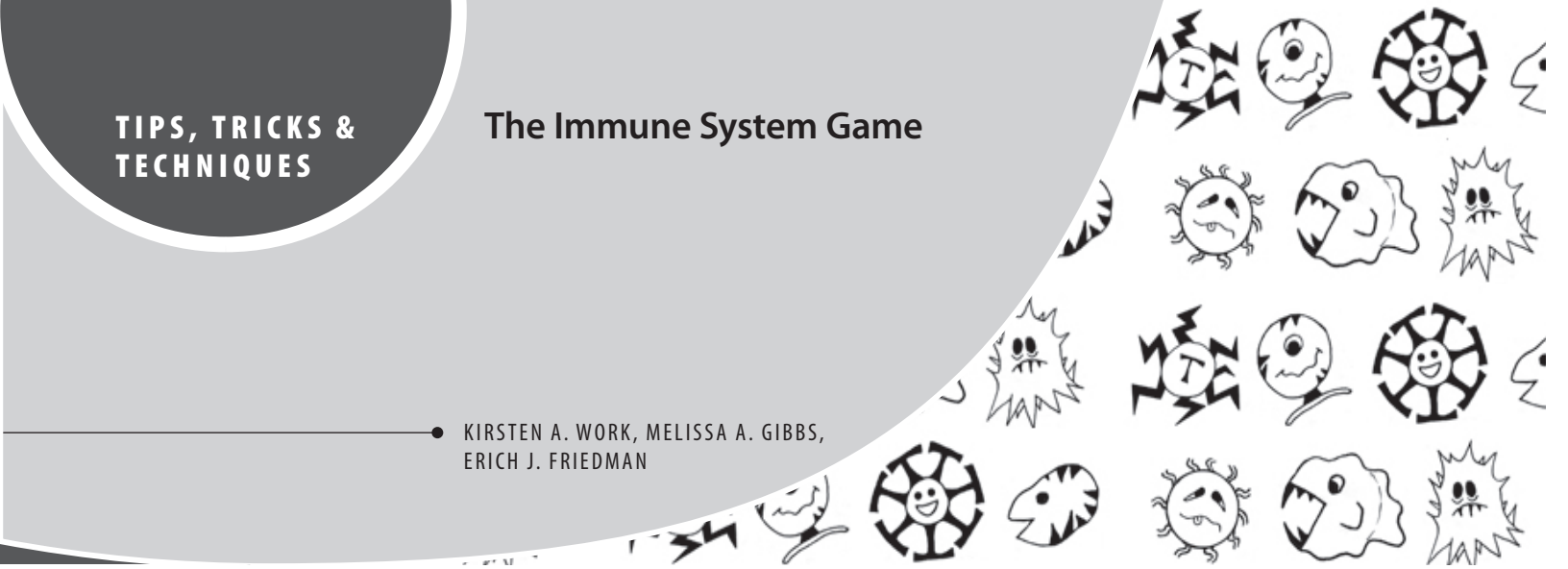
The Immune System Game



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Abstract

We describe a card game that helps introductory biology students understand the basics of the immune response to pathogens. Students simulate the steps of the immune response with cards that represent the pathogens and the cells and molecules mobilized by the immune system. In the process, they learn the similarities and differences between the immune responses to viral and bacterial pathogens and why the primary and secondary responses differ.

Key Words: *Immune system; card game; pathogen.*

Biological literacy is a commonly desired goal of biological education; however, there are multiple levels of biological literacy that represent different levels of mastery of material (Uno & Bybee, 1994). A student who is nominally literate may recognize terms but have major misconceptions. A student who is functionally literate may have memorized terms and processes but cannot explain processes in his or her own words. A structurally literate student, on the other hand, has a conceptual knowledge of biological processes that includes an understanding of how these processes proceed (Uno & Bybee, 1994). Subjects such as the immune system are of interest to many students but are sufficiently complicated – with many cells with different functions activated at different times during an immune response – that structural literacy and self-efficacy eludes many or most students in introductory biology courses.

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Here, we describe a game designed to simulate a simplified human immune response to bacteria and viruses. The immune system is often given short shrift in the typical introductory biology courses, so we created a game that students can play either during or outside of class. The game simulates a simplified immune response to viral and bacterial infections (both primary and secondary exposures). Before playing the game, students should be familiar with the concepts of innate and adaptive (specific) immune responses, but the game will teach them about the basic components and actions of the specific immune response (only the key immune cells of each system are included in this simulation), as well as emphasize the similarities in the immune responses to viruses and bacteria. The game is also useful as a pre-exam review of material covered during lecture.

