T_H1 cell — were higher in people with severe disease than in those with moderate COVID-19. This occurred even though blood levels of CD4 T cells and CD8 T cells, which are generally linked to expression of these molecules, were similarly decreased (a condition called lymphopenia) in people with moderate or severe disease. More remarkably, cytokines associated with immune responses to fungi (cytokines released by a type of CD4 T cell called a T_H17 cell) were elevated and remained so in people with severe disease. The same was true for cytokines associated with immune responses to parasites, including worms, or with allergic reactions (cytokines such as IL-5, released by a type of CD4 T cell called a T_H2 cell). The discovery that parts of the immune system unrelated to viral control would be triggered by a viral infection was unexpected. Less surprising was the finding that levels of inflammatory cytokines in the blood, especially the proteins IFN-α, IFN-γ, TNF-α and TRAIL, correlated with viral RNA levels in the nasal passage, independently of disease severity.

From their analysis of proteins in people's peripheral blood mononuclear cells, the authors divided individuals into three groups on the basis of their subsequent clinical course and disease severity. In general, at early time points after infection, those who went on to have moderate disease had low levels of inflammatory markers and a rise in the level of proteins associated with tissue repair. By contrast, people who went on to develop severe or very severe disease had increased expression of IFN-α, IL-1Ra and proteins associated with T_H1-, T_H2- and T_H17-cell responses, even at early time points (10–15 days after the onset of symptoms). These results were validated using data for the entire patient population, across all time points, thus demonstrating that these characteristic expression patterns persisted over time in people with each type of disease severity.

What have we learnt from this report, and what still needs to be done? It is clear from this and other studies that the immune response in hospitalized patients with severe COVID-19 is characterized by lymphopenia and the expression of molecules associated with ongoing inflammation[8], whereas these same molecules are expressed at a lower level in people with mild or moderate disease. Differences in immune responses between the different categories of disease severity are even more evident when people with very mild or subclinical disease are included in the analyses[4].

A key next step will be to analyse samples from people with extremely early signs of COVID-19, and to compare longitudinal data in those who do and those who don't require hospitalization. Some people who develop severe disease seem to have a suboptimal immune response initially, which might allow uncontrolled viral replication[9]. Such high replication might, in turn, contribute to severe disease.

Further analyses should identify molecules that are useful for predicting which individuals will later be hospitalized and require intensive care. It will also be crucial to understand how severe disease results in an upregulation of cytokines usually linked to the immune response to parasites and allergic reactions, and whether this apparent dysregulation of the immune response to viral infection is unique to COVID-19. It will also be worth determining whether these changes in the expression of inflammatory molecules in the blood also occur in cells at the site of infection — the airways and lungs. Lucas *et al.* analysed blood samples because obtaining cells from an infected lung is much more tricky and results in the production of aerosols that might contain SARS-CoV-2.

For results to be clinically useful, it will be necessary to define a limited number of biomarkers that can be both readily measured and used to predict disease outcomes. This could be difficult, because many of the changes in cytokine expression observed in studies such as that of Lucas and colleagues are useful for population-level analyses but less so for predicting outcomes in individual patients. Levels of specific cytokines vary substantially between people, making it hard to benchmark a level of cytokine expression that constitutes a sign of abnormality. Therefore, groups of cytokines, each with different degrees of inter-individual variability, must be measured to identify useful alterations.

The identification of infected people on course to develop severe COVID-19 will be a key step forward in patient care. For example, it would increase the possibility of correctly selecting individuals most in need of targeted early treatment, such as with therapies that directly inhibit viral replication. There has been progress in identifying such treatments, and the continued development of antiviral drugs that have increased efficacy and specificity will be crucial for alleviating the disease and reducing the death rate associated with the COVID-19 pandemic. Ideally, such drugs will be administered orally, and will reduce the need for hospitalization. Continued progress in unravelling the immune response to SARS-CoV-2 infection will help to improve clinical treatments for COVID-19.

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Ecology

Species that can make us ill thrive in human habitats

Richard S. Ostfeld & Felicia Keesing

Does the conversion of natural habitats to human use favour animals that harbour agents causing human disease? A global analysis of vertebrates provides an answer to this pressing question. **See p.398**

Humans have altered more than half of Earth's habitable land to meet the needs of our burgeoning population[1]. The transformation of forests, grasslands and deserts into cities, suburbs and agricultural land has caused many species to decline or disappear, whereas others have thrived[2]. The losers tend to be ecological specialists, such as rhinoceros or ostriches, that have highly specific feeding or habitat requirements and that are comparatively larger, rarer and longer-lived than are non-specialists. The winners are often generalists that are small and abundant and that have 'fast', short lives, such as rats and starlings.

