

Harnessing the Power of the Immune System: Influenza Vaccines

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Abstract

Because most people have been infected by and/or immunized against influenza, students should know how the immune system responds to the infection and how vaccines protect against disease. Vaccines have played an instrumental role in disease prevention and control since the late 1700s, but the mechanism by which they work is still a black box to many people. Therefore, we designed this lesson to provide an introduction of the immune response to a pathogen, vaccines, and the process involved in testing human-grade vaccines. The course in which this lesson was taught focused on homeostasis and using feedback loops to illustrate factors affecting homeostasis. This lesson incorporates feedback loops to demonstrate how the immune system maintains organismal homeostasis and how vaccines contribute to this. The learning goals of this lesson are to collaboratively generate hypotheses, design experiments, and describe how vaccines harness the power of the immune system to protect against disease. This activity uses various student-centered strategies, including think-pair-share, group discussions, and jigsaw. We have successfully implemented this activity in a biology class for a combination of majors and non-majors, after which students reported being more knowledgeable about how vaccines protect against disease. Further, students can have sophisticated discussions about the benefits and risks of vaccines, which is an especially meaningful outcome, given debates regarding their side effects. In the current climate of a pandemic and the need for an expedited vaccine for SARS-CoV2, a better understanding of how vaccines work and are developed is more important than ever before.

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Supporting Materials: Supporting Files S1. Stress and Immune System – Introduction Influenza Pre-Class Worksheet; S2. Stress and Immune System – Influenza In-Class Worksheet; S3. Stress and Immune System – Influenza II In-Class Worksheet; S4. Stress and the Immune System – Inflammation Pre-Class Worksheet; S5. Stress and the Immune System – Pre-class Assignment Grading Rubric; S6. Stress and Immune System – Introduction Influenza Pre-Class Worksheet Answer Key; and S7. Stress and the Immune System – Inflammation Pre-Class Worksheet Answer Key.

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Learning Goal(s)

Students will:

- create a feedback loop to illustrate how the immune system functions to maintain homeostasis of the human body.
- evaluate the efficacy of vaccines in animal model systems and human trials.
- define variables that affect the beneficial outcome of influenza vaccines.
- ask questions, formulate hypotheses, design experiments, analyze primary data, model, and communicate results about factors that impact vaccine efficacy.
- assess various model systems for experimentation based on accessibility, finances, and ethics.
- reevaluate feedback loops based on data analyses and explain their relevance in computational and mathematical modeling of biology, specifically in the context of vaccine design.

Learning Objective(s)

Students will be able to:

- discuss how the immune system functions to maintain homeostasis of the human body, especially during an influenza infection.
- describe how biological factors, such as sex and age, affect immune system functions.
- propose hypotheses regarding the impact of sex hormones and age on the immune response to influenza and vaccine efficacy based on feedback loops.
- design experiments with mammalian model systems and immunology-based lab assays to test hypotheses.
- analyze primary data that support or refute proposed hypotheses.
- communicate findings through poster presentations in a manner similar to a research conference.

INTRODUCTION

The generation and production of vaccines is a long and stringent process (1), but it is often considered mysterious by the average person. For example, many people are wondering why it took a year to develop a SARS-CoV2 vaccine and why extensive clinical trials were necessary before mass distribution (2). Moreover, the use of vaccines has become a point of contention in American society (3), which increases students' interest about them and places the onus on educators to address the value of vaccines with scientific evidence. This lesson deepens students' appreciation of vaccines by teaching them how the immune system responds to a vaccine to maintain organismal homeostasis. In this lesson, which we developed before the coronavirus pandemic began, we focus on influenza because many students are familiar with flu shots, even if they have not received one, and because the flu perturbs a person's homeostasis.