To play the game, students can work alone or in groups of two or three, and they should be able to complete all four simulations within 1 hour. Some students may kill off the pathogen before their specific immune system is fully functional, and a few others may find their immune systems quickly overwhelmed (death or at least in need of medical attention), while most students will activate a normal, robust immune response that eventually overwhelms the pathogen. If time permits, students can reset and restart the game if they immediately kill or are killed by the pathogen. If class time is limited, those exceptions can illustrate varying degrees of response of the immune system to pathogens.

Each kit contains all of the materials needed to model both the primary and secondary responses to both viral and bacterial pathogens. After completing the exercise, presentation of a review sheet can reinforce the concepts presented in the game. See the Appendix for game cards and review sheets.

Materials for Each Kit

- Playing cards printed on different colors of card stock (plus some extras)
- Body bag (paper lunch bag with body outline attached)
- Coin
- Paperclip (to attach a memory cell to the body bag)
- Snack-size Ziploc bags to keep each type of playing card organized
- Gallon Ziploc bag for storing each kit

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○ Instructions for Students

The object of the game is to eliminate an infectious agent from your body by removing all of the pathogen. At the completion of this game, you should be able to

- identify the cells involved in the immune system from diagrams;
- put the steps of immune system response in the appropriate order;
- distinguish between primary and secondary immune responses; and
- describe why an infected person will feel sick shortly after infection and why this feeling of sickness will dissipate.

In most cases, when a new infectious agent gets into your body, the bacteria or viruses are never able to proliferate because the phagocytic cells of your innate immune system recognize and destroy many common benign pathogens before you can get sick. This innate response is not very specific and cannot protect us from all pathogens, but it can activate the adaptive immune system when a more powerful immune response is needed. When the infectious agent is able to proliferate, the cells (T & B) and proteins (antibodies) of the adaptive immune system efficiently distinguish between self and nonself (the infectious agent) cells and mount an immune attack directed specifically at that particular infectious agent. The adaptive immune response is, however, relatively slow to develop the first time a particular infectious agent is detected (the primary response). After detection of the infectious agent, it takes time to develop a specific response that has mobilized a sufficient number of antibodies and immune cells; during that time, the infectious agent can proliferate and make you sick. Eventually, your specific immune response to that specific infectious agent will trigger the production of antibodies that help your immune system fight off the pathogen. Additionally, in the process of making antibodies, your adaptive immune system will have made memory cells that will allow you to mount a rapid immune response the next time you are exposed to the infectious agent (secondary infection). This response typically happens so fast that the infectious agent cannot proliferate, and usually you do not get sick.

For a Bacterial Infection

Add the bacterial starter kit to your body bag (Table 1). At this point, there are four types of cards in the body bag: (1) three pathogens, (2) one macrophage, (3) one B cell, and (4) one helper T cell. The body bag represents your body, and the playing cards are the immune cells and infectious agents that are circulating in your body and doing battle.

For a Primary Bacterial Infection

1. Draw a card from the body bag. If you draw a bacterial pathogen, put it on your desk and add another to your body bag (it has replicated). If you draw a Helper T cell or a B cell, return the card to the body bag; those cells cannot recognize or act against a pathogen without first having the antigens presented to them by a macrophage. Draw again from the body bag.
2. If you draw a macrophage and have a pathogen on your desk, flip a coin. If you get heads, the macrophage finds and eats a pathogen (cover the pathogen with the macrophage card, and then add two macrophages to the body bag to represent the movement of that macrophage to the lymph nodes and activation of macrophages there). If you get tails, the macrophage can't see your pathogen and returns to the body bag.
3. If the macrophage eats the pathogen, it presents the pathogen's antigens to the immune system. The antigen will also will attract T_H cells (add two T_H cards to the body bag to represent the increased density of these cells in the vicinity of the infection).
4. Continue drawing until you get a T_H card and place it on the macrophage–pathogen stack to represent the maturation of the T_H cell.
5. **Primary Infection:** Activated T_H cells will activate B cells (add two B cells to the body bag to simulate the proliferation of cells that occurs during activation). Continue drawing until you get a B cell (place it on the T_H cell stack to represent the activation of naive B cells by T_H cells). (Continue to step 6.)

