

The Use of a Multimodal Case Study To Illustrate Microbial Genetics, Metabolism, and Evolution: The Emergence of VRSA-1

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Antibiotic Resistance (ABR) is a global concern and while many students are aware of this issue, many of them are unclear on the mechanisms by which ABR may emerge. The mechanism of horizontal gene transfer is something many students are not familiar with. In this curriculum contribution we present 2 versions of an ‘interrupted case study’ that is designed as an introduction to horizontal gene transfer for early major students and as a review case for advanced major students in biology and life sciences. The case is based on an authentic patient who developed infections with both methicillin resistant *Staphylococcus aureus* and vancomycin resistant *S. aureus*. The interrupted case study is appropriate for small and large groups and engages students while content is introduced in a highly structured way. This type of case study can be done by novice and seasoned instructors and lead to considerable learning gains in both introductory and intermediate microbiology courses.

KEYWORDS antibiotic resistance, case study, epidemiology, horizontal gene transfer, evolution

INTRODUCTION

Antibiotics Resistance (ABR) has become a serious and worldwide concern in the last 20 years (1, 2), and many students in the life and health sciences have some level of awareness of this issue and of the importance to be prudent when it comes to dispensing antibiotics to patients (3, 4). However, the mechanisms by which bacteria become resistant are complex and not always clear to students. Concepts that are central to evolution, such as natural selection, mutation and gene transmission are topics that many students struggle with to understand. Many researchers have studied what makes it hard for people to understand and apply these concepts. Coley and Tanner (5) grouped common misconceptions into three categories: teleological reasoning which is based on the assumption of a goal, purpose or function that informs a design (6, 7), essentialist thinking which is based on the “assumption that there is some unobservable essential property common to members of a

category that conveys identity and causes observable similarities among category members (5) (p. 212),” and anthropocentric thinking that is based on attributing human traits to other organisms. Kelemen (8) established that intuitive thinking develops at a young age and Kelemen and Rosset (9), Stern et al. (10) and Briggs et al. (11) found intuitive thinking is still found in adults, even after years of scientific training, although over time students in biology become less receptive to this kind of reasoning (12).

Many researchers studied what biological concepts are hard for students to grasp and found that many concepts that pertain to ABR are troublesome. Queloz et al. (7) found that students in the last years of secondary education struggled with intuitive reasoning about change being intentional, with the randomness in biological processes and with the application of concepts of physics and chemistry in biological processes. Briggs et al. (11) found that many students in biology think that change in organisms occurs only through mutation, and that transfer is only vertical. Richard et al. (12) specifically looked into misconceptions non-major students, entering, and advanced biology major hold on ABR and found that most students hold teleological beliefs on concepts that pertain directly to ABR. Custers and 10 Cate (13), Engelbrecht et al. (14), and Alshamrani et al. (15) found that students tend to forget non-rehearsed and rehearsed basic scientific knowledge over the course of time. For these reasons it is important to revisit basic knowledge and challenge intuitive reasoning throughout a student’s course of study.

Helping students to overcome their misconceptions on ABR can be challenging as these misconceptions are

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widespread and deeply rooted. Pickett et al. (16) and Hartelt and Minkley (17) found that giving students the correct, factual information on biological processes does not help them address their misconceptions, and observe that not much research has gone into how to address these challenges effectively. However, Wingert et al. (18), Ginnobili et al. (19), and Kampourakis (6) propose to use active learning that is designed to help students identify and destabilize their intuitive thinking, for instance through having students verbalize their reasoning and assess it for elements of teleological, essentialist, or anthropocentric argumentation.

