Immune Force




RULE BOOK

PHOSPHOR LEARN
Light for learning

Rules

A game about Microbes and the Immune System

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Visual design by Leith Walton

A cooperative game for any number of players (best if 1-4) ages 5+. For players under 10, an adult probably needs to read the cards and remind them of each step in the turns.

Goal

The goal is to cure the patient of 5 diseases – or whatever number is chosen by the players at the start of the game. (Some young players like to intentionally let the patient die.)

Game ends

- When the patient survives an agreed number of diseases (PLAYERS WIN). We recommend starting with 5. A SUPER WIN defeats all 25 diseases.
- When any disease reaches 15 (PLAYERS LOSE).

Parts

MICROBES

- 15 bacteria
- 15 viruses
- 15 cancer cells
- 15 parasites or fungi

DEFENDERS

- 28 macrophages
- 28 neutrophils
- 8 dendritic cells
- 28 killer T-cells
- 14 bacteriophages

- 6 6-sided dice
- 1 2-sided TURN FLIP token
- 68 cards (26 DISEASE cards, 14 PREVENTION cards, 10 TREATMENT cards, 18 DEFENDER cards)
- Board: image download. Print at 17x22 inches or 18x24 inches.

download: https://www.ideategames.org/immune_board.png

Setup

- 12 neutrophils, 10 macrophages, and 6 dendritic cells spread throughout the body on blood squares.
- 3 bacteriophages: 1 in each of nose, mouth, stomach
- 6 killer T-cells in any of the bone marrow (arms or legs)
- The remaining defenders remain in stock.
- 4 piles of cards shuffled, face-down: DISEASE, PREVENTION, TREATMENT, DEFENDER

General

- Defenders are neutrophils, macrophages, dendritic cells, bacteriophages, and killer T-cells.
- New macrophages, neutrophils, and killer T-cells start in bone marrow, split between arm and leg as the players decide.
- New bacteriophages start in the nose, mouth, stomach – players decide how many where.
- **There must be a dendritic cell in a location before immune system pieces can act against disease pieces.**
- Immune system pieces kill only those diseases listed on their cards.
    - To kill virus, malaria, fungus: macrophage or killer T-cell or treatment.
    - To kill bacteria: neutrophil or bacteriophage or treatment (except antibiotic does not kill MRSA).
    - To kill cancer: killer T-cell or treatment or T-cell plus neutrophil (each neutrophil must have a T-cell with it).
- Antibiotics work on any bacterial disease except MRSA. (Malaria, foot fungus, cancer, and PCP are not bacterial.)
- Antivirals work on any viral disease.
- Antifungal treatment works on foot fungus and PCP.
- Bacteriophages do not move. They are not listed on the cards, but effective against any and all types of bacteria (including MRSA) in their location.
- Each immune system piece takes out one pathogen or cancer cell in their location with exceptions noted below.
- Antibody cards double the effectiveness of any immune system piece (1 immune system piece takes out 2 disease pieces) against any disease except cancer.
- Each T-cell+neutrophil pair takes out 4 cancer cells or 4 virus-infected cells.
- Dendritic cells are signalers, do not capture microbes (in this game; in real life they do) and are not removed from the board.

- Keep any vaccine PREVENTION card drawn, vaccine immunization is permanent. NOTE: **washing hands** and **vegetables** are not vaccines and not permanent, return them to the bottom of the PREVENTION pile when used.
- Return DEFENDER cards to the yellow pack when used.
- Place DISEASE cards in the 'victory' pile when defeated.
- Only one disease at a time (except PCP); use the TURN FLIP token only when there are no diseases.

Play

Turn without DISEASE

1. Flip the TURN FLIP token: green = PREVENTION, virus = DISEASE

   For a better-balanced game, use 1 die with 5 or 6 = PREVENTION

2. if DISEASE
   - Check for an appropriate PREVENTION.
     - Apply if appropriate (round up germs on a .5 result).
     - If a vaccine completely prevents the disease ('all'), move the disease to 'victory' pile and roll again.
     - **Washing hands** is a magic card, it can prevent any disease except cancer. If the PREVENTION card is **washing hands**, then flip the TURN FLIP token again. If green, then the disease was completely prevented! If not, continue as below.
   - When the result is some DISEASE remaining:
     - Place the number (on the left of the card) of the correct germ on one of the locations indicated on the card, players decide (use dice for a challenge).
     - Continue as 'Turn with DISEASE' skipping step 1.