   OR

   Secondary Infection: After a T_H cell binds to the macrophage, it will activate the memory B cell you clipped to the body bag during the primary infection. The memory B cells immediately proliferate and produce antibodies. (Skip to step 7.)
6. Once the B cells have been activated, your immune system needs 14 days (14 draws from the body bag, during which you continue to follow the rules governing pathogen and macrophage behavior; steps 1 and 2) to produce antibodies and memory B cells (be sure to clip a B cell to the body bag for use during the secondary infection).
7. Place an antibody on every exposed pathogen on your desk. Any pathogens that are subsequently drawn from the body bag after the antibodies have been produced will also bind to an antibody and will not be able to reproduce (antibodies interfere with basic pathogen functions, such as reproduction).
8. Continue drawing from the body bag until you have drawn enough macrophages to kill all of the pathogens (remember that once the pathogen binds to an antibody, macrophages will always find the antibody-labeled pathogen; no need for a coin flip).
9. Once the pathogens on your desk have been consumed, count and record the ratio of pathogens to white blood cells (WBCs) in the body bag.
10. Return the cards to their bags. After you have modeled the primary infection, run a secondary infection.
11. How do the pathogen: WBC ratios compare between the primary and secondary infections?

    Teachers: Because of the 2-week (14 draws) interval between activating B cells and the production of antibodies, students should find (on average) that during primary infections, the pathogens are more likely to overwhelm the immune system (increased pathogens, decreased WBCs), while the rapid response of the secondary response should overwhelm the pathogens with WBCs (decreased pathogens, increased WBCs).
12. What is the relationship between the innate and adaptive immune systems?

Table 1. Bacterial starter kit.

Bacterial Pathogen	
	**Bacterial pathogens** represent the infection. The surface of these cells is covered with unique antigens, which the immune system can recognize as "nonself". Although macrophages can recognize pathogens as "nonself" and consume them as part of the innate immune response, the pathogen's antigens must be presented to the immune system before an adaptive immune response can be initiated.
White Blood Cells	
	**Macrophages** are part of the innate immune response. They are phagocytic cells that recognize the pathogens as "nonself," eat the pathogens, and present the pathogen's antigens to the immune system (activating the adaptive immune system). Until the adaptive immune system is activated by the macrophage-presented antigens and starts making antibodies (humoral response), the macrophages may or may not find the pathogens. Once a macrophage has consumed a pathogen, it migrates to the lymph nodes, presents the antigens to T and B white blood cells, and secretes cytokines. Helper T cells are activated by the cytokines and begin to proliferate, producing their own cytokines, which in turn induces proliferation of more macrophages.
	**Helper T cells (T_H)** are part of the adaptive immune system. They are activated by macrophage cytokines. Activated T_H cells proliferate and then produce cytokines that activate B cells. T_H cells also produce cytokines that induce proliferation of macrophages.
	**B cells** are part of the adaptive immune system. They make antibodies for immediate use and memory cells, which are stored for future use. After B cells are activated, it takes 14 days for them to produce specific antibodies that will target the invading pathogen. B cells are inactive until a macrophage has consumed one of the pathogens, T_H cells have been activated, and T_H cells activate the B cells.
	**Antibodies** are part of the adaptive immune system. They are proteins that label pathogens and interfere with cellular function, making it easy for macrophages to find them.

Teachers: The innate immune system activates the adaptive immune system when the phagocytic cells present antigens to the inactive adaptive immune system in the lymph nodes.

For a Viral Infection

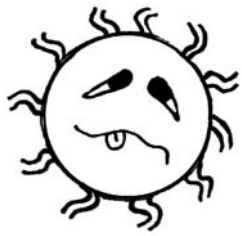
Add the viral starter kit to your body bag (Table 2). At this point, there are five types of cards in the viral body bag: (1) three virus-infected cells, (2) one dendritic cell, (3) one cytotoxic T cell, (4) one helper T cell, and (5) one B cell. The body bag represents your body, and the playing cards are the immune cells and infectious agents that are circulating in your body and doing battle.

Teachers: Although T_C and dendritic cells both can destroy virus-infected cells during the immune response, for the purposes of this game and simplicity, only the dendritic cell will serve as the antigen-presenting cell, and T_C cells as the primary destroyer of infected cells.

For an Initial Viral Infection

1. Draw a card from the body bag.
2. If you draw a virus-infected cell, lay the card on your desk and add one virus-infected cell to the body bag (to represent the virus reproducing).
3. If you draw any WBC before you have any virus-infected cells on your desk, return the WBC to the body bag (the WBCs can't act until there is an infection).

Table 2. Viral starter kit.