We taught this lesson in a seminar course for second year students from multiple majors. The specialty course focused on homeostasis and feedback loops in three different areas of biology: ecology, organismal biology, and molecular biology. Homeostasis is a self-regulating process that allows a system to maintain equilibrium while adjusting to dynamic external factors (4). An organism encounters perturbations and stressors throughout life that often interrupt homeostasis. In vertebrate biology, several systems contribute to the maintenance of organismal homeostasis, including the endocrine, nervous, and immune systems (5). The immune system is especially noteworthy as it protects against foreign invaders, such as bacteria and viruses. Feedback loops are a simple way to understand homeostasis and the forces that contribute to or detract from it (6). Feedback loops are a natural mechanism to maintain homeostasis and rely on negative and positive feedback. Negative feedback serves to dampen a response to perturbation while positive feedback serves to amplify a response. Homeostasis is generally maintained by negative feedback loops that act to oppose a stressor and ultimately bring the system back to its target value, or setpoint. Feedback loops are important for all biological systems and their use in this activity allows students to understand the topic of this lesson and appreciate their use in other scientific contexts. Examples of feedback loops in biology are presented in "Pre-Requisite Teacher Knowledge: Homeostasis and Feedback Loops." This lesson was developed for the part of the course on organismal biology and focuses on how feedback loops model ways in which the immune system maintains homeostasis in the human body.

We aligned our learning goals with core competencies outlined in Vision and Change (7). We specifically attempted to address "ability to apply the process of science," "ability to use quantitative reasoning," and to a lesser extent, "ability to use modeling and simulation" and "ability to understand the relationship between science and society."

Few lessons and/or case studies that are designed for undergraduate biology courses have addressed vaccine design and immunology behind vaccine efficacy (8-12). In our lesson, students were provided with a specific toolkit to design experiments and worked as a team to generate and test influenza vaccines. Students were asked to interpret primary

data (derived from (13-16)) and compare their experimental designs to those from the primary literature. This exercise powerfully engaged students to think critically about various factors that play a role in vaccine research, including cost-effectiveness, time, and animal model systems.

Intended Audience

We developed this lesson for undergraduate biology and non-biology majors at a public, four-year, master's regional university. This activity can be used for both introductory and advanced biology courses, with slight modifications to the scaffolding questions for advanced courses (See Teaching Discussion).

Required Learning Time

Pre-class work takes between 30 and 45 minutes (Supporting File S1. Stress and Immune System – Introduction Influenza Pre-Class Worksheet). The rest of the lesson was completed in 3 hours that were distributed across two class meetings. However, we think the amount of time required would probably be less in an advanced biology course. Answering the guided questions takes approximately 2 hours (Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet), and the optional poster session (Supporting File S3. Stress and Immune System – Influenza II In-Class Worksheet) takes approximately 1 hour.

Prerequisite Student Knowledge

This activity was designed for biology majors and non-majors and some specialized scientific knowledge is required. All students should have a basic understanding of how to interpret line and bar graphs--but if they do not have this skill, then more time can be added to the lesson for instructors to teach it. Students who have taken other biology courses may have more insights into different animal model systems and testing of vaccines, which are covered in this lesson. Students should have some background knowledge on inflammation, homeostasis, and hormesis, as these concepts appear in the activity. To prepare for class, students should review the following materials:

- "Inflammation - Inflammatory Response - What Is Inflammation in The Body?" <https://www.youtube.com/watch?v=XSTagULmTFA>
- "How the Immune System Responds to Influenza Virus" <https://www.youtube.com/watch?v=z6TWFHf0g1s>
- "Homeostasis and Negative/Positive Feedback" <https://www.youtube.com/watch?v=lz0Q9nTZCw4&v=en>
- An optional, but highly recommended, video for students to review is "COVID-19 Immunology 101 for Non-immunologists" <https://www.youtube.com/watch?v=jeN8v5I5VNA>. This video provides an excellent introduction to immunology and COVID-19, including how SARS-CoV2 affects the immune system and the principles of herd immunity, vaccination, and social distancing.
- Supporting File S1. Stress and Immune System – Introduction Influenza Pre-Class Worksheet. Homework assignment to prepare students for lesson (Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet).
- Supporting File S4. Stress and the Immune System – Inflammation Pre-Class Worksheet. Homework or

classwork assignment administered prior to the lesson (Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet), to introduce concepts in immunology.

Prerequisite Teacher Knowledge

Instructors should have a basic understanding of homeostasis, feedback loops, inflammation, immune responses to vaccines and infection, and vaccine design.

