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THE TIES THAT BIND HUMANS TO ANIMALS

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INTRODUCTION

In 2020, COVID-19 shone a spotlight on zoonoses — diseases caused by pathogens that are naturally transmitted between humans and other animals. These pathogens can take the form of microorganisms, most commonly bacteria or viruses, or macroparasites, such as worms.

Since its beginnings 3.8 billion years ago, the biological world has been a web of interactions among organisms. Indeed, every living creature is, in fact, an amalgamation of other living creatures. Given this permanent web of interactions, certain microorganisms and parasites may end up in new host species, an erratic process facilitated by a range of factors. Sometimes these new relationships are beneficial. Sometimes they are catastrophic. Of the myriad interspecific exchanges taking place, very few ultimately succeed. The above should serve to remind us that all species host microorganisms. It is the nature of life. However, under certain circumstances, this otherwise banal reality can end up threatening the health of individuals and societies.

As human beings, we have complex relationships with animals. These connections differ across the world, as they are shaped by cultural practices, customs, traditions, and religious beliefs. Some animals are the objects of our affection. Others terrify us. In either case, animals are front and centre among our emotional connections to the living world. They improve our daily lives. Some provide us with joy, labour, or nourishment, while others simply share natural spaces with us. Each one of these interactions represents an opportunity for pathogen exchange. Certain pathogens are part of our evolutionary heritage because they were present in our great ape ancestors. The advent of domestication created an opportunity for frequent, routine contacts between humans and farm animals, thus favouring zoonosis transmission. Human and farm animal populations grew in tandem, reducing the relative representation of wildlife species among terrestrial vertebrates. At present, the ways in which we humans exploit the environment have increased how frequently we interact with

wildlife. Simultaneously, intensive animal farming has transformed the conditions under which these interactions take place, with young and genetically homogenous animals crowded together at high densities.

In this book, we explore what is currently known about zoonoses, drawing upon multifarious examples. We seek to answer certain key questions: What are zoonoses? How are they transmitted? How do we learn to safely live with them? Are zoonoses on the rise? This book is an invitation to learn more about these diseases so that we can better protect ourselves and others. An essential part of this work is transforming how we interact with animals and the living world in general.

DEFINING ZOONOSES

The term "zoonosis" comes from the Greek roots *ζῷον (zôon)*, meaning animal, and *νόσος (nosos)*, meaning disease. As far back as the classical era, people observed that certain diseases seemed to pass from animals to humans, rabies serving as one notable example. However, it was not until the 19th century that the concepts of microbes, contagion, infection, and transmission were elucidated in their modern form, paving the way for the fields of microbiology and epidemiology. German physician and researcher Rudolph Virchow (1821–1902) coined the term zoonosis after noting parallels in a parasitic disease found in both pigs and humans: trichinellosis (see p. 88). The modern definition of a zoonosis is an infectious or parasitic disease whose microbial or parasitic agents are naturally transmitted between humans and other animals. In this book, we discuss disease transmission between humans and other vertebrates, mainly mammals and birds, using the terminology defined by the World Health Organisation (WHO). We also wish to specify that, in the context of this book, we use the phrase "naturally transmitted" to mean the opposite of "experimentally transmitted" and/or "rarely transmitted".

Zoonoses have been around for as long as humans have. The direct ancestors of the genus *Homo*, and more generally all the members of the various hominid lineages, were exposed to and/or infected by pathogens coming from other animal groups. Humans were interacting with animals long before *Homo sapiens* gained self-awareness. Anthropology has taught us that, earlier on in our evolutionary history, the boundaries between humans and other animals did not exist or were highly dynamic. They were shaped by context, region, and time period. In the mid-2010s, studies were carried out in northern Australia that explored how Hendra virus was viewed by Indigenous populations with traditional lifestyles (e.g., resembling those prior to European colonisation). The findings illustrate the great disparity in the attitudes of Australia's Indigenous *versus* settler populations towards this viral disease. The reservoirs for Hendra virus are flying foxes (genus *Pteropus*), which are large fruit bats. European settlers destroyed tropical forests

and planted orchards, which has brought fruit bats into increasingly frequent contact with humans in inhabited areas. Hendra virus infections in humans seem to have arisen from infections in horses, animals brought to Australia from Europe. Indigenous Australians espouse certain practices when hunting flying foxes and view these animals as beneficial for the environment. Even though the pathogen has long existed in Australia, Indigenous populations have never experienced any Hendra virus outbreaks.