Virus-infected Cell	
	A viral pathogen is represented by a **virus-infected cell**, which contains many individual viruses; if it ruptures, it will spread those viruses to healthy cells and infect them. The infected cells bear antigens that identify the cell to the immune system as "nonself," but the immune system still needs to be activated in the lymph nodes by an antigen-presenting cell (the phagocytic dendritic cell).
White Blood Cells	
	**Dendritic Cells** are part of the innate immune system. They are phagocytic cells that behave a lot like the macrophages in the bacterial immune response, in that they detect and consume pathogens, travel to the lymph nodes, and present the pathogen's antigens. The physical interaction between the antigens the dendritic cell is presenting, inactive T_H and T_C cells, and the cytokines the dendritic cell produces activate the T_H and T_C cells.
	**Cytotoxic T cells (T_C)** are part of the adaptive immune system. They are primarily responsible for binding to and destroying virus-infected cells. T_C cells are activated and begin proliferating after physical interaction with antigen-presenting dendritic cell and dendritic cell cytokines. They are also activated by T_H cells. When T_C cells proliferate and produce cytokines, they will also activate T_H cells.
	**Helper T cells (T_H)** are part of the adaptive immune system. Once activated, T_H cells will use their own cytokines to activate B cells and more T_C cells.
	**B cells** are part of the adaptive immune system. They make antibodies and memory cells. After B cells are activated by T_H cytokines, it takes 14 days for them to produce antibodies that will specifically target the virus-infected cell. B cells can't act until a dendritic cell has consumed one of the virus-infected cells and a T_H cell has been activated.
	**Antibodies** are proteins that interfere with cellular function and label virus-infected cells for destruction by T_C cells.

4. If you draw a dendritic cell and have infected cells on your desk, flip a coin. If you get tails, the dendritic cell can't find your infected cell and returns to the body bag. If you get heads, the dendritic cell finds and consumes the virus-infected cell (represent this by covering the infected cell with the dendritic cell) and moves to the lymph nodes, where T_C and T_H cells are activated by dendritic cell cytokines.
5. If you then draw a T_H cell after a dendritic cell binds the infected cell, because it is now activated, it will first recognize and bind to the infected cell and then activate B cells using cytokines (represent the activation of the T_H cell by covering the dendritic stack with the T_H cell, and then add two B cell cards to the body bag to represent activation of B cells by the T_H cells). If you already had a memory B cell clipped to your body bag, you can immediately initiate a secondary immune response.
6. **Primary infection**: When you draw a B cell, this represents full activation of a primary immune response. Your newly activated

B cells need time to produce antibodies (14 days), so you must draw from the body bag 14 more times, and continue to follow the original rules for pathogen reproduction.

OR

Secondary infection: The memory B cells immediately produce antibodies (get the antibody bag from your kit and place an antibody on every exposed infected cell on your desk). Any infected cell you draw from the body bag after the antibodies have been produced will also bind to an antibody from your antibody bag and will not be able to reproduce.

7. Continue drawing cards from the body bag until you have drawn enough T_C cells to kill each of the virus-infected cells.
8. Once all of the virus-infected cells have been consumed, count and record the ratio of virus-infected cells to WBCs in the body bag.
9. Return cards to their bags and reset the game. After you have modeled the primary infection, run a secondary infection.
10. How do the infected cell:WBC ratios compare between the primary and secondary infections? Why?

    Teachers: Because of the 2-week (14 draws) interval between activating B cells and the production of antibodies, students should find (on average) that during primary infections, the pathogens are more likely to overwhelm the immune system (increased pathogens, decreased WBCs), while the rapid response of the secondary response should overwhelm the pathogens with WBCs (decreased pathogens, increased WBCs).

Reference

Uno, G.E. & Bybee, R.W. (1994). Understanding the dimensions of biological literacy. *BioScience, 44,* 553–557.