For those who require more background information on homeostasis in the human body and feedback loops, the following materials are recommended (in addition to the student review materials listed above):

- The Immune System in the Maintenance of Organismal Homeostasis (17). This reference provides an overview for instructors to better understand the roles of the immune system in regulating homeostasis of the human body. As it provides more detail than the background knowledge required for this lesson, we recommend reading the introduction, which provides information on homeostasis, homeostatic range, and stress responses, and the section on inflammation to better understand how the immune system works to preserve homeostasis in humans.
- Homeostasis and feedback loops: <https://www.khanacademy.org/science/high-school-biology/hs-human-body-systems/hs-body-structure-and-homeostasis/a/homeostasis>. This resource provides an excellent summary of homeostasis in a biological system and how positive and negative feedback play a role in maintaining homeostasis. There are also examples of positive and negative feedback loops, which may be helpful to instructors.

Instructors may also want to further familiarize themselves with the fundamentals of vaccine immunology, how vaccines are made, and animal model systems with the following resources:

- CDC guide to Vaccines: The Basics (<https://www.cdc.gov/vaccines/vpd/vpd-vac-basics.html>). This resource provides a summary of three major ideas:
 1. It covers how vaccines prevent disease in lay terms and introduces some of the ingredients and side effects of vaccines.
 2. It provides an overview of the history of vaccines in the form of animations, beginning with “how vaccines work,” which outlines how the immune system responds to vaccines. The “types of vaccines” and “how vaccines are made” animations are also covered under the history of vaccines and introduce the various types of vaccines, such as inactivated, attenuated, and recombinant. Inactivated vaccines are made from a bacteria or virus that has been killed via chemical or physical means. Attenuated vaccines are made from a bacteria or virus that has been made to be less virulent, often by mutations that render it less harmful. Recombinant vaccines are made by synthesizing small portions of a pathogen that elicit an immune response. Another animation discusses

herd immunity in a segment entitled “how the vaccinated protect the unvaccinated.”

3. It describes the ingredients of vaccines and immunization schedules in the United States, using preventable diseases in the US, such as polio and measles, as examples of successful vaccination programs.
- Fundamentals of Vaccine Immunology (18). This resource provides a detailed summary of immune system components, including the types of immune cells, such as B and T lymphocytes, as well as cell-derived mediators, such as antibodies and cytokines. Further, the resource discusses types of immunizations and current/under development vaccine types. Within this reference, there is an excellent overview of how the immune system works to mount a robust response to different types of vaccines.
 - Use of animal models in vaccine development (19). This resource discusses several animal model systems used in vaccine research, such as mice, pigs, and horses, and the advantages and disadvantages of each. Further, the criteria for appropriate animal models are addressed.

SCIENTIFIC TEACHING THEMES

Active Learning

Students actively engage in learning concepts through a self-paced homework assignment and groupwork during class time. The group work strategies used in the lesson included think-pair-share, collaborative experimental design, whole class discussion, jigsaw, and poster session.

Prior to class, students complete a homework assignment that introduces them to how the immune system responds to influenza. The homework engages all students through a video that introduces the immune system and ties in concepts that were previously addressed in the course, such as inflammation. This exercise, therefore, not only introduces new concepts that are expanded upon in class, but also builds on previous knowledge. The homework assignment also introduces vaccines and the length of time that is needed to develop them. Students are asked to think about why it often takes more than a decade to develop and manufacture a vaccine, which is an especially relevant topic amid the development of a SARS-CoV2 vaccine.

In class, we review concepts from the homework assignment. This check-in ensures that students’ questions are answered and helps students who did not complete the homework learn the basics that set the stage for the next activity. This is a whole class discussion facilitated with random call. We use random call because it provides instructors with a more accurate perception of class-wide knowledge retention and understanding. Further, as females tend to voice their opinions less frequently in class than their male counterparts in undergraduate biology courses, we use random call to equalize classroom participation (20).

Next, we implemented another inclusive strategy, think-pair-share. Here, students first work independently to draw a model to relate different principles that were covered in their homework assignment and from previous classes, specifically influenza, immune response to influenza, homeostasis,

antibodies, hormones, age, and vaccines. Students compare their models to those of their neighbors and discuss the differences that exist between them. Lastly, students share any notable differences between their models as a class. We utilized think-pair-share in this activity to allow students to think critically about concepts that were previously introduced and express their thoughts with peers to promote social learning.