In this contribution we describe a teaching case study based on the emergence of VRSA-1, or vancomycin resistant *Staphylococcus aureus*. Evolution of VRSA begins with its penicillin-derivative precursor, methicillin. Introduced in 1959 to treat penicillin-resistant *S. aureus*, reports of methicillin resistance began to appear as early as 1961 (20). Resistance to methicillin is typically incurred from the *mecA* gene, which encodes a penicillin-binding protein that is not sensitive to methicillin. Interestingly, the origin of acquisition of the *mecA* gene is unclear; no other genera have been found to possess this resistance gene (21). Nevertheless, the genetic element conferring resistance to methicillin integrated near the origin of replication in the *S. aureus* chromosome and has several observed variations (21). The complete resistance to β -lactam antibiotics conferred by *mecA* led to the use of vancomycin as an alternative, and a last line of defense against MRSA (22). Vancomycin is one of the oldest antibiotics in use and is effective against many Gram-positive bacteria such as *S. aureus* (23). It inhibits bacterial growth by binding to peptides attached to N-acetyl muramic acids, blocking the action of transpeptidase enzymes that are required to cross-link newly formed peptidoglycan (23). By the late 1980s, while vancomycin was being used for recalcitrant MRSA infections, strains of *Enterococcus faecalis* had been observed to carry transposons on plasmids which bore resistance to vancomycin via the *vanA* 5 gene cluster (23). This gene cluster encodes genes that change the terminal peptides attached to N-acetyl muramic acid, which prevents vancomycin binding. Here, we describe the first patient to present full vancomycin resistance in a hospital setting, leading to development of VRSA-1.

We have designed this teaching module for 2 different classroom settings. The first version is intended for use in introductory microbiology or biology courses and focuses on the general concepts that play a large role in ABR, such as epidemiology, horizontal gene transfer, and antibiotic use. The second version was designed for upper-level students and focuses on the physical and chemical processes that come into play in processes that lead to ABR, linking antibiotic mechanism of action, horizontal gene transfer, and evolution. Both versions of this case study were designed according to the principles of the staged 'interrupted case method', where information is given piecemeal to students, and they work toward the solution to a problem (24). To facilitate the use of this case study in large classrooms, we designed both versions as 'clicker cases'. The clicker questions in each version were designed to reveal and explicate misconceptions on evolution, mutation, and gene transmission. This method is well suited for a single class

period and manageable for instructors with little experience in active learning. Both versions of this exercise describe a published medical case study revealing the details of the emergence of vancomycin resistance in *S. aureus* in the United States (25). The multifaceted approach to this medical case study facilitates classroom discussion of antibiotic resistance at multiple points in a biology or microbiology student's program of study.

Intended audience

We chose to develop 2 versions for early and advanced biological science students, as literature showed that misconceptions on principles of evolution and ABR are highly persistent and even advanced students still struggle with some of these concepts. Both sections are 50-minute 'interrupted case studies' with clicker questions that are appropriate for small and large lecture-style classes. They are both built on the same authentic case report of a single patient who developed VRSA after a long history of antibiotic use (25). Version #1 (Introductory Biology) is intended for early biology students and serves as an introduction to the principles of antibiotic resistance, epidemiology, and horizontal gene transmission, and was part of a 100-level introductory microbiology course. The second, advanced, version is intended for third year students in the biological sciences and was constructed as a review case to revisit and connect several Vision and Change concepts, including structure-function, genetics, evolution, and metabolism through an authentic example.

Learning time

Both versions are designed to be taught in a single 50-minute lecture. The students in Version #1 (Introductory Biology) were required to complete a short self-guided study of epidemiology and antibiotics and pretest before class (S1, S2). This would typically require 30 to 45 min and would not be graded. The students in Version #2 (Advanced Biology) were instructed that the case study would be a review of basic principles of antibiotic use, evolution of antibiotic resistance, microbial genetics, and metabolism. They completed a short pre-exercise quiz (S8). This was graded for completion rather than correctness. If this exercise is due before the case study day, results can inform the instructor of the strengths and weaknesses of the class regarding the learning objectives.

Prerequisite student knowledge

For the first version of this case study, introductory biology students were required to complete self-guided studies on epidemiology and antibiotics. The Version #2 advanced students are expected to have basic knowledge of cell structure and function, information flow (e.g., central dogma and horizontal gene transfer), and metabolism (cellular respiration). As this lecture was part of a course, students were asked the week before to refresh their knowledge of these topics and complete a quiz (S8).