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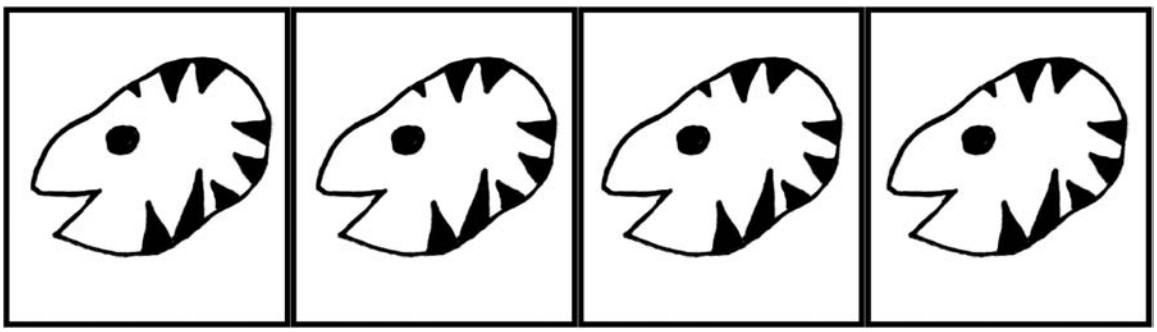
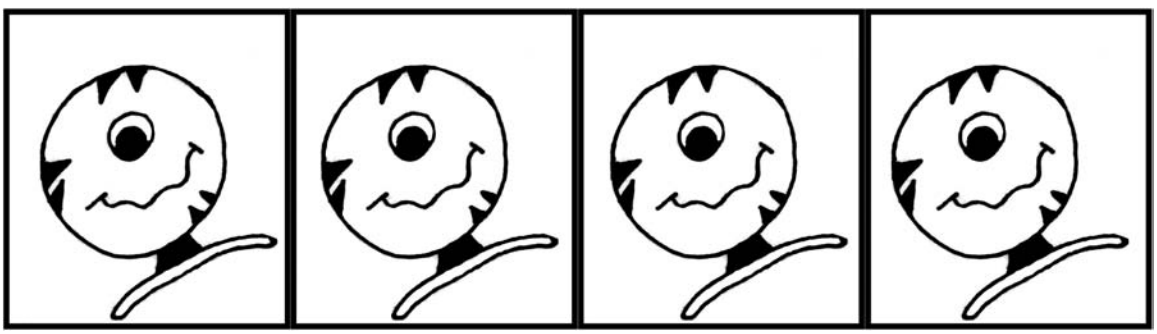
Appendix

Immune System Game Playing Cards

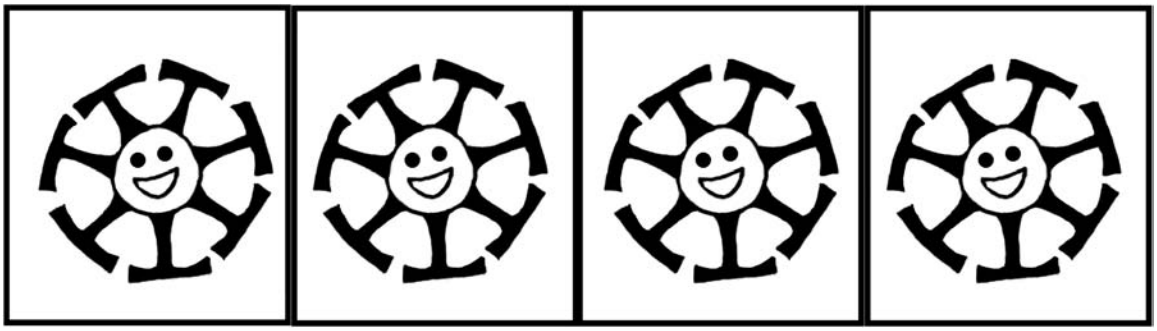
Print out each different type of card on colored cardstock. The number in parentheses is the number of cards you are likely to need per kit.



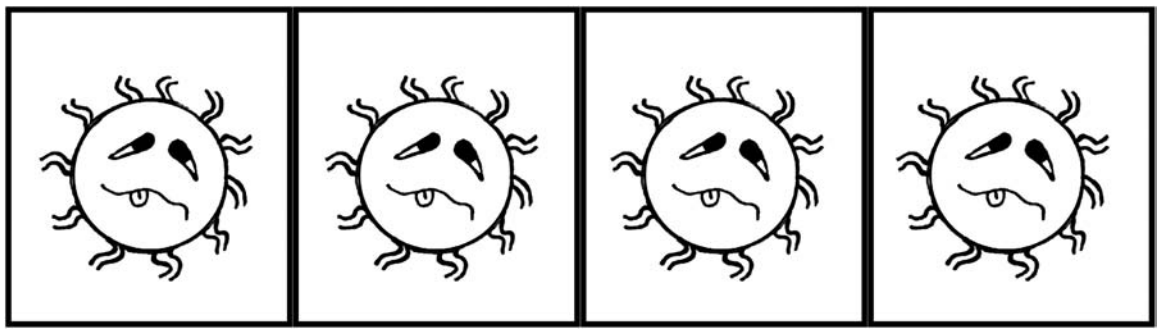
Antibodies (30)



