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What happens if we take laboratory mice outside?

Authors:
Jacqueline M. Leung, Sarah A. Budischak, Hao Chung The, Christina Hansen, Rowann Bowcutt, Rebecca Neill, Mitchell Shellman, P'ng Loke, Andrea L. Graham

Associate Editors:
Seda Dawson and Rachel Watson

Abstract

Do you know what a mouse model is? The bodies of humans and mice have a lot in common. So scientists often use mice (*Mus musculus*) as a *model organism* (or stand-in) to *mimic* human diseases and discover how the body can stay healthy. Scientists usually keep mice in super clean environments and test them under constant conditions. But most humans don't live in labs! So how well can a mouse model represent real life? We decided to test how a realistic environment impacts the ability of mice to fight off intestinal worms. We took our laboratory-born mice outdoors to dig in dirt, search for food, and live like wild mice. But when we gave them intestinal worms, the mice that lived outdoors couldn't clear the *infection* as well as indoor mice. In fact, the mice that lived outdoors the longest developed fatter and longer worms in their guts. Our outdoor mouse model shows the effects of the environment on experimental results.

Introduction

Did you know that your body is a walking *ecosystem*? This ecosystem consists of millions of organisms (bacteria, virus, fungi, archaea, and *parasites*) that live in or on the human body. Some of these organisms are harmful and try to take over the body. Luckily your *immune system* defends your body against these *pathogens* by producing *immune responses*. When immune responses are not effective, pathogens can take over the body, making you sick with *infectious diseases*.

Surprisingly, everybody's *susceptibility* (vulnerability) to infections is different. Even when everyone has the same pathogen, some individuals become heavily infected while others stay *resistant* (don't get sick). We know that *genetics* play a key role in *host* susceptibility. But does the environment also impact who gets sick?

Here, we studied the effects of environment on host susceptibility to parasitic worms. We used a mouse model (Figure 1) infected with parasitic worms to mimic billions of people who have worms in their bellies, because it isn't ethical to infect people for a study. Laboratory tests often run under super clean, *microbe*-free environmental conditions. But most of us don't live in labs, so that's not the best way to mimic human lives. That's why we moved our mice outdoors to live like wild mice. This exposed the mice to environmental microbes so that their bodies could mimic the complex ecosystems of human bodies. We hypothesized that life outdoors would impact the parasitic worms in two ways: 1) by impacting worm hatching, growth, and development and 2) by changing the mice's immune responses.

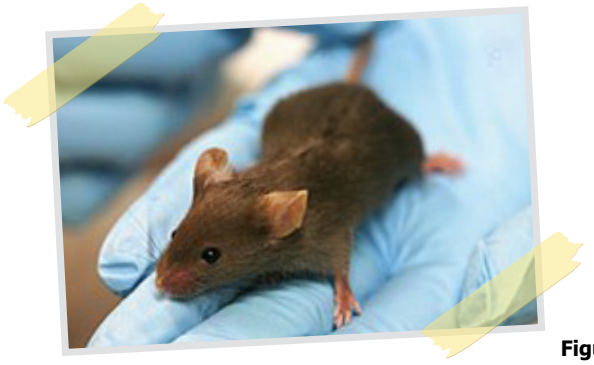


Figure 1:
Scientists have been using mouse models for years to study the human body and diseases. But lab mice live in super clean conditions. This might influence how well these models mimic human lives.

Methods

Outdoor enclosure: We designed 8 escape-proof, predator-proof, open-air pens (Figure 2). Each had plants and insects, a shed for shelter, and water and feeding stations serving lab-style mouse food.

Mice: We used genetically identical mice to eliminate any genetic factor contributing to host susceptibility. We infected each mouse with 200 *Trichuris muris (T-muris)* worm eggs. *T-muris* is an intestinal parasite for mice, and the lab mice we used are resistant to this dose of worms under laboratory conditions.