Student learning objectives

The learning objectives of both sections combined several of the fundamental statements that pertain to mutations and horizontal gene transfer, the human impact on the evolution of microorganisms through influence on the environment, how genetic variations can impact microbial functions, and how microorganisms interact with hosts. We achieve this by discussing how the epidemiologists and clinical staff applied the process of science in this case study.

ASM fundamental statements

Some ASM fundamental statements include:

2. Mutations and horizontal gene transfer, with the immense variety of microenvironments, have selected for a huge diversity of microorganisms.

3. Human impact on the environment influences the evolution of microorganisms (e.g., emerging diseases and the selection of antibiotic resistance).

15. Genetic variations can impact microbial functions (e.g., in biofilm formation, pathogenicity and drug resistance).

28. Ability to apply the process of science, meaning to demonstrate an ability to formulate hypotheses and design experiments based on the scientific method.

The learning objectives for Version #1 (Introductory Biology) and #2 (Advanced Biology)

Students will be able to:

1. Interpret the results of a Kirby-Bauer disc diffusion assay.
2. Explain the process of contact tracing and interpret results to identify methods for novel disease spread.
3. Analyze the course of treatment for a patient to identify risk factors for the emergence of novel antibiotic resistant strains.
4. Describe how the use of antibiotics selects for resistant strains within a population in terms of fitness cost for resistance.
5. Compare and contrast horizontal and vertical gene transfer as methods to spread antibiotic resistance.

However, Version #2 (Advanced Biology) includes an additional learning objective:

6. Describe the action of different antibiotic classes in terms of bacterial cell physiology, and compare and contrast mechanisms for bacterial resistance.

PROCEDURE

Materials

Version #1 (Introductory Biology). The materials include:

1. Homework assignments – students were given a homework assignment (S1) which consists of a slide deck with information and thought questions that help students reflect on their understanding of the materials.
2. Pretest and posttest – there are open-ended pre and posttests available (S2), with a rubric to assess the answers for completion. The posttest includes questions on the student experience with the format of the lecture.
3. Cast cards – There are 3 sets of 4 cast cards that represent four stakeholders in the process: the patient, health care providers, family and friends, and colleagues of the patient in a real estate office (S3). The first set introduces the case, the second set shows initial test results in these four stakeholders and the third set reveals the conclusions that are based on a second set of test results that are introduced by the instructor (S4).
4. Slide deck – we prepared a slide deck with thought questions and slides on gene transmission (S5). These slides could also be used as a homework assignment, rather than as a section in the lecture. We also prepared a document with the lecture notes and pointers to timing of the activities (S6).

Version #2 (Advanced Biology). The materials include:

1. Slide deck – we prepared a slide deck with clicker questions that are designed to assess knowledge and scientific reasoning and to integrate topics that are placed in the lecture at strategic moments where new information is given as part of the interrupted case study (S7). The notes of the slide deck contain the correct answers to the questions and some explanation. The multiple-choice clicker questions are integrated in the slide deck and could be transferred into any clicker system.
2. Pre- and posttest – We designed a multiple-choice assessment to probe student understanding of the learning objectives before and after instruction. The posttest included additional questions on student experiences with the case study and perceptions of learning and engagement (S8).

Student instructions

In Version #1 (Introductory Biology), students work on self-guided homework assignments that include thought questions for them to reflect on their mastery of the subjects. The work is not graded but used during the in-class discussions.

The classroom activity in both versions is instructor-led. In Version #1 (Introductory Biology), the instructor works with a modified jigsaw method where students work in groups of 4, yet the groups stay the same during the lecture so

students do not need to move through the classroom (26, 27). Every student has a role in their group (the cast cards match these roles), and, in the classroom discussion, the instructor sometimes calls on a group and sometimes calls on all students who have a particular role in their group.

In Version #2 (Advanced Biology), prior to the lecture, students are asked to review the topics of cell structure and function, information flow, and metabolism. Prior to starting the interrupted case study, students work through a pretest individually. This pretest (S8) is graded based on completion, and is used to orient the students to the learning objectives and refresh their knowledge of several topics covered in previous course work. Once all the students complete the pretest, the class begins the interrupted case study. We use a modified team-based learning (TBL) approach that allows students to expose inconsistencies between their current understanding and new information (28, 29). In this lecture, we created groups of 2 or 3 students and ask the students to answer each clicker question alone, then explaining their responses within their group. The instructor then called on multiple groups while discussing their answers with the entire class. The case study and clicker questions describe the medical care the patient received, the mechanism of action of several different antibiotics, and the emergence of a new multidrug-resistant strain of *S. aureus*, VRSA-1.