We then transitioned into groupwork for the majority of class time. A jigsaw is a cooperative learning technique in which students are assigned into groups and the assignment is broken into pieces that must be assembled by the groups for a complete understanding (21,22). We used this technique to illustrate a collaborative research environment that is driven by teamwork. The class divides into four groups with four students in each group based on the number designation on their worksheets. For example, one group would have 4 students with worksheets designated “A1”, “B1”, “C1”, and “D1”. In these small groups, students work together to develop a hypothesis based on content covered in the homework assignment. The instructor randomly selects a representative from each group to articulate the team’s hypothesis. Subsequently, students design experiments to test the hypothesis and review primary data. This exercise allows students to develop skills aligned with core competencies of undergraduate biology, such as experimental design and data interpretation. During the final part of the jigsaw, the groups reshuffle such that all students with the same letter designation are in the same group, which allows one student from each expert group to disseminate student expertise. For example, a reshuffled group would have four students with worksheets designated “A1”, “A2”, “A3”, and “A4”. Students in the reshuffled groups describe and discuss their findings, which provides each student with the knowledge of each topic in the activity.

Finally, the expert groups reconvene and the lesson concludes with a “poster session” in which each group presents to the class in order to encourage peer discussion. This exercise allows students to creatively describe their experimental approach and present their efforts in a manner similar to a research conference. To ensure that students in the audience are engaged during this session, they are encouraged to ask questions and write down key aspects of the information that is shared, as outlined in Supporting File S3. Stress and Immune System – Influenza II In-Class Worksheet.

Assessment

Each of the strategies discussed above in Scientific Teaching Themes: Active Learning represents an opportunity for formative assessment to measure students’ progress toward the learning goals. During class, students write answers to the questions on the worksheet during both the individual brainstorming session and the groupwork session. As we circulate through the classroom, we listen to conversations based on the worksheet questions and make comments about what we hear and what we read on the worksheet as necessary and provide immediate feedback to students. We assess learning and student equity within groups based on participation during the poster session.

For summative learning, the students submit the homework prior to class via the learning management system; we evaluate

the assignment for accuracy, effort, and level of completion (Supporting File S6. Stress and Immune System – Introduction Influenza Pre-Class Worksheet Answer Key and Supporting File S7. Stress and the Immune System – Inflammation Pre-Class Worksheet Answer Key). We evaluate the written responses on the worksheet after class as another form of summative assessment. Our rubric for the worksheets is based on the thoroughness, effort, and accuracy of the answers (Supporting File S5. Stress and the Immune System – Pre-class Assignment Grading Rubric).

Inclusive Teaching

This lesson was designed to include all students and acknowledge the value of diversity in science in multiple ways. We use think-pair-share to include students who are not comfortable with classroom-wide participation. Think-pair-share is a collaborative learning technique that encourages students to think independently about a question (think), discuss their ideas with a partner (pair), and share their responses with a larger group, such as the whole class. This technique encourages participation as students become more comfortable with participating in whole class discussion after gaining confidence by first sharing their thoughts with a partner (23). We use a jigsaw in this lesson because it encourages inclusiveness and student equity (24). A jigsaw is a teaching strategy that breaks down the class into groups and assigns each group a piece of a puzzle that that the groups assemble to complete the jigsaw together. Finally, we use random call, or an unbiased selection of a student to answer questions, to equalize classroom participation (20) and ensure that all students are attentive and participating in class. Successful completion of the activity requires that each individual participates in the exercise. We acknowledge that some students do not thrive in a group setting, but they can still engage in the activity by writing their thoughts and ideas on worksheets that are collected and evaluated.

LESSON PLAN

Table 1 provides a plan for the learning activities.

Teacher Preparation

Teachers should assign pre-class homework (Supporting File S1. Stress and Immune System – Introduction Influenza Pre-Class Worksheet) at least 24 hours prior to class, either as an electronic or physical copy. Homework assignments are due prior to class or collected at the beginning of class and evaluated based on accuracy and effort (Supporting File S5. Stress and the Immune System – Pre-class Assignment Grading Rubric). Instructors should prepare the data figures obtained from the primary articles indicated in the worksheet and paste them into the in-class handout (Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet). While we would have liked to include the figures or tables in Supporting File S2, we could not do so due to copyright. The in-class assignments should be printed out, marked with “A(1-4)”, “B(1-4)”, “C(1-4)”, or “D(1-4)” to indicate groups, and provided to students at the beginning of class. For optional class session 2, teachers should bring large poster boards and materials for poster design (markers, scales, etc.).