CAUSES OF ZOONOSES

Zoonoses are caused by pathogens transmitted between humans and animals. These pathogens may be microorganisms invisible to the naked eye, such as bacteria, viruses, tiny fungi, protozoa, or prions. They may be macroparasites, such as helminths or parasitic arthropods (see Figure 1). While we have been using the term pathogens, it would be more accurate to say potential pathogens. These species only become pathogenic under certain conditions, in certain species, and in certain individuals. Pathogenicity arises from interactions between the potential pathogen and its host (i.e., the individual that has been infected).

In fact, microorganisms are an integral part of the environment. They occur on and in our bodies. The vast majority of microorganisms do not cause sickness. Quite the opposite — they often help ensure that our bodies are functioning properly. Such is the case for our microbiota, the symbiotic or commensal microorganisms that make up the normal flora living in our intestines or on our skin, for example. It is worth noting that, since the 2000s, researchers have identified a few animal species, notably arthropods, that have few to no microbiota. In contrast, the human digestive tract houses around one trillion microorganisms, which are involved in tasks such as digestion and immunity. This figure is two to ten times greater than the number of cells making up the human body. Healthy adult humans may also harbour more than three trillion viruses, mostly bacteriophages that infect bacteria found in the intestines and mucous membranes. Furthermore, the human genome contains endoviruses, or endogenous retroviruses, which have been making

themselves at home in our DNA for more than 30 million years. Their sequences represent around 8% of our genome. Generally, they are not pathogenic in humans, and some sequences have even brought us benefits. Such is the case for the genetic material contributed by the HERV-W virus, whose products are involved in physiological mechanisms and promote placenta formation.

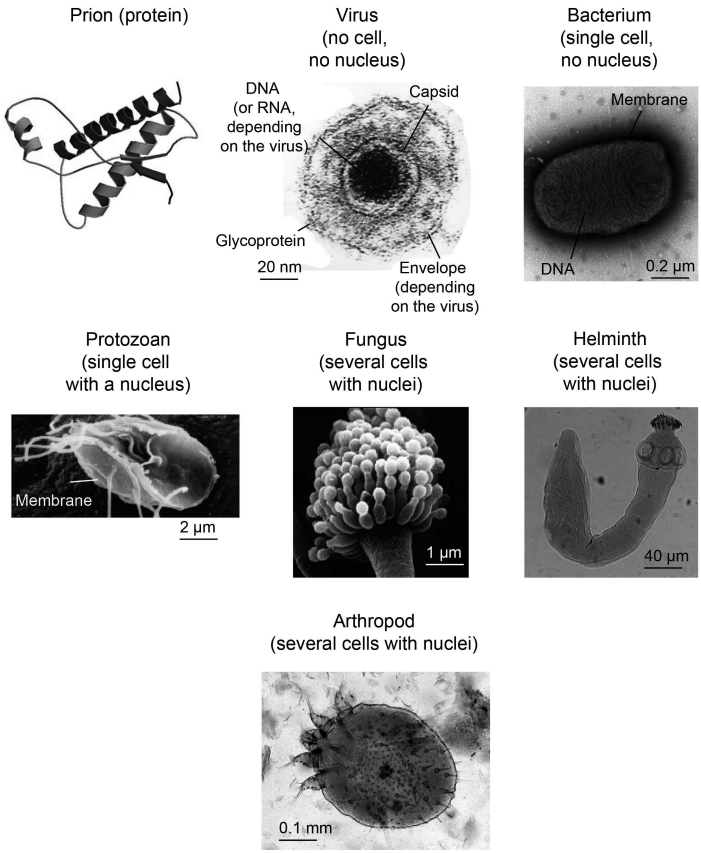

Figure 1. Examples of different zoonotic agents.

Prions, viruses (HHV-6 © Bernard Kramarsky), bacteria (*Salmonella enteritidis* © Philippe Velge/INRAE), protozoa (*Giardia intestinalis* © NIH), fungi (*Aspergillus fumigatus* © NIH), helminths (*Echinococcus multilocularis* © VetAgro Sup - Parasitology Laboratory), *and arthropods* (*Sarcoptes scabiei* © VetAgro Sup - Parasitology Laboratory).

