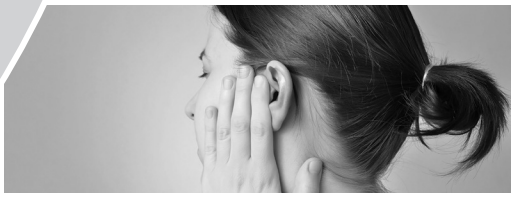
FEATURE ARTICLE

Evolutionary Medicine: An Introduction



CHAY BEESON, ERICA KOSAL

Abstract

Evolutionary medicine is a growing area of research and practice; however, it is not widely discussed in introductory biology courses. Because of the interest in human biology, using evolutionary medicine is a great way to hold students' interest, placing topics in context, making the subject of evolution relevant. Too often students lose interest in learning about evolution because they think it is not pertinent. The pedagogical technique of using case studies in the classroom engages students in a way that will grow their understanding of topics, in this case evolution, as well as helping students with critical thinking and process skills, growing their scientific literacy.

The following case study is appropriate for an introductory biology course that focuses on evolution, an AP biology course, or an introductory evolution course for undergraduates. The case focuses on the evolutionary perspectives of what might be causing human ear infections, as well as the role of beneficial species of gut bacteria in maintaining a healthy immune system. It is advantageous for students to know about natural selection and coevolution before using the case study.

Key Words: *evolutionary medicine; evolution; natural selection; case studies; ear infections; bacteria.*

○ Introduction

Case studies are stories based on data that can be used in the classroom to paint a picture of relevance to students. Instead of giving a traditional lecture to a class, using a case study is more engaging and interactive, with students becoming involved in solving parts of the case study, working through different problems and scenarios. To students, it is like solving a puzzle of sorts. Case studies can be fun for students, providing relevance for topics, and helping students learn concepts more fully as a result. Case studies have been shown to help develop a student's critical thinking skills (Popil, 2011). Additionally, there is evidence that case studies are more effective than classroom discussions and textbook reading when it comes to students learning key biological concepts and that students find they have gained in oral and written communication skills as well as the ability to see connections to aspects of life (Bonney, 2015).

The following case study is for implementation and use in the classroom. The focus is on evolutionary medicine and consists of two parts to work through in class, followed by a third part for homework to reinforce the concepts covered in the case study. Evolutionary medicine is a field where questions surround why the human population is susceptible to particular diseases or ailments due to human evolutionary history, in hopes of providing medical solutions to these problems. Instead of solely focusing on treating a disease or illness once acquired, evolutionary medicine tries to be proactive in understanding how to prevent diseases based on natural selection. For this reason, some people refer to evolutionary medicine as Darwinian medicine, in reference to the intersection between evolution and medicine. This field broadly addresses why natural selection, over evolutionary time, has given us traits that leave us vulnerable to disease and illness.

If traits of humans are influencing the population of a pathogen via coevolution, how might this affect how physicians treat a pathogen that is causing a bacterial infection?

This case study is appropriate for an introductory biology course that focuses on evolution or for an introductory evolution course, both of which are likely at the 100 or 200 level for undergraduates. It may also work well for an AP biology course in high school where an emphasis is placed on evolution.

See the Supplemental Material available with the online version of this article for an answer key to the questions asked in this lesson.

Learning Objectives

Students who successfully complete this case study will be able to do the following:

- Explain the value of using evolutionary medicine to tackle a medical problem.

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- Describe briefly the evolution of the human ear that lends itself to fluid buildup and ear pain today.
- Explain how coevolution works, specifically with respect to human ear infections and bacteria.
- Describe from an evolutionary perspective why beneficial species of bacteria are necessary to keep human systems in balance.
- Interpret data from graphs.