Student Preparation

Students should complete the homework assignments

(Supporting File S1. Stress and Immune System – Introduction Influenza Pre-Class Worksheet and Supporting File S4. Stress and the Immune System – Inflammation Pre-Class Worksheet) prior to class. Students are permitted and encouraged to use outside resources to answer the questions. We do not provide resources that directly answer these questions as searching for information better enforces the concepts and provides students with a sense of independence. Before the lesson begins, teachers should ask students to reiterate some concepts from the homework assignments for review. Students can access their homework assignments from the online learning management system during class for reference during the activity.

Lesson Introduction

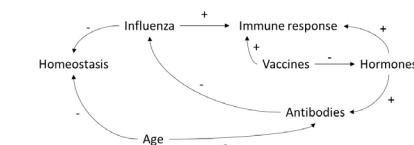
The jigsaw activity is implemented using letters (i.e., “A”, “B”, etc.) and numbers (“1”, “2”, etc.) to organize expert and jigsawed groups. Teachers should distribute worksheets (Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet) to students such that each group has worksheets that are labeled with the same number (either 1, 2, 3, or 4) regardless of letter. We introduce the lesson by addressing the learning goals outlined on the worksheet so that students are cognizant of the topics that are addressed in class. This lesson (Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet) was taught in a mixed majors biology seminar course, so we introduced concepts in immunology, such as inflammation, in earlier classes through homework and classwork assignments, such as Supporting File S4. Stress and the Immune System – Inflammation Pre-Class Worksheet. Alternatively, instructors may choose to assign both Supporting File S1. Stress and Immune System – Introduction Influenza Pre-Class Worksheet and Supporting File S4. Stress and the Immune System – Inflammation Pre-Class Worksheet prior to this lesson. Using random call, we ask students to define major concepts from the homework assignments (Supporting File S1. Stress and Immune System – Introduction Influenza Pre-Class Worksheet and Supporting File S4. Stress and the Immune System – Inflammation Pre-Class Worksheet). This allows students to be on the same page, which is important in an academically and socially heterogeneous classroom.

Individual Brainstorming

The activity begins with a think-pair-share exercise; students individually generate a feedback loop using concepts that are written on the worksheet (Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet). Students should have been introduced to feedback loops and the differences between positive and negative feedback from a video presented in “Pre-requisite Student Knowledge”. Based on the homework assignment and the brief review from the lesson introduction, students should have a basic understanding of individual concepts. The feedback loop should illustrate the relationships among influenza, immune response to influenza, homeostasis, antibodies, hormones, age, and vaccine (example shown in Figure 1). Drawing this feedback loop encourages students to think critically about the relationship between these ideas. We designed the first section of this lesson to be higher order thinking (synthesis) as it engages students and prepares them to apply themselves throughout the remainder of the lesson.

Vaccine Efficacy Based on Age

Hypothesis: Young and geriatric populations have lower vaccine efficacy.



Experimental design:



Results: Young vaccinated monkeys have higher vaccine efficacy based on higher overall antibody count.

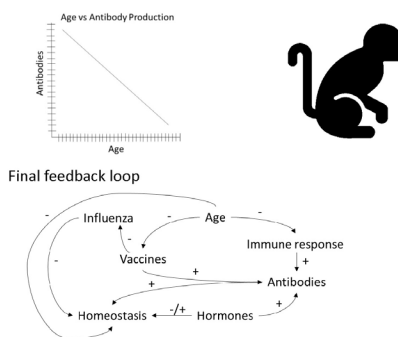


Figure 1. Sample student-generated poster as a product of S3. Stress and Immune System – Influenza II In-Class Worksheet. Students write a hypothesis based on their assigned topic (i.e., age and vaccine efficacy), draw a feedback loop based on their background knowledge and hypothesis, and create an experimental schema based on the toolkit they were provided in S2. Stress and Immune System – Influenza In-Class Worksheet. Based on their data analysis, students summarize and draw a graphical representation of their results, and finally provide an updated feedback loop based on the newfound empirical evidence.