NAMING CONVENTIONS FOR INFECTIOUS DISEASES

Historically, it was common to name new infectious diseases for the places they had originally been identified. For example, Crimean-Congo haemorrhagic fever was initially observed in Crimea, and its viral pathogen was isolated in the Republic of Congo. The first reported instance of Lyme disease came from the town of Lyme, Connecticut, USA. West Nile fever is caused by a virus that was isolated in the West Nile region of Uganda. However, this naming system does not reflect any sort of epidemiological reality, nor does it necessarily express accurate geographical origins. For example, the Spanish flu of 1918 was so named because Spain was the first country to publicly acknowledge the disease's existence, even though it seemingly was also present in the US. Many diseases are also named after their etiological pathogens (e.g., tuberculosis or toxoplasmosis), which may, in turn, be named after the people responsible for their discovery. Finally, some diseases are named for the animal source of transmission to humans (e.g., swine flu). However, in 2015, the WHO released recommended naming practices that do not stigmatise peoples, nations, geographical areas, and/or species. This work to change the nomenclature of emerging infectious diseases was carried out in close collaboration with the World Organisation for Animal Health (whose acronym, OIE, refers to the group's original name, *l'Office international des épizooties*); the United Nations Food and Agriculture Organisation (FAO); and the experts behind the International Classification of Diseases (ICD) tool. A disease's official name is now ultimately chosen by the ICD. Thus, the "swine flu" or "Mexican flu" that appeared in Mexico in 2009 was officially named influenza A(H1N1)pdm09.

In a 2001 study, Louise Taylor and colleagues estimated that bacteria represent one-third of zoonotic pathogens in humans. Bacteria are single-celled organisms that measure around one micrometre (μm), which equals one thousandth of a millimetre. They possess a single chromosome composed of DNA that is not contained within a nucleus. Bacteria also display a characteristic cell wall. In general, they are autonomous organisms that reproduce by binary fission. This process can be extremely

fast, on the order of one division every 30 minutes. Bacteria are omnipresent within the environment, but only a small fraction of them are pathogenic. One well-known infectious agent is the bacterium responsible for tuberculosis (see p. 80). Bacteria can normally be treated with antibiotics (but see p. 82).

Parasitic worms (i.e., helminths) are thought to represent another third of zoonotic pathogens in humans. This group includes the round worms, also known as nematodes (e.g., *Trichinella spiralis*), and the flat worms, alternatively called cestodes (e.g., tapeworms and trematodes, such as the blood flukes). Their adult stages tend to be visible to the naked eye. Helminths are generally found in the digestive system, the blood, and various other tissues. Some have complex transmission cycles involving multiple host species. Parasitic worms can be treated with anthelmintics. The compounds used specifically to eliminate gastrointestinal worms are called vermifuges or vermicides. Depending on the helminth, humans may act as definitive hosts (i.e., harbour reproductive adults), intermediate hosts (i.e., harbour larvae), or dead-end hosts (i.e., do not transmit the parasite).

Viruses appear to account for one sixth of zoonotic pathogens. Generally extremely small in size (< 0.1 μm), they are composed of nucleic acids (DNA or RNA, which convey genetic information) surrounded by a protein shell called a capsid. Enveloped viruses sport an additional outer wrapping composed of lipids. They are obligate parasites that must infect cells to replicate, which ultimately disrupts normal host functioning. The rabies virus is an emblematic example of a zoonotic virus (see p. 103). Although viruses can sometimes be treated using antiviral drugs, which block the replication cycle, control strategies largely rely on shutting down transmission chains and, when possible, vaccinating populations.

Microscopic fungi are thought to account for 10% of zoonotic pathogens in humans. Like all other fungi, they sport cell walls and can spread via spores. They display a variety of lifestyles: they can grow on decomposing organic matter, live in symbiosis with other organisms, or form part of the digestive, skin, or genital flora found in humans and other animals. Fungi such as

ringworm or aspergillosis can be pathogenic, especially in immunocompromised people, who may experience infections on their skin, in their mucous membranes, or in other tissues. Fungal infections are treated with compounds called antifungals. While this book does not discuss zoonotic fungi in great detail, a few examples are mentioned in the section on contact transmission.