○ Part I: How the Past Can Affect the Present

Dr. Penny Selin had the treatment for every disease and infection. The common cold? She knew all the right remedies for a speedy recovery. A broken foot? An easy fix. Yet, above all else, Dr. Selin's expertise was treating bacterial infections. For as long as she had been a doctor, Dr. Selin had prescribed antibiotics, medications that either kill bacteria or hinder their growth and reproduction. Some of the antibiotics that she prescribed include cephalosporins and fluoroquinolones. Cephalosporins treat strep throat, while fluoroquinolones treat pneumonia, urinary infections, and other infections (Lewis, 2021). And, most of the time, the bacterial infection would completely disappear, never to return!

However, sometimes the antibiotic treatment would not work, as was the case for her most recent patient, Ray Z. Stance.

Ray Z. Stance had a terrible ear infection, even after many doctor visits and prescriptions. Dr. Selin prescribed him clarithromycin, a common antibiotic used to treat ear infections (Lewis, 2021). However, she was surprised when her prescription of clarithromycin did not cure Mr. Stance. Perhaps she should have prescribed a higher dosage of clarithromycin? Or, maybe she should have told the patient to take the drug twice a day, rather than once a day? Unsure of what the problem might be, Dr. Selin consulted her colleagues, who reminded her about evolutionary medicine—a field that considers medical problems through an evolutionary lens. In other words, it is the study of the root causes of why the human body evolved the way that it did.

Dr. Selin's colleague explained how evolutionary medicine might be used to study the origins of, and subsequent problems found with, another organ or structure. "Let me use the illustration of the appendix," the colleague started. He explained that the appendix, a blind sac that is found at the junction of the large and small intestines, was traditionally cited as a "vestigial structure"—a structure that was inherited from an ancestor but, on a superficial level, is no longer serving a necessary function for the body.

"Because a traditional belief was that the appendix was not vital, a common medical practice was to remove the appendix if it became inflamed or irritated. Recent research, however, has called this into question, and we now know that the appendix is designed to protect good bacteria in the gut."

Study of the appendix detected lymphoid tissues inside; essentially, these tissues are sites of lymphocytes and other white blood cells. The lymphocytes are important because they determine the specificity of the immune response. The appendix can therefore protect good bacteria by attacking harmful pathogens. Researchers have found that appendixes of species that contain high average concentrations of lymphoid tissue promote the growth of beneficial gut bacteria in the digestive tract, aiding in the body's immune response (Smith et al., 2017).

Dr. Selin was glad for the reminder and thought, "Evolutionary medicine offers a perspective on how to treat diseases that may lead to insights overlooked without the use of an evolutionary lens. This gives me some great new ideas for my patient. Because the bacteria causing the ear infection seem to be showing antibiotic resistance, I need to consider other contributing factors and how the design of the ear itself may be contributing to the problem."

According to natural selection, an environmental pressure is a factor exerted on a population that allows organisms with a certain genotype within the population to reproduce more and pass on that genotype to the next generation. The individuals with this genotype have an advantage over the other members in the population that do not have this genotype. In other words, the individuals with this genotype reproduce more, resulting in an increase in alleles producing those traits in the next and subsequent generations. How might this help us understand the evolution of ear infections?

An ear infection is an inflammation of the middle ear that occurs when fluid builds up behind the eardrum. It is usually caused by bacteria (Figure 1). The middle ear is located between the eardrum and the inner ear. Small amounts of fluid are normally produced in the middle ear and then drained through the eustachian tube, which connects to the nasopharynx, the upper part of the throat. If this fluid gets trapped, it can cause an earache. This fluid can accumulate when allergies cause inflammation or cause mucus to block the eustachian tubes. And often, an ear infection is preceded by a respiratory infection that is caused by bacteria. These bacteria can move to the middle ear, which can stimulate the buildup of fluids.