Faculty instruction

Both versions of this activity are instructor-led and are set up as an 'interrupted case study', which means that the narrative of the case is staged and the instructor provides limited information to the students, who discuss the information they receive to find and interpret clues on how to move the case forward. Version #1 (Introductory Biology) was designed for a small group of students, with students working in groups of 4. This works best if groups are created by the instructor in advance but can work with *ad hoc* short-term groups as well. Supplement 6 contains the lesson plan with timing for all activities. Students were working in groups of 4, so it was important to make sure students could be grouped together, so they could easily share the information on their cast cards and discuss. In the class discussions, the instructor could call on groups, as well as on all students with a particular role in their group. It was important to give clear instructions to the groups about the expectations of each role, the discussion questions, and how long they had for each group activity. Additionally, it was important to check for understanding and questions regularly. The students filled out a post-case study survey to assess the learning gains as a formative assessment (S2).

Version #2 (Advanced Biology). The instructor led the interrupted case study, which was designed to be taught in larger classes within fixed-seat lecture halls. Students worked cooperatively in small teams of 2 or 3 students who were sitting close to each other (30). Students explained and discussed their answers to the clicker questions after they answered by themselves, and the instructor discussed

the answer options with the class before discussing both the right answer, and the reasoning behind the distractors. It was important to make sure there was time for a summary and debrief at the end of the lecture. S7 contains the slide deck, the lecture notes, and the clicker questions.

Determining student learning

The interrupted case study format created pauses where students could ask questions every time information was presented. With every new piece of information that was presented, the instructor created opportunities to ask questions to the students. In a small class, this can be done by posing thought questions that elicit classroom discussion. In large classes, the clicker questions provide a way to discuss misconceptions and intuitive reasoning students may have. The thought and clicker questions in these slide decks were designed to bring out common misconceptions in the areas of gene transfer, mutation, and antibiotics.

DISCUSSION

Field testing

Version #1 (Introductory Biology). The students reported that they had not been previously exposed to epidemiology as a field nor to antibiotics resistance, which shows us that these are important topics to cover. The instructor paid specific attention to the timing of the various activities in the lecture. His observations are included in the final notes on timing in the lecture slides. He also found that the third set of cast cards should be handed out folded to retain the surprise effect of the outcome of the case.

Version #2 (Advanced Biology). In this lecture, it turned out that students took longer to answer the clicker questions than anticipated, which meant that one clicker question remained unanswered. This question was designed as a reinforcer of topics that had been discussed just prior to the question. Thus, this question became a part of the debriefing of the case, which is the last element of this lecture.

Evidence of student learning

For both versions, students were given a test before and after the lecture to measure their understanding of core topics in microbiology, specifically in areas of gene transmission, human influence on the evolution of microorganisms, the impact of variations, and microorganism/host interaction (S2 and S7).

In the first version of this case study, 9 students participated in the pre and posttest. In the second version, 44 students participated in the pre and posttest. We used SPSS 26 to analyze the data (31). In Version #1 (Introductory Biology), the tests consisted of open-ended questions that were coded for correct use of terms and argumentation by

TABLE I
Evidence of student learning. Students in both the introductory (Version #1) and advanced class (Version #2) had higher scores after instruction as measured by mean score and normalized learning gains

	Mean	SD	t-value	Sig. (2-tailed)	r (effect size)	Normalized learning gains
Version #1 (Introductory Biology) (n = 9)						
Pre test	5.16	2.03	-4.50	0.002	0.71	0.67
Post test	7.72	1.37				
Version #2 (Advanced Biology) (n = 44)						
Pre test	6.66	2.11	-4.72	0.000	0.34	0.22
Post test	7.84	2.19				

a TA. The tests for Version #2 (Advanced Biology) were multiple-choice.