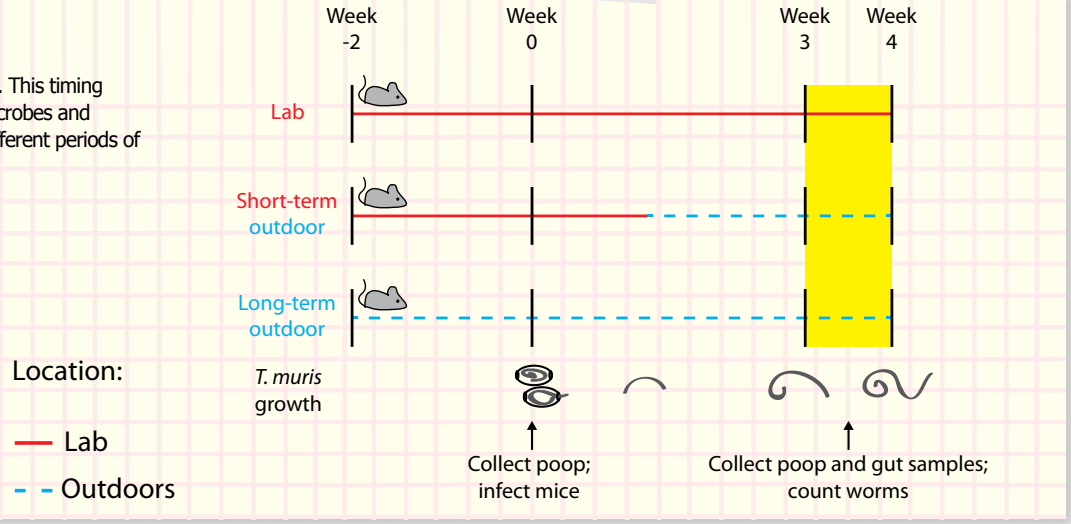
We split the mice into three environmental groups (Figure 3).

1. Lab group: started, got infected and stayed in the lab
2. Short-term outdoor group: started and got infected in the lab, but moved into the outdoor enclosures after *T-muris* eggs hatched (10 days after infection).
3. Long-term outdoor group: started, got infected, and stayed outdoors

Collecting samples: We caught, weighed, and took poop samples from the mice weekly. We identified the organisms in the gut of each mouse and kept track of changes in their gut ecosystem. Finally, we put the mice to sleep and removed their intestines. We counted the worms and measured the worms' length and width to calculate the total worm *biomass* in each mouse. We also took cells from the gut of each mouse to measure their immune responses to worms.

Figure 2:
Our unique escape-proof, open-air mice farm. We installed an electrical fence to keep the predators out. Here the mice faced many challenges that they have never experienced in the lab: finding their way outdoors, digging in dirt, and searching for food.

Figure 3:
Three mice groups and sampling times. This timing helped us to track the effects of gut microbes and immune responses to worms during different periods of *T-muris* growth.



Results

Worm infection: As we expected, the indoor lab mice combatted the worms effectively (with less than 10 worms left in their guts). But the outdoor mice still had up to 105 worms each. And the long-term outdoor group had significantly longer and fatter worms in their guts than the short-term outdoor group. Thus, the longer the mice lived outdoors, the greater the number and biomass of the worms (Figure 4).

Gut microbes: As we expected, there was a big difference between the ecosystems of microbes living in the lab mice and outdoor mice. The gut microbes of the mice that lived outdoors contained different types and a wider variety of bacteria.

Immune responses: The lab mice and outdoor mice also developed different immune responses. The lab mice made the right kind of immune response to fight off the worms quickly. For instance, their immune response was good at poking holes in worms and pushing them out of the gut. The outdoor mice, on the other hand, made an immune response that was better for fighting off bacteria and viruses. This type of immune response did not help them get rid of worm infections, however.