CHARACTERISTICS OF ZOONOTIC VIRUSES

It is more common for zoonotic viruses to have an RNA than a DNA genome because RNA accumulates uncorrected replication errors, which can serve as fodder for evolution. RNA viruses also tend to replicate within the cytoplasm of host cells; they do not need to enter the nucleus. As a consequence, they must only make it past the cell membrane, a trait that enhances their ability to infect multiple species. As underscored by epidemiologist Mark Woolhouse, the vast majority of new viruses with epidemic potential in humans are related to, but not directly descended from, other viruses capable of spreading within human populations.

Sometimes, the genetic differences between zoonotic and non-zoonotic pathogens are quite small. For example, severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) has a 29-nucleotide deletion that is absent from a closely related coronavirus found in masked palm civets *(Paguma larvata)*; the former virus is pathogenic in humans, but the latter is not. Thus, while genomic comparisons can provide hints about a virus' zoonotic potential, they do not indicate whether or not emergence is likely.

Protozoa are estimated to represent about 5% of zoonotic pathogens. Unlike bacteria, protozoa are complex single-celled organisms whose DNA is organised into chromosomes and contained in a nucleus. They vary in size from one micrometre to one millimetre. They occur in soils and aquatic environments, and only a small percentage can cause disease in humans and other animals. That said, some are obligate parasites. Given the metabolic similarities between protozoa and vertebrates, compounds that could be used to treat protozoa also tend to have harmful effects on their hosts. Consequently, only a limited arsenal of

drugs can effectively be deployed against protozoa. Examples of zoonotic diseases caused by protozoa include toxoplasmosis (see p. 87); leishmaniasis (see p. 62), vectored by small, blood-sucking phlebotomine sand flies; sleeping sickness (African trypanosomiasis), vectored by tsetse flies; and Chagas disease (American trypanosomiasis), vectored by kissing bugs. Malaria is also caused by a protozoan. While this disease is thought to have started off as a zoonosis, it is no longer transmitted from animals to humans. The only exceptions are the malaria pathogens *Plasmodium knowlesi* and *P. cynomolgi* in Southeast Asia (see p. 18).

The main parasitic arthropods are insects and mites that parasitise the skin (i.e., ectoparasites). Sometimes, they are simply a nuisance. However, at other times, they can cause intense itching, resulting in pronounced lesions with serious health impacts. Certain members of this group, such as mosquitoes and ticks, vector pathogenic viruses, bacteria, and protozoa. Insecticides and acaricides are the most common compounds used to control arthropod pests.

Prions are proteins with abnormal spatial configurations or folding patterns. They mainly occur in the brains and spinal cords of adult mammals. Unlike viruses, bacteria, and parasites, they do not provoke infection by expressing information contained in DNA or RNA. Because of their abnormal configurations, prions are impervious to enzymatic degradation and can induce abnormal folding in normal proteins. Nervous tissue containing large quantities of prions has a sponge-like appearance, which is why prion-mediated neurodegenerative diseases in humans and other mammals are called transmissible spongiform encephalopathies. Prions are extremely resistant to conventional disinfection techniques and methods of protein inactivation. As a result, there is currently no treatment for prion diseases. To date, the only known prion-provoked zoonosis is bovine spongiform encephalopathy (see p. 105). Other prion diseases exist but are either specific to humans (Gerstmann-Sträussler-Scheinker syndrome, or kuru) or to other mammalian species (e.g., scrapie in sheep).

NON-INFECTIOUS DISEASES CAUSED BY ANIMALS

Animals can cause human illnesses via agents other than pathogens. However, such diseases are not zoonoses. For example, animals produce allergens, which provoke reactions in around 3% of the French population. Allergies to dogs and cats might affect up to 20% of the world population. People commonly react to an allergen in cat saliva, which cats spread across their fur during grooming. Horses also produce allergens, which are found in their hair, dander, and urine. Rodents can provoke extremely serious allergic reactions, especially via allergens present in their urine. In birds, the best-known allergens are found in droppings. Some of these allergens are highly volatile and can travel long distances before they end up being inhaled. Arthropods can also provoke allergies in a variety of ways: via bites, stings, or inhalation (e.g., dust mites).
Additionally, animals can transfer the genes of the pathogenic or non-pathogenic organisms that they host. One example is drug resistance genes, which can be bidirectionally transmitted between humans and other animals. Bacteria tend to utilise a ubiquitous set of resistance mechanisms. More than sixty years of unrestricted antibiotics usage strongly selected for resistance in bacteria. The prevalence of antibiotic resistance is alarming and underscores the need to greatly decrease the use of these compounds in humans and other animals (see p. 82). Consequently, this topic is increasingly a part of discussions centred on zoonoses.