The sample size for Version #1 (Introductory Biology) was very small, which may skew the normalized learning gains (32, 33) and the effect size. However, in both versions, there is a significant difference in knowledge about the topics covered in the interrupted case study lecture (Table I). The effect size of 0.3 to 0.7 indicates this exercise had a small to medium effect (34).

Student perceptions

In Version #1 (Introductory Biology), almost all students responded positively to this case study. All of them communicated that the concept of horizontal gene transfer was new to them, and how they are surprised about how easy it is to develop resistance. The case raised the students' interest in the topic: they all mentioned topics they would like to pursue further after this introductory case study, ranging from wanting to learn more about the mechanisms of horizontal gene transfer to applications in agriculture. The students enjoyed the combination of lecturing and group work. One student remarked they would have appreciated more time to discuss horizontal gene transfer, while another student mentioned they would have liked more clues to draw their conclusions.

In Version #2 (Advanced Biology), we surveyed students about their perceptions of the case study in a series of 3 questions included in the post test. In the first question, the students unanimously stated that the case study helped them apply the material they learned in the course to a real-world example. When asked if they felt they learned better with case studies, a large majority of the students stated that they learned better. When asked about the frequency of case studies in general microbiology, nearly 75% of the students would like to have 1 case study every week during the course if it addresses course-relevant topics.

Possible modifications

Version #1 (Introductory Biology). Instructors can vary their application of the Gene Transfer slide deck.

Currently, this topic is taught in the lecture, though it could also be given as a homework assignment, which would free up time in the lecture to apply the content of the slide deck to the case. We decided to include these slides in the lecture to use the cognitive dissonance induced by the case to explain horizontal gene transmission, and to be able to pace it to the level of understanding of the students in the group.

Another modification could be to create a slide deck with an outline of the program, the learning goals of the lecture, and the lab results. By including the learning goals, the instructor can evaluate the learning gains of the lecture at the end by asking the students to reflect on them. Some students might benefit from more guidance while discussing the lab results.

The thought questions can be used and assessed in many ways. One option is to require written reflections on epidemiology and antibiotics, and assess these prior to class or ask some clicker questions at the beginning of class.

Version #2 (Advanced Biology). We asked the students to review the topics of cell structure and function, information flow, and metabolism before the lecture. This could be an option to create a homework assignment that is more structured.

This case study provides an excellent opportunity to discuss equity in medical care. One adjustment that could be made is the addition of a homework assignment after the lecture for students to reflect on the impact of equitable access to care on the patient and public health. The patient had multiple surgeries and chronic health problems – they needed help with wound care, home health care, and extra social support which was not available to them. The lack of this type of care aggravated the situation.

The format of the interrupted case study is well suited to be used in online environments. It is effective in capturing students' attention. In small and medium sized classrooms, the instructor could use break out rooms to facilitate group discussions. Since groups have clear instructions, students can be called on as a group and as representatives of their roles, meaning there is a certain level of accountability for students to use the breakout sessions effectively. In Version #1 (Introduction), the instructor will have to post the cast cards on an online platform or in the chat in a way that students have access to the

information that pertains to their own role only, as this makes the discussion more meaningful.

The 2 versions of this case study also illustrate some flexibility in its utility as a teaching case. In Version #1 (Introductory Biology), it is used as an introduction to several concepts (e.g., horizontal gene transfer, evolution, antibiotic resistance), and our goal with Version #2 (Advanced Biology) is to review and contextualize concepts that were discussed throughout the term (microbial genetics, metabolism, antibiotics, and evolution). Both versions could also be combined to create a middle-level interrupted case study lecture by integrating the slide decks and adjusting the level of the slides to the appropriate level of the class. This case could also be used to teach content on cell envelopes and peptidoglycan, metabolism, and horizontal gene transfer if this information is added. These additions, however, would likely increase the time needed for this case study from a single 50-minute class period to 2 class periods.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PPT file, 8.1 MB.

SUPPLEMENTAL FILE 2, PPT file, 3.8 MB.

SUPPLEMENTAL FILE 3, PPTX file, 2.6 MB.

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