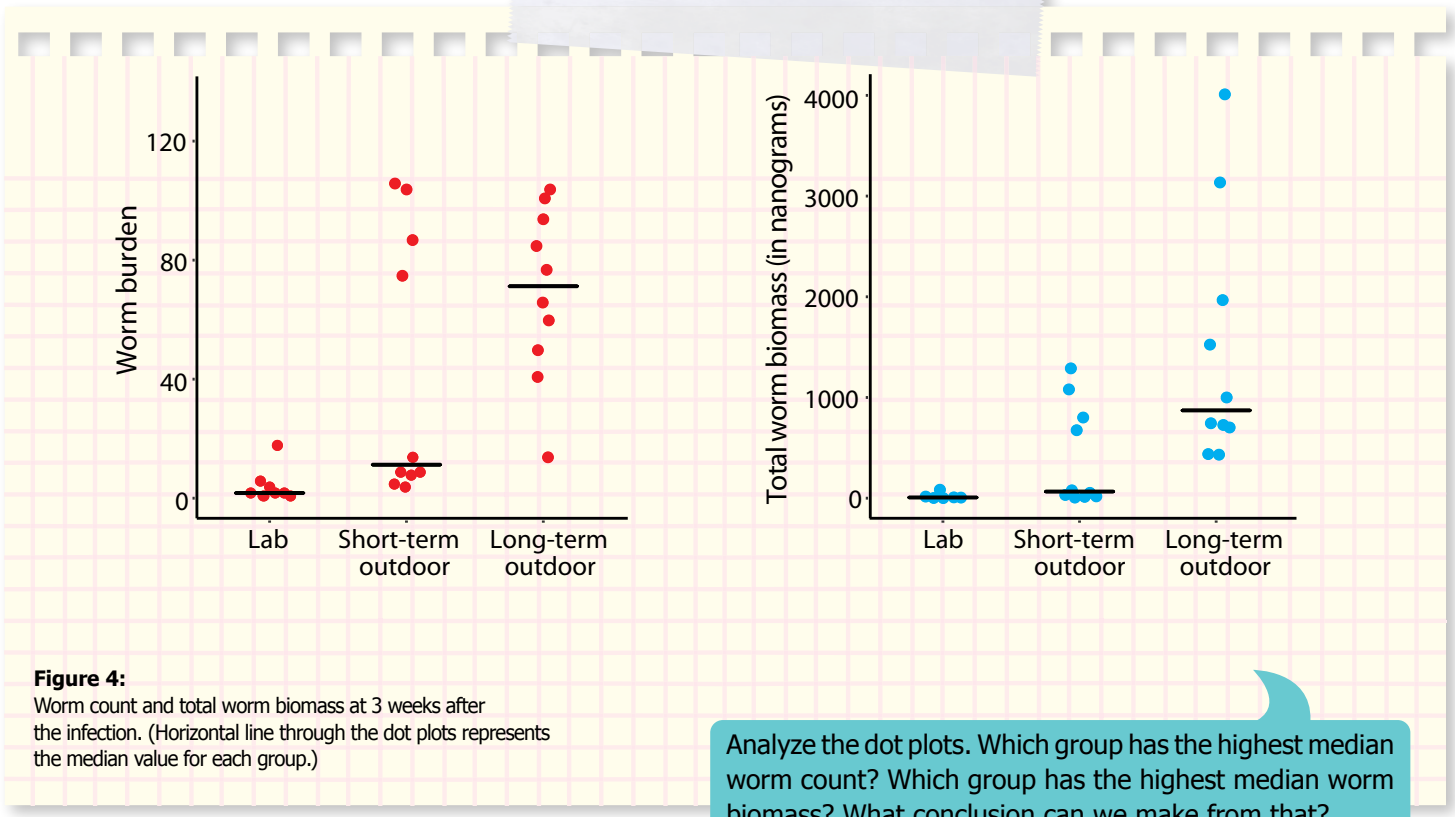


Figure 4:
Worm count and total worm biomass at 3 weeks after the infection. (Horizontal line through the dot plots represents the median value for each group.)