DISEASE RESERVOIRS

A disease reservoir is an ecological system in which a pathogen is perpetually maintained and from which it can spread into a "target" population, such as into humans in the case of zoonoses. Reservoir structure can be simple or complex. For example, the reservoir may be a population of a single animal species or a community comprising populations of various species, with each making a different contribution to pathogen transmission. There may also be an environmental component to the disease reservoir. Different reservoir hosts may vary in their susceptibility to infection.

For example, the red fox *(Vulpes vulpes)* is the only flightless mammal to serve as a reservoir for rabies virus in Western Europe

(see p. 103). In contrast, an array of species act as the reservoir for Lyme bacteria, which circulate among rodent, bird, and tick populations (see p. 74). Another illustration can be seen in *Cryptosporidium parvum*, a protozoan parasite that causes acute gastroenteritis in humans. Its reservoirs are communities of numerous mammal species that occur within excrement-contaminated environments.

Ultimately, a population's capacity to act as a reservoir at a given location depends on its ability to maintain pathogen transmission on its own (i.e., intraspecifically) and successfully pass the pathogen to other host species. When pathogens are transmitted by vectors, competence can be quantified using the percentage of vectors that become infected after feeding on an infected animal. It is important to note that the above capacity is also shaped by epidemiological and ecological conditions, including factors such as population density, contact frequency, the surrounding biological community, and environmental characteristics. For example, several non-human primate species are reservoirs for chikungunya and dengue viruses because they are fed upon by *Aedes sylvestris* mosquitoes. However, in places where non-human primates are absent (other than in zoos), such as in urban areas or on Réunion Island, transmission occurs directly between humans and mosquitoes (e.g., *Aedes albopictus*).

A question naturally arises: are certain taxonomic groups more likely to act as reservoirs for zoonoses? If so, do they display particular characteristics? For example, for humans and non-human primates, it has been established that greater phylogenetic relatedness favours pathogen exchange. Similarly, there have been opportunities for pathogen exchange among humans and the species with which they have long cohabited (e.g., domestic or commensal animals). Indeed, species with a longer history of domestication share a greater number of pathogens with humans (see p. 39).

It is possible that certain taxonomic groups, such as rodents or bats, could be better reservoirs because of their life-history traits (e.g., number of offspring or lifespan); their ecology (e.g., habitat preference, gregarious *versus* solitary lifestyle, or position within

the food web); their immune systems; or their physiology. This issue is still being explored (see sidebar p. 70). The number of viruses found in the different mammalian orders largely seems to correlate with order species richness but also with relative research intensity. For instance, rodents (Rodentia: 2,552 species) and bats (Chiroptera: 1,386 species) harbour significantly more viruses than do carnivores (Carnivora: 305 species). It also appears that the percentage of viruses that are zoonotic is consistent across taxonomic groups, accounting for factors such as phylogenetic relatedness (i.e., primates) and a history of cohabitation with humans (i.e., domestic animals). Thus, rodents and bats might be expected to host the highest numbers of zoonotic viruses. In addition, it may be that certain taxa are overrepresented in available data because of historical research interests.

INFECTION RISKS ASSOCIATED WITH HEALTHY ANIMALS

Zoonotic agents may be pathogenic to humans without being pathogenic to animals. For example, commensal flora in animals can cause disease when transmitted to humans. Take the case of *Pasteurella* bacteria, which occur asymptomatically in the upper aerodigestive tracts of most cats. After being bitten or scratched by cats, humans may experience local bacterial infections that must often be treated with antibiotics. Animals can also display a high level of pathogen tolerance: even when infected, hosts may not show any symptoms. Such is often seen in reservoir species, as illustrated by the rodent and bird reservoirs of Lyme disease or the bat reservoirs of various emerging viral diseases. Intestinal parasites also commonly go unnoticed in animals (e.g., roundworm infestations in dogs and cats), but can cause health issues if ingested by humans. Finally, animals may be in the incubation phase of a disease—contagious but not yet symptomatic.