Children tend to get ear infections more than adults, due to the smallness of their eustachian tubes, which makes it difficult for fluid to drain out of the ear. This issue is compounded when a child

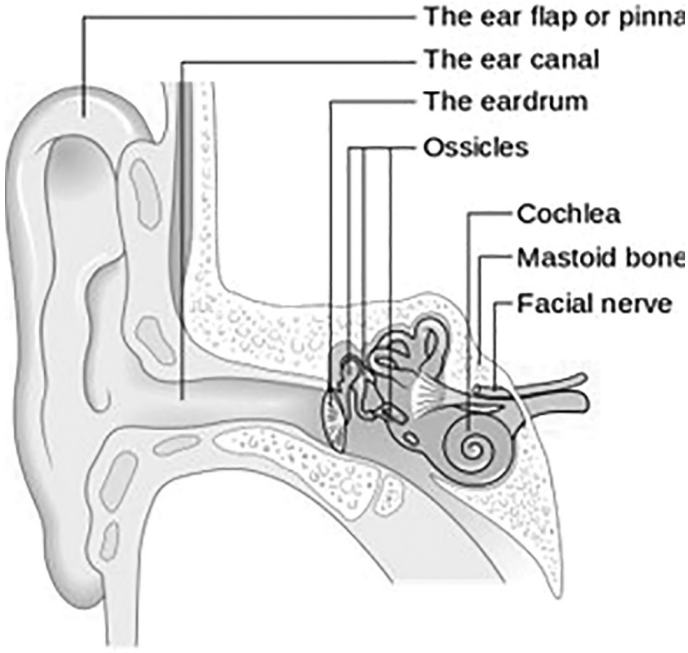

Figure 1. The parts of the human ear. Notice that the eardrum marks the boundary between the outer and middle ear—this is where fluid can become trapped, causing an earache. The cochlea is part of the inner ear, which produces nerve impulses in response to sound vibrations, therefore assisting with hearing. *Cancer Research UK, 2014; available on Wikimedia Commons.*

has a cold or a respiratory illness, because mucus can block the tubes and prevent the fluid from draining at all. Additionally, the immune system of a child is still developing, which makes it harder for children to fight infection compared with adults.

Why did this evolutionary design happen? The evolution of the eardrum and the middle ear is what has allowed mammals to hear through the medium of air. In vertebrate ancestors, the three bones that make up the middle ear were instead parts of the jaw. These reptile-like mammals (called cynodonts) had a primary jaw joint that served for both chewing and hearing. The multiple skeletal remains of an ancient species of mammal have revealed that hearing and chewing separated as a definitive mammalian middle ear was evolving, which likely improved hearing (Mao et al., 2019). Modern mammals have three tiny bones in the middle ear that help them hear. The old-style jaw joint of the earliest ancestors of mammals has evolved to become part of the mammalian middle ear. Many early mammals were small insectivores that probably hunted at night, and having more bones in the middle ear would have improved their hearing, allowing them to detect their prey and to avoid predation themselves. With this improved hearing, mammals could likely detect higher-frequency sounds than other types of animals such as reptiles (Kitazawa et al., 2015). The cavity of the middle ear is thought to form as an extension of the pharynx, which connects to the middle ear with the eustachian tube, and its diameter is dictated by growth of the brain and head anatomy (Tucker, 2017).

Questions

1. Define evolutionary medicine in your own words. Why might it be beneficial to study evolutionary medicine alongside traditional medical fields like immunology or pathology?
2. How do antibiotics influence a bacterial population?
3. What would happen if a few individuals in an infection-causing bacterial population have a gene that allows them to withstand antibiotics? Moreover, what would happen to the bacterial population over several generations?
4. What will happen when bacteria develop antibiotic resistance?
5. How are antibiotic resistance and evolutionary medicine connected?
6. Over evolutionary time, the human middle ear evolved. Summarize the major change that occurred with the middle ear and how that led to a predisposition for ear infections.
7. If eustachian tubes had evolved larger than their current sizes, what possible consequences might be the result of this change. Would ear infections still occur? Regardless of your answer, elaborate.
8. Do you think natural selection will influence the human body such that it will eventually evolve to prevent ear infections? Explain.

