] *Acanthamoeba* spp. [48], nontuberculosis mycobacteria [49], and, occasionally, fungi, such as *Scopulariopsis* spp. [50]. Many cause nosocomial infections or are found in a clinical setting. Often, human infections caused by sapronotic agents require a hospital setting to circumvent natural barriers to entry into the body. Documented modes of transmission include inhalation of spores or contaminated, aerosolized water droplets, ingestion (foodborne or waterborne), and traumatic wound and/or abrasion inoculation, either accidental trauma or insect bites [46,51–57], or nosocomial traumas, such as catheterization, prosthetic insertion, or surgery, [47,58–60] or insufflation [61]. A few sapronoses cause keratitis of the eye following contact lens use [48]. For many sapronoses, the mode of transmission is unknown or unclear. Some sapronotic agents are commensal, harmless, sometimes transient inhabitants. For example, trichosporon fungi are ubiquitous inhabitants of a variety of habitats, including soil, seawater, air, rivers, and bird droppings. Eleven percent of 1004 healthy male volunteers were colonized by *Trichosporon* spp. on normal perigenital skin [62]. However, they can sometimes cause superficial or deep infections in immunocompromised hosts.

Despite their rarity as pathogens, most sapronotic organisms are common, even ubiquitous, in nature. Among the 50 sapronoses recognized in our random sample of human infectious agents, most were terrestrial (28 of 50), with the next most common habitat being fresh water (nine of 50 were aquatic). The remainder could be found in both habitats or their natural habitat was uncertain. Several of the bacterial sapronotic agents, such as *Legionella* spp., *Mycobacterium mucogenicum*, and *Chryseobacterium meningosepticum*, can occur intracellularly within aquatic amebae. This association might enable them to resist disinfection in hospital settings [63,64]. An ameba association could also offer a pre-adaptation toward acquiring the ability to invade human cells. For instance, in *Legionella pneumophila*, the same genes are required to invade ameba and human macrophages [65].

Concluding remarks: sapronoses and human health

The sporadic emergence of many sapronotic diseases makes them difficult to investigate. Hence, they are underdiagnosed [6]. Sapronoses also enter into the discussion of emerging diseases, not only due to improved diagnostics, but also probably for the biological reason that human populations increasingly occupy and use diverse habitats. Recent barcoded pyrosequencing of diverse soil samples has demonstrated that the diversity of protists in soil is staggering [66]. The conjunction of great microbial diversity and expanding human habitat use presents an emerging disease opportunity, especially for sapronotic hazards. Hence, the contact rate with potential sapronoses continues to expand. Although most sapronotic agents are not threats to otherwise healthy people, some are virulent, and often there is no effective treatment. Bioterrorism security pays particular attention to sapronotic agents (e.g., anthrax) because one can propagate many spores or other infective stages on organic substrates in the laboratory, then store them as resting stages.

Controlling sapronoses is not about treating infected hosts. Risk of infection by sapronotic agents will not be diminished because they can spring back from their free-living sources. Whereas treating infected individuals will remain the most important and urgent response to combat sapronoses, controlling them requires reducing contact with, or sterilizing or otherwise altering, the environments where they proliferate.

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