Analyze the dot plots. Which group has the highest median worm count? Which group has the highest median worm biomass? What conclusion can we make from that?

Discussion

Here, we used a mouse model to study how a natural environment changes host susceptibility to intestinal worm infections. In the lab, mice were resistant to the worms. They developed the right kind of immune response a mouse needs to fight off the infection.

However, when we moved the mice outdoors, they quickly became susceptible to the worms! Their gut microbes became more diverse and contained new types of bacteria. Some of these bacteria probably helped trigger worm eggs to hatch and provided food to growing worms. Additionally, changes in

gut microbes impacted the immune systems of the mice. The outdoor mice produced immune responses effective to combat bacteria but NOT worms. As a result, the worms in the outdoor mice grew faster and survived better than the worms in indoor mice. Interestingly, the outdoor mice were still very healthy despite all their worms!

Our results show that the environment significantly changes host gut microbes and immune responses to parasitic worms. It is thus important for future studies to include diverse environmental conditions in their experimental design.

Conclusion

Parasitic worms can live in your intestines and if you are infected with a lot of them, you can get sick. But most people are only infected with a few worms and often do not even realize they are infected. Worm infections are most common in hot and humid regions.

Here are some tips to avoid becoming a host to too many whipworms or pathogenic occupants of the gut ecosystem:

- Wash your hands, especially before handling food.
- Wash, peel, or cook food thoroughly before eating them.
- If you suspect contamination, boil or purify your drinking water.
- Don't walk barefoot in places where the soil may be contaminated with poop.
- Clean animal waste wherever possible (carefully!) and wash your hands afterward.

Glossary of Key Terms

Biomass – the mass of living matter (in grams or pounds, for example).

Ecosystem – a biological community of interacting organisms and their physical environment.

Genetics – the study of characteristics that come from an organism's parents or ancestors, and how the characteristics are passed on.

Host – an animal or plant on or in which a parasite lives.

Immune response – how your body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful.

Immune system – the body's defense against infectious diseases.

Infection, infectious diseases – the invasion of an organism's body by disease-causing organisms. Infectious disease is illness resulting from an infection.

Microbes – organisms that are so small that you have to use a microscope to look at them. (Sometimes they are so small that millions of them can fit in the eye of a needle.) They are bacteria, archaea, fungi or other tiny organisms.

Mimic – to appear similar to something else or to imitate something. In this case we used a mouse model placed in a natural environment to draw conclusions about human infections.

Model organism – a species that has been widely studied, usually because it is easy to maintain and breed in a laboratory. We study these organisms because it is less expensive or more ethical. For example, it wouldn't be right to infect some people with worms just to see how their immune systems respond! Scientific discoveries in model organisms can often tell us a lot about the workings of many other organisms, too. Some common model organisms are mice, fruit flies, zebrafish, the bacteria *Escherichia coli*, etc.

Parasite –an organism that lives inside or attaches to another organism, called the host. The relationship is always the same – good for the parasite, bad for the host. Examples: whipworms, lice, tapeworms, and pinworms.

Pathogen – a virus, bacteria or other tiny organisms that can cause disease in another organism; for example HIV, which causes AIDS; or *Vibrio cholerae*, that causes cholera.

Resistant – having the the power to resist or fight off something else. This word is often used medically, like when someone is resistant to a parasite or other infection: that means they can't get sick from the parasite.

Susceptibility – the state of being easily affected, influenced, or harmed by something. For example, some individuals are susceptible to parasitic worms.

Check your understanding

1 Why did the scientists move the mice outdoors?

2 Why did the scientists test genetically identical mice?

3 Living outdoors exposed mice to natural microbes. How did this environment affect the ecosystem living inside the mice?

4 How did the changes in the mice's gut microbes affect the mice's susceptibility?

5 Scientists use models to study the natural world, to mimic human diseases, and to communicate explanations for what they observe. Although models are very useful and helpful, they may have limitations. Think about a model you used or created in science class. How was the model helpful? In what ways was it limited in representing the real world?

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