○ Part 2: How the Present Can Affect the Future

After collaborating with her colleagues, Dr. Selin prescribed a different antibiotic, amoxicillin, for Ray Z. Stance. Soon enough, the antibiotic worked, and the ear infection that plagued Ray eventually vanished.

A few days later, Ray Z. Stance's sister Prudence showed up to Dr. Selin's office, concerned about the possibility of developing an ear infection herself. So far, she had no medical history of ear infections, due to her cautious nature, yet her brother Ray, as well as her other siblings and parents, had all had ear infections in the past. Attentive to Prudence's concerns, Dr. Selin considered other ways to treat ear infections. Dr. Selin knew there was a relationship between gut bacteria and humans that could influence how a human's immune system functioned, and she wondered if there might be some connection to ear infections.

Coevolution is a form of natural selection in which two species (in this case, humans and bacteria) evolve based on the adaptations of each to the other. Many species of animals coevolve with bacteria that live in their gut. In one study, a group of researchers looked at fecal samples from humans and 59 other mammalian species and sequenced the DNA of bacteria found in those feces. By analyzing the DNA of a sequence of a gene found in every organism (16 S ribosomal RNA), they found that mammalian host diet and phylogeny (evolutionary relationships among species) influenced bacterial diversity. They found the *most* bacterial diversity with herbivorous mammals and the *least* bacterial diversity among carnivorous mammals. Modern humans are omnivorous, and our gut biomes closely match those of other omnivorous primates (Ley et al., 2008). The bacteria living in the guts of humans can act as selective agents on humans, and adaptations of humans can act as selective agents on these bacteria as well. For example, reduced fiber in the diet of humans results in microbes competing for this limited resource. Since fiber is a major factor that defines niche space in the gut, if fiber is decreased, the number of microbe species decreases as well. Antibiotics can also reduce the microbes in the human gut, reducing the number of species present. In turn, the reduced niche space and biodiversity in the gut seem to destabilize how the host can respond and recover from illness. For example, in a study with mice, a reduced-fiber diet led to a decrease in microbe diversity, and the mice failed to recover from antibiotics (see Venkatakrishnan et al., 2021). Dr. Selin was pondering all of this as well and putting things together. She then turned to consider whether replacing some species of bacteria in the host could be beneficial to restore "balance" and therefore help with minimizing ear trouble.

Since ear infections are caused by harmful species of bacteria, with the inflammation and fluid buildup in the middle ear resulting in pain, could a coevolutionary relationship be present here? Could additional beneficial species of bacteria outcompete the harmful ones and minimize ear infections? Dr. Selin was considering as many angles as she could possibly think of. She recalled an article that discussed how inflammation caused by the immune system responding to infection can be aided with probiotics—beneficial species of bacteria found in pill form that supplement the natural microflora of the human gut.

When the gut microflora is harmed, beneficial bacteria naturally found in the human gut are destroyed and cannot aid in healing certain infections, including respiratory ones (Shahbazi et al., 2020). To replace these missing bacteria, probiotics are used. As Dr. Selin was contemplating her patient, she remembered a recent conference she attended where research was presented on the use of probiotics. A group of researchers assessed whether probiotics could help prevent the occurrence and reduce the severity of middle ear infections in children. Seventeen randomized controlled trials with children up to 18 years, with comparisons of probiotics and placebo, were included in the study that involved 3488 children. In this large sample, the number of

children who presented with an ear infection was lower for those taking probiotics than for the control kids, especially for children who were not prone to infections in the first place. Additionally, probiotics decreased the proportion of children taking antibiotics for any infection (Scott et al., 2018). Dr. Selin concluded that probiotics may help keep the gut biome healthy, which is advantageous, as a healthy gut biome aids with the immune system overall and helps prevent pathogen invasion (Shahbazi et al., 2020); various researchers have pointed out the correlation between probiotics and reduced ear infections, but Dr. Selin knew of one study in particular that stood out to her. In this case, the probiotic bacterial species *Lactobacillus rhamnosus* was likely boosting the immune system and preventing the growth of harmful bacteria known to cause ear infections (Gasta et al., 2017).