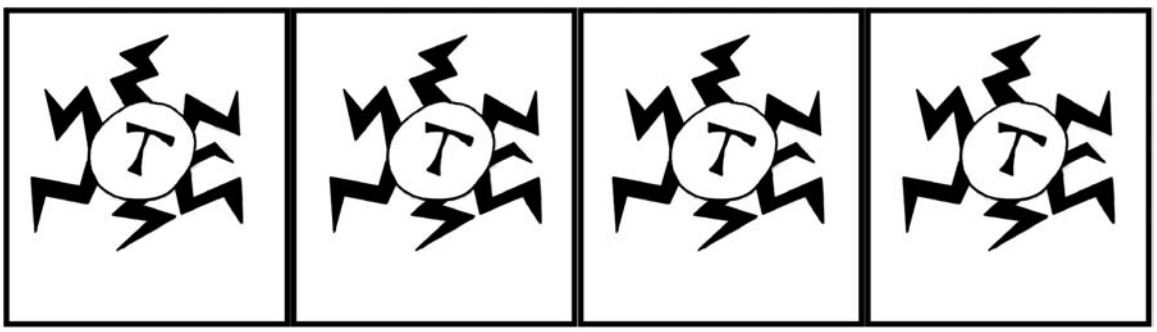
B-cells (4)



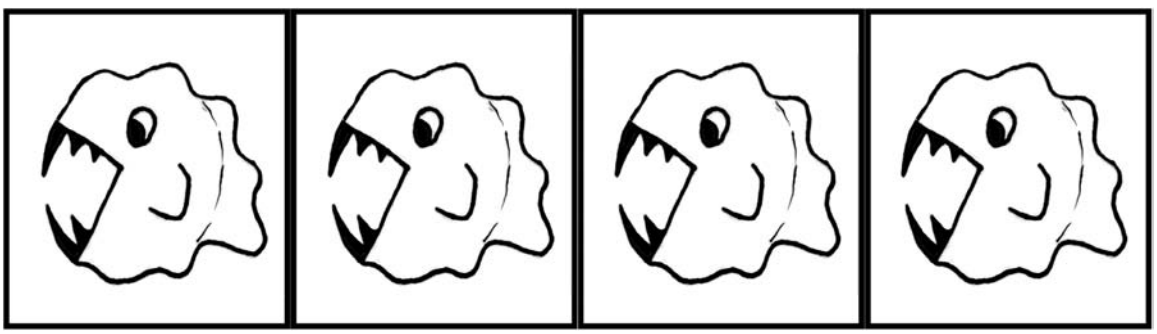
Helper T-cells (4)



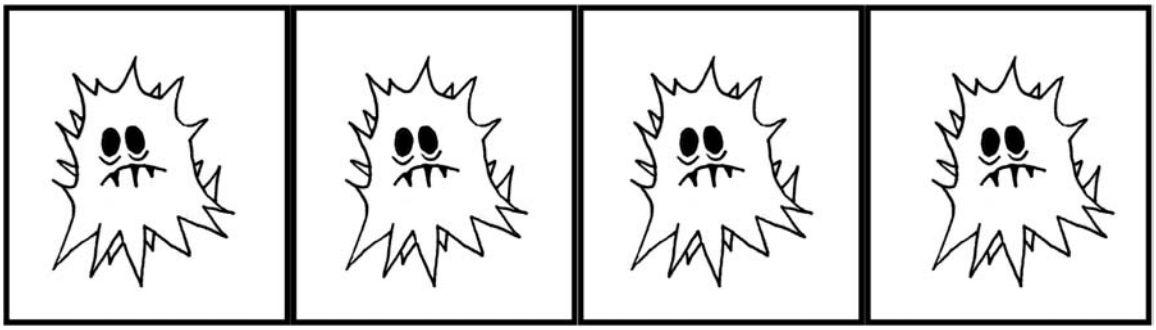
Virus-infected cells (40)