In short, it seems best to avoid handling unfamiliar animals, even more so if the species is wild and conditions are not conducive to ensuring health and safety. With such in mind, there is no reason to expect danger around every corner. The risk of becoming infected with a zoonosis is very low if you are interacting with familiar, asymptomatic animals kept under healthy living conditions and you are not immunocompromised.

FROM ONE SPECIES TO ANOTHER: HOST SPECIFICITY, SPECIES JUMPS, BARRIERS, FILTERS, AND OTHER CONCERNS

Compared to predator-prey interactions, host-pathogen interactions can be long lasting and quite intimate. The adjective "sustainable" has even been used on occasion. Some pathogens have coevolved with their hosts over millions of years. One result of these interactions is that pathogens may end up utilising the range of transmission possibilities available to them. Specific terminology has been developed to describe different scenarios.

Host specificity refers to the set of species that a given pathogen can infect. Thus, a generalist pathogen can infect numerous host species, while a specialist pathogen can infect a more limited number of species. A higher degree of host specificity is favoured in environments containing smaller numbers of species with high population densities. Consequently, pathogens can more effectively "utilise" the fewer species available to them. More generalist pathogens are less dependent on a given resource (i.e., host). Alternatively, we now know that different strains of a given pathogen species may be adapted to specific animal hosts, a discovery that has come about thanks to advances in genomics, which have improved our ability to characterise intraspecific pathogen diversity.

"Species jumps" describe situations in which pathogens move from one host species to another. This term is mostly employed when a pathogen has recently been detected in a new species or when such situations come as a surprise to epidemiologists, who sometimes use the questionable phrasing "crossing the species barrier". It is challenging to quantify the frequency of such "jumps". When we examine pathogen transmission patterns (see p. 35), we only see successful transmission events. Indeed, we will never know how many unsuccessful transmission events or asymptomatic transmission events have occurred because, by their very nature, such incidents slip past unnoticed. Life is woven from both continuous and discrete phenomena. An illustration is "mad cow" disease in the UK (see p. 105), which was transmitted by the consumption of contaminated meat. It was

immediately apparent that meat-eating species were differentially affected. Only felids, notably domestic cats, displayed signs of illness. No domestic dogs, or indeed any other canids, showed any symptoms of the disease, even if both animal groups likely experienced the same degree of exposure.

A small-scale species jump can be seen in the history of the *Plasmodium* species occurring in humans and some non-human primates. Members of the genus *Plasmodium* cause malaria, a mosquito-vectored disease. To date, four species have been found to provoke malaria in humans: *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. The origin of *P. falciparum*, the deadliest of the four, remains shrouded in mystery. The parasite seems poorly adapted to life in humans given its high level of virulence. Phylogenetics research from the 2010s suggests *P. falciparum* recently evolved from a parasite found in gorillas *(Gorilla gorilla)*. The parasite is still present in gorillas but is no longer zoonotic. Instead, it served as the ancestor for a *Plasmodium* species that became a human pathogen. Other research from the 2010s described a new *Plasmodium* species responsible for human illness in tropical Asia: *P. knowlesi*. This parasite had already been observed in local macaque populations. Was this finding evidence of a species jump? Of the parasite's recent adaptation to a new host? It seems more likely to be the result of a shift in diagnostic methods: genetic tests replacing the use of light microscopy. Since then, researchers have come to realise that *P. knowlesi* was regularly confused with *P. malariae* because of their morphological similarities. It now seems that *P. knowlesi* was never actually transmitted among humans. The same morphological confusion was observed between *P. vivax* and *P. cynomolgi*, another *Plasmodium* species found in simians. Ultimately, *P. knowlesi* and *P. cynomolgi* should be viewed as macaque parasites with zoonotic potential. However, there is no indication that either is becoming a human pathogen.

People often evoke the concept of the "species barrier" in the context of species jumps, notably in research on emerging zoonoses. A "species barrier" expresses the notion of a hurdle that impedes a pathogen from moving from an established host species to a new host species. Such barriers are seen as specifically