Groupwork: Propose Hypothesis

Students share their feedback loops with their neighbor and compare and contrast their loops by writing down one similarity and one difference. Subsequently, students work in groups of four based on the number designation of the in-class worksheet to discuss their feedback loops and collectively generate hypotheses about how influenza vaccine efficacy or influenza immune response are affected by sex and age (e.g., “Group 1: [hypothesize how] influenza vaccine efficacy is related to age”) based on all of the group members inputs. For this portion of the jigsaw, students in the same group should have the same number designation regardless of letter on the worksheet (Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet). The instructor can randomly call on one student per group to articulate the group’s hypothesis, which allows for instructor feedback and can promote class discussion.

Jigsaw Activity: Experimental Design and Data Analysis

After proposing their hypotheses, students design experiments to test them. The activity was designed such that half of the expert groups designed vaccines and tested them in humans or rhesus macaques and the other half of the expert groups designed ways to best measure the immune response to influenza infection in mice or humans. During the vaccine expert group session, students learned about three possible ways to design vaccines- attenuation, inactivation, or small viral proteins with an adjuvant- and evaluated the advantages

and disadvantages to each one. During the immune response expert group session, students learned about three possible ways to measure the immune response- antibodies, CD8+ T cells, or neutrophils- and evaluated the advantages and disadvantages to each one. The lesson provides information for each method in order to allow students to choose the method they find most appropriate.

We designed this activity to be mindful of financial and laboratory resources, which are often limited in a research lab setting, by providing a toolkit that outlines the availability of resources for the experiments (e.g., “laboratory with three technicians”, “400 mice”, “10 rhesus macaques”, etc.). Students work in their expert groups to cooperatively design an experiment to test their hypotheses. While designing experiments, students engage in discussions about animal model systems and how standards can vary depending on the country in which the experiments are done. Students also discuss how to design a study that encompasses a broad range of races, genders, and socioeconomic status and why this is a priority in science. These dialogues allow students to appreciate the value of diversity in science and hear perspectives that are different from their own.

Throughout the activity, students evaluate the pros and cons of their experimental choices. Subsequently, students analyze primary data from published studies that investigated the same concepts as outlined in the activity. Students also compare the experimental methods between the published reports and their own. It is required that students write responses to the questions and details about their experimental designs based on group discussions in order to share with the reshuffled groups.

Jigsaw Activity: Dissemination of Expertise

The expert groups are reshuffled by the pre-labeled letter designation on the worksheet (Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet); that is, students with “A”, “B”, “C”, or “D” are grouped together. For example, all students with the letter designation “A” form one group, students with letter designation “B” form another group, etc. In their new groups, students take turns explaining their expert group’s hypothesis, experimental design, data analysis, and conclusions while the others are responsible for completing the worksheet and asking pertinent questions. All groups share their sections and all sections of the worksheet should be completed.

Data, Feedback Loops, and Mathematical Modeling

The final portion of the worksheet (Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet) poses two questions that students think about individually and are subsequently discussed as a class. The first question, “How can you change your feedback loops [from Section 1 of the activity] to more accurately reflect experimental data?” encourages students to think about how feedback loops incorporate empirical evidence and how they serve as models that can be used for prediction. This model, in turn, can be put into mathematical form and more accurately predict the response of a biological system. Though students are not exposed to the nuances of mathematical modeling and simulation, as it is outside the scope of this course, they are aware of the principles behind these concepts.

Poster Session (Optional)

In the next class, students design posters to practice effective science communication and discuss their work as a class. Students reconvene in their expert groups based on the previous class and design a poster based on a worksheet that outlines the necessary components to include on their posters (Supporting File S3. Stress and Immune System – Influenza II In-Class Worksheet). Each group takes turns presenting their posters, which elicits peer discussion and further reinforces the content. A sample poster recreated from students’ submissions is shown in Figure 1.

TEACHING DISCUSSION

Teaching Insights

This lesson has been successfully implemented in a mixed majors biology seminar at a master’s regional university. The course had both biology and non-biology majors, some of whom were familiar with basic immunology, although this was not a prerequisite. The students responded favorably to the jigsaw activity and enjoyed designing their own experiments. We found that students were motivated by the ability to make choices about their experiments. As we anticipated, many students were not aware of how the vaccines are made, how they are tested, or how they work prior to this lesson. It was also unclear to students how sex hormones and age affect the immune response to influenza and the vaccine. Thus, we designed this lesson to introduce students to the basic principles of influenza, vaccines, and other variables that affect the outcome of vaccine efficacy.