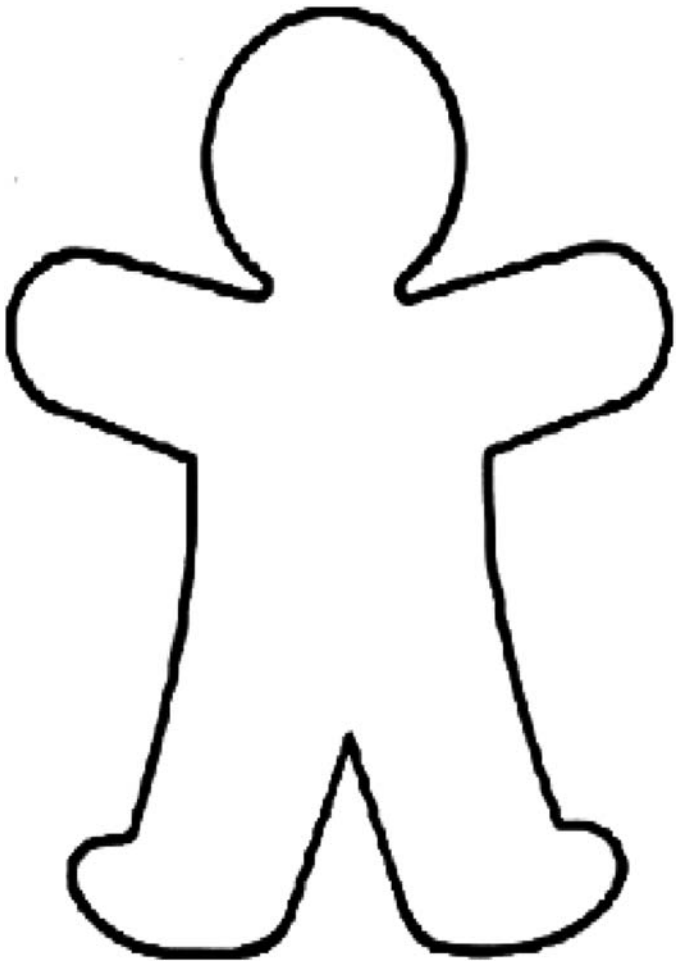
Cytotoxic T-cells (40)



Phagocytes (40)