By evolutionary design, the middle ear is susceptible to fluid buildup in small eustachian tubes. To help prevent harmful bacteria from taking hold in the ear and setting up a chain of events that leads to ear infections, probiotics may be part of the solution.

By studying the ear and ear infections through the lens of evolutionary medicine, Dr. Selin was reminded that keeping the entire human body in homeostasis through any means possible, including introducing beneficial bacteria to the human gut via probiotics, is a key to staying healthy.

With all of this information in mind, Dr. Selin recommended to Prudence that she take several probiotics in hopes that they would make Prudence less susceptible to ear infections. Prudence thanked Dr. Selin multiple times for the visit, feeling at ease knowing that she could take preventative measures against possible ear infections.

Questions

1. As mentioned above, the gut biome is filled with bacteria that can influence the effectiveness of the human body's immune system against pathogens. Describe a plausible mechanism by which probiotics can help with ear infections.
2. The data in Figure 2 focus on a species of bacteria, *Pseudomonas fluorescens*, and its predator, *Tetrahymena thermophila*, a species of protist (Friman et al., 2013). The optical density of the bacteria population (an indirect measurement reflecting the overall size of the population) was measured for six hours at one-hour intervals via bacterial dilutions.
    a. What can be concluded from the data? Does population density/size tell us anything about coevolution despite frequencies of traits or alleles not being present on the graph? Justify your thoughts.
    b. If more data were collected over a longer period of time, for example several months, would they show that coevolution had occurred? If so, what patterns would you expect to see on the graph? Would you need more data or different types of data to make this determination? Explain.
3. If traits of humans are influencing the population of a pathogen via coevolution, how might this affect how physicians treat a pathogen that is causing a bacterial infection?

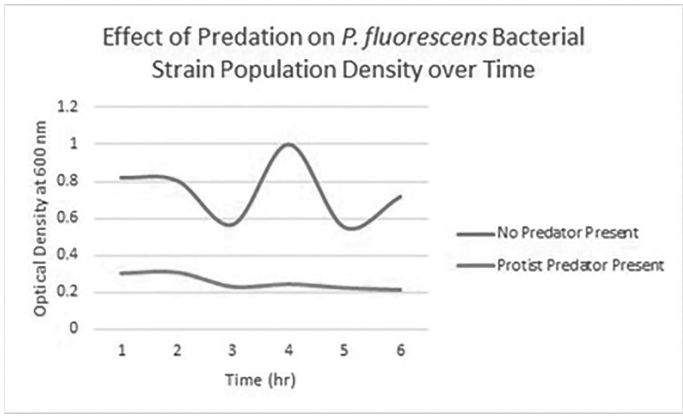

Figure 2. Optical density of *Pseudomonas fluorescens* with (bottom) and without (top) the presence of *Tetrahymena thermophila*.

○ Part 3: Homework

1. To help summarize what has been learned through this case study, create an infographic that covers at least three of the main topics that have been covered (coevolution, evolutionary medicine, ear infections, probiotics, etc.). Be as creative as possible!

○ Helpful Video Clips

The Traits That Spawned the Age of Mammals from PBS, https://www.youtube.com/watch? v=R7IaRQPJHf4

This Ancient Mammal's Ears Were Built for Chewing from SciShow, https://www.youtube.com/watch? v=3jXdKcqkeQ4

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CHAY BEESON (cmbeeson@ncsu.edu) is a University Honors Program Student at North Carolina State University, where he is double majoring in human biology and mathematics. He is a member of the class of 2024. ERICA KOSAL (efkosal@ncsu.edu) is the director of the Life Sciences First Year Program as well as an associate teaching professor of biological sciences at NC State University. Correspondence should be directed to Erica Kosal.