Although this lesson was developed prior to the COVID-19 pandemic, many of the concepts presented in this lesson are relevant to better understanding current issues involved in the development of a vaccine. Because the pandemic has altered everyone’s lives, it is common to wonder why a vaccine was not immediately available. The development of a vaccine involves funding, research, and multiple clinical trials. Although scientists have a head start on coronavirus research from the related 2003 SARS and 2012 MERS outbreaks, clinical trials are the most time-consuming and have the highest failure rate of any step in the vaccine development process (25). Less than 10% of drugs that enter clinical trials are approved by the Food and Drug Administration (FDA) (26). There are stringent criteria by which vaccines are deemed safe and effective by the FDA, and it takes, on average, 10 years before a vaccine is developed (27). Given the current urgency for a SARS-CoV2 vaccine, however, the process was expedited. This requires testing as many vaccines as possible and invoking emergency-use provisions to bypass the typical time constraints imposed by regulatory demands. To further speed up the process, experimental vaccines are being tested on more people with a reduced waiting period and phases of clinical trials are being combined. By providing an introduction to vaccines and a basis for appreciating current efforts towards making a SARS-CoV2 vaccine, this lesson may also help to ease anxieties related to the pandemic.

Throughout the lesson, students learned about how research related to influenza and vaccines is done. Students were surprised by the number of animals that are necessary for experiments and the financial burden to perform these experiments. Students engaged in productive and collegial

dialogues during the group activity that introduced new perspectives beyond the scientific material. In-class discussions even led to topics about society and science; some students had suggested doing the experiments in China or India, where there are fewer regulations regarding animal experimentation and it is more affordable. However, one student had pointed out that monkeys are sacred in India, which makes it impossible to carry out the experiments there. These cultural and societal insights were the product of a diverse classroom and excellent groupwork, as students comfortably and collegially exchanged ideas.

We found that student participation within groups was equitable as each student played an important role in piecing together the lesson. Students who were normally quiet and minimally participated were visibly more involved and enthusiastic during the experimental design portion of the lesson. During the reshuffling of the groups, students were empowered by the knowledge that they fulfill a significant part of the puzzle.

Lesson Limitations and Suggested Adaptations

This lesson introduces the immune system, influenza, and vaccine design. This lesson can effortlessly be incorporated into different courses in its current form or it can be significantly expanded. During the lesson, students asked basic immunology questions, such as “how do antibodies work?” and “how are T cells different from B cells?” Thus, in courses where there has not been any previous exposure to immunology, it is worth teaching the basics of immunology prior to this lesson, or providing readings to familiarize students with the topic. Another way in which this lesson can be expanded is to read and review magazine and news articles that call the efficacy and side effects of vaccines into question.

Because student backgrounds varied considerably in the course, we designed this activity to account for different knowledge bases and still challenge all students. However, the lesson can be modified for more introductory and advanced courses. This activity can be modified for a more introductory class by providing graphical representations of data instead of primary data, for example. The lesson can be made more appropriate for a higher-level biology course with additional questions and a more advanced experimental toolkit in Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet (provided in the lesson for each group). An advanced course is also amenable to more deeply exploring mathematical modeling in biology. This lesson only briefly and incompletely addresses mathematical modeling in biology. As a core competency in undergraduate biology, it will greatly benefit students to further explore this topic. We suggest using computational software to simulate the impact of age and sex on vaccine efficacy and influenza immune response based on the data. The use of computational modeling to teach complex topics has been shown to improve student performance and even bridge the gender gap in STEM classes (28).

This lesson is presented as a single 2-hour class session followed by an optional 1-hour session. As many courses may not meet for 2 hours at a time, we suggest splitting the lesson into two 1-hour class sessions. The first class session should end after the first portion of the jigsaw activity and the second class should begin with reorganized jigsaw groups. Though this modification will result in several class sessions,

we believe that the breadth and depth of information covered justifies the time.

Yet another limitation of this lesson is the lack of outcome data, such as that based on the Expanded Experimental Design Ability Test (EDAT), which measures students’ understanding of the parameters for experimental design (29). We acknowledge that this report only provides anecdotal evidence, but think that our findings still contribute to the scholastic goals of undergraduate STEM classes.