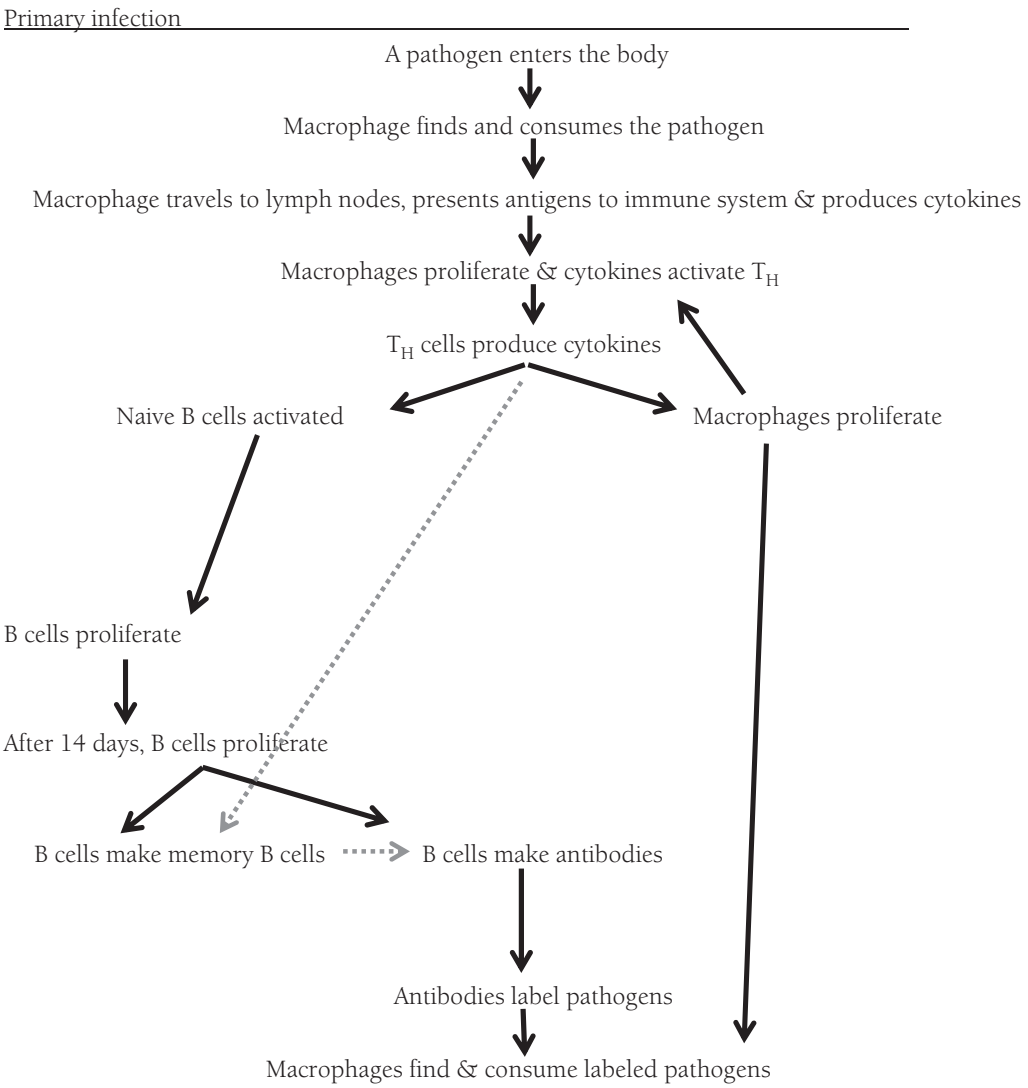


Bacterial pathogens (40)



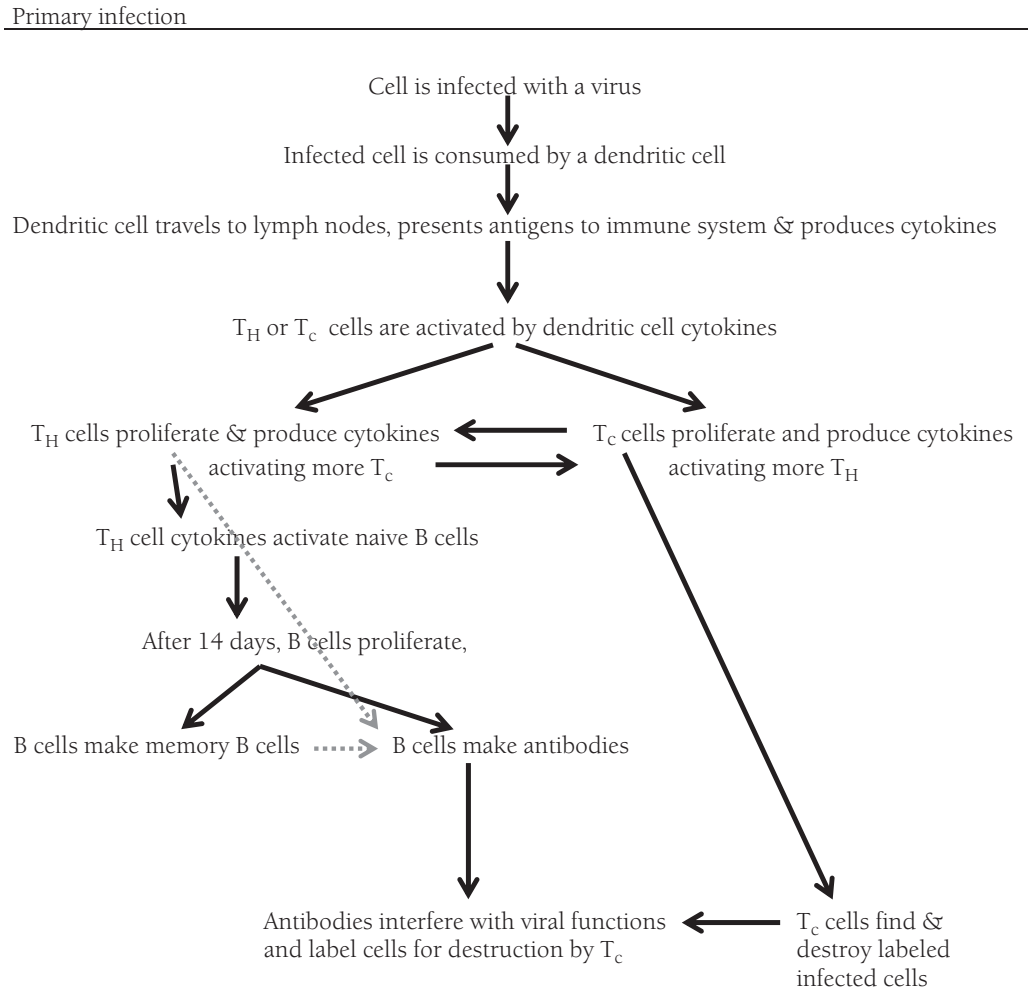
Body outline to tape to the outside of the Body Bag

Bacterial Invasion



*** *For a secondary infection, memory B cells are activated instead of naive cells, and there is no 14-day waiting period; memory B cells will immediately produce antibodies*

Viral Invasion



** ⇢ *For a secondary infection, memory B cells are activated instead of naive cells, and there is no 14-day waiting period; memory B cells will immediately produce antibodies*

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