On page 398, Gibb *et al.*[3] show that, worldwide, these winners are much more likely to harbour disease-causing agents (pathogens) than are the losers. As a result, when we convert natural habitats to our own uses, we inadvertently increase the probability of transmission of zoonotic infectious diseases, which are caused by pathogens that

can jump from animals to humans.

Examples of how land-use change increases the risk of zoonotic disease have been accumulating for decades. For example, rodents that amplify the abundance of pathogens that cause Chagas disease, several tick-borne illnesses and a suite of what are termed hantaviral diseases thrive in human-dominated landscapes where other species have been lost[4]. But the generality of this pattern, and the specific mechanisms that underlie it, have been questioned[5].

Gibb and colleagues had to overcome two obstacles in investigating whether, at a global scale, human-caused changes to ecosystems favour vertebrate species that are most likely to cause illness. One challenge was determining which animal species tend to disappear and which tend to thrive, along a gradient from undisturbed, natural habitats to the most human-dominated areas. The authors accomplished this using the database of the PREDICTS project (Projecting Responses of Ecological Diversity In Changing Terrestrial Systems). It contains more than 3.2 million records from 666 studies that counted animals along land-use gradients around the world[6].

The second hurdle was determining which of these species harbour pathogens that can infect humans. To do this, Gibb *et al*. compiled information from six databases that report host–pathogen associations. They found 20,382 associations between 3,883 vertebrate host species and 5,694 pathogens. Unfortunately, finding that an animal and a pathogen are associated does not necessarily indicate that the animal can transmit the pathogen to humans or other animals. Recognizing this, Gibb and colleagues used more-stringent criteria to ascertain host–pathogen associations, including determining whether there was direct evidence of the pathogen existing in the host, and of the host's ability to transmit the pathogen.

The patterns that the authors detected from these analyses were striking. As human-dominated land use increased, so did the total number of zoonotic hosts, whereas the total number of non-hosts declined. In more intensively used areas, both the number of host species and the number of individuals of those species increased, with the latter effect being the stronger of the two. The abundances of rodents, bats and songbirds increased notably in human-dominated sites (Fig. 1). The effect on the abundances of carnivores and primates was more modest. However, host species could be misclassified as non-host species if a lack of in-depth research effort resulted in a failure to detect zoonotic pathogens. To take this into account, Gibb *et al*. incorporated a statistical process called bootstrapping into their analysis. This allowed them to reclassify non-hosts to host status using an approach that included the amount of published research on the species. Their conclusions using this approach remained the same.

ALAMY

Figure 1 | A rat on a city street. Gibb *et al*.[3] report that vertebrates, such as rodents, that can harbour agents that cause human disease flourish in human-altered landscapes.

The COVID-19 pandemic triggered by a coronavirus of animal origin has awakened the world to the threat that zoonotic diseases pose to humans. With this recognition has come a widespread misperception that wild nature is the greatest source of zoonotic disease. This idea is reinforced by popular-culture portrayals of jungles teeming with microbial menaces, and by some earlier scientific studies[7,8]. Gibb *et al*. offer an important correction: the greatest zoonotic threats arise where natural areas have been converted to croplands, pastures and urban areas.

Is it simply a coincidence that the species that thrive in human-dominated landscapes are often those that pose zoonotic threats, whereas species that decline or disappear tend to be harmless? Is the ability of animals to be resilient to human disturbances linked to their ability to host zoonotic pathogens? Gibb *et al*. found that the animals that increase in number as a result of human land use are not only more likely to be pathogen hosts, but also more likely to harbour a greater number of pathogen species, including a greater number of pathogens that can infect humans.

Using a different approach to address the same general questions, a recent study[9] found that mammals that are increasingly widespread and abundant carry more zoonotic viruses than do mammals that are declining, threatened or endangered. These observations support previous research that documents a trade-off between the high reproductive rates associated with ecological resilience and the high immune-system investment associated with lower pathogen loads[10]. In other words, creatures that have rat-like life histories seem to be more tolerant of infections than do other creatures. An alternative, although not mutually exclusive, explanation is that generalist pathogens, which are more likely to spill over into new hosts, tend to adapt to target the hosts they are most likely to encounter over evolutionary time[11]. These hosts are the rats, and not the rhinos, of the world.

The analyses by Gibb *et al*. and others[9] suggest that restoring degraded habitat and protecting undisturbed natural areas would benefit both public health and the environment. And, going forward, surveillance for known and potential zoonotic pathogens will probably be most fruitful if it is focused on human-dominated landscapes.

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