Although this lesson sufficiently encourages groupwork, individual work is limited. This can be modified by incorporating more think-pair-share opportunities. Of course, this will also increase the length of the lesson and will likely require more than one class period. Given the value of individual brainstorming in an active learning setting (30), we encourage instructors to incorporate more individual work. Finally, we recognize that Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet is a 19-page handout and is not ideal for either the student or the instructor to print or carry the document. One possible solution to this is to make the activity online to ease the environmental burden. It is also more likely to alleviate grading as it can be easier to read and a search can be done for keywords. Another possibility is to have a single representative handout for each expert group, but this will decrease individual accountability.

SUPPORTING MATERIALS

- S1. Stress and Immune System – Introduction Influenza Pre-Class Worksheet. This pre-class worksheet introduces influenza and prepares students for the in-class activity (Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet).
- S2. Stress and Immune System – Influenza In-Class Worksheet. This in-class worksheet is used to educate students on influenza infection and vaccines.
- S3. Stress and Immune System – Influenza II In-Class Worksheet. This optional in-class worksheet is a follow-up exercise to Supporting File S2.
- S4. Stress and the Immune System – Inflammation Pre-Class Worksheet. This pre-class worksheet is an introduction to the immune system and inflammation, which is prerequisite information for Supporting Files S1 and S2.
- S5. Stress and the Immune System – Pre-class Assignment Grading Rubric. This rubric provides guidelines for instructors on how to award points for the pre-classwork assignments.
- S6. Stress and Immune System – Introduction Influenza Pre-Class Worksheet Answer Key. This answer key provides the correct answers to pre-class worksheet Supporting File S1.
- S7. Stress and the Immune System – Inflammation Pre-Class Worksheet Answer Key. This answer key provides the correct answers to pre-class worksheet Supporting File S4.

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Table 1. Recommended timeline for Harnessing the Power of the Immune System lesson.

Activity	Description	Estimated Time (min)	Notes
Preparation for Class			
Teacher preparation	Print out necessary number of worksheets (Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet): and label with one of the four jigsaw groups (A(1-4), B(1-4), C(1-4), D(1-4)).	10	
Student preparation	Complete homework assignments (Supporting File S1. Stress and Immune System – Introduction Influenza Pre-Class Class Worksheet and Supporting File S4. Stress and the Immune System – Inflammation Pre-Class Worksheet) before class.	40	
Class Session 1			
Lesson introduction	Teachers distribute worksheets (Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet) to students, address the learning goals for the session and briefly review some major concepts from the homework assignment.	10	Use random call to define major concepts, such as inflammation, influenza, and immune cells.
Draw a feedback loop	Students work independently, building on their homework learning, to use the words provided on the worksheet to design a feedback loop that illustrates the relationship between concepts.	5	
Think-pair-share	Students compare and contrast their feedback loops with their neighbors'. Student volunteers share any notable differences in their feedback loops with the class.	5	
Propose group hypothesis	Students convene in groups of 4 based on the number designation on worksheet. and each group discusses their topic and collectively propose a hypothesis.	5	Teacher should circulate to ensure that all students are contributing to the discussion.
Share group hypotheses	A representative—chosen by the students—from each group shares the group hypothesis with the class.	5	Teacher and students provide feedback to groups.
Jigsaw activity: 4 expert groups	Students collaborate to design experiments and analyze results related to their topic using a toolkit that is provided on the worksheets.	35	
Jigsaw activity: Jigsawed groups	Groups are re-organized based on the letter designation of the worksheet to include one expert from each of the four groups. Students take turns explaining the hypotheses, experiments, results, and conclusions to their groupmates.	45	Teacher should circulate the room at this time and provide assistance to groups.
Class discussion about feedback loops and modeling	Students revisit the feedback loop they drew at the start of class and revise it based on their data analysis. Questions 2 and 3 under the “New Group Exercise” section of Supporting File S2. Stress and Immune System – Influenza In-Class Worksheet are discussed as a class.	15	
Class Session 2 (Optional)			
Lesson recap	Review the previous session	5	
Make posters	Students create posters using the template provided to them (Supporting File S3. Stress and Immune System – Influenza II In-Class Worksheet), which outlines the sections to include in their posters- topic, hypothesis, experimental design, results, conclusion.	15	Example of a student generated poster is shown in Figure 1.
Poster and group sharing	Each group takes turns sharing their findings and presenting their posters.	40	