- if PREVENTION
  - Take a PREVENTION card. Place it in the **Antibody Memory Bank**
  - Roll 2 die and move DEFENDER pieces anywhere to anticipate the next disease, players decide.
  - Player rolls again until a disease is started.

killer t- cell

Turn with DISEASE

1. Except for the first turn of a disease, replicate the DISEASE, adding its 'replication' number (upper right with a +) on the card. PREVENTION only works on the first turn with a DISEASE.
2. Draw a DEFENDER card and apply, adding new pieces at their start locations (keep antibodies for the duration of the disease; return other cards to the pack, shuffled); if player draws an antibody and already has an antibody card, return it to the DEFENDER pile and draw another card.
3. Apply any previously-drawn appropriate TREATMENT card (return to the TREATMENT pack if used).
4. Roll 1 die: if 4, 5, or 6, and if the team does not hold a TREATMENT card, draw a TREATMENT card.
    - Player may apply the card if appropriate (return to pack if used) but not on the first turn of a new disease. Treatment is only effective with the 'replicate' turns of a DISEASE, not on the turn it first breaks out.
    - If the TREATMENT card held is not helpful, player may return the TREATMENT card to the pack at any time or retain for a future disease (cancer and PCP are hard to defeat without TREATMENT).
    - Returning a TREATMENT card is not a trade – only draw a replacement on a new turn.
5. Roll the number of dice (1-6) equal to the first die roll.
6. Move dendritic cells and any of the DEFENDER cells (neutrophils, macrophages, killer T-cells) as needed to fight the disease.
7. NOTE: Dendritic cells are important for signaling T-cells and other parts of the immune system about the presence of a pathogen. For our simple game, **a dendritic cell must reach the infection before any other DEFENDER cells can move**. (If the infection is in more than one site, a dendritic cell need only reach one of the locations.) The idea is that dendritic cells must raise the alarm for the other parts of the immune system.
8. For defenders that reach the disease site, pair up appropriate defenders (neutrophils, macrophages, killer T-cells) with disease cells and remove all pairs (or 2:1 with an antibody card, or 4 virus or cancer with each T-cell+neutrophil pair).

dendritic cell

Rule guidelines

- Players take turns starting a new disease, no matter whose turn ended the previous disease.
- Players are a medical team: no player 'owns' any cards or pieces, they belong to the team.
- Rules can be relaxed depending on the age and inclination of the players.
- We usually play where the players younger than 9 place the pieces wherever they want within the limits of the game – for example, one player likes to start all the macrophages in one lump on one blood square, another put a malaria attack in the foot extremity. Older players can use dice to make a more random and more difficult game.
- When there is no disease, a PREVENTION flip does not count as a turn; player keeps the turn until a DISEASE is flipped.
- Only one antibody card can be used for a disease; if a second is drawn, return it to the yellow pile. Do not draw another card.
- Only one treatment can be held at any time; the current card can be returned to the blue pile at any time (not a trade) to allow a better card at the next TREATMENT card draw.
- It is acceptable to put new bacteriophages right on top of a stomach or nose or mouth disease (eg, botulism, ulcers, MRSA) and kill them immediately.
- For younger players, match one die rolled to one piece to move; for older players, DEFENDER pieces can move as the player wishes up to the total of all the dice.
- Washing hands only works for pathogens, which in this game is everything except cancer. Most cancers – 80-85% – are not caused by microbes. There are 2 washing hands cards to emphasize the importance in preventing infection.
- Washing hands card (as with all PREVENTION cards) can only be played on the first turn of a disease.
- For any DEFENDER piece type, when they are all on the board, no more can be added until some are used and are returned to the stock.

bacteriophage 

Interpreting the cards

DISEASE: Each card lists the locations where the disease starts, and the player can divide up the pieces any way they want across those places. The red circle on the left indicates how many microbes the disease starts with, and the pink circle on the right indicates how many microbes are added each turn. The bottom section lists the immune system pieces effective against the disease. (Bacteriophage is not listed but effective against all bacteria.)

> A special card is the OPPORTUNISTIC DISEASE card. When this card is drawn, draw another DISEASE card and start attacking that disease. On the 3rd turn of that disease, introduce pneumocystis pneumonia (PCP, a fungus) as a second disease.

PREVENTION: Each card lists the disease it can help prevent. Each is specific to one disease except washing hands and vegetables. The green circle indicates how much of the disease is eliminated on the first turn by the prevention card.

DEFENDER: Each card lists the kinds of pathogens it can attack and, in the yellow circle, how many can be added when this card is drawn. The circle on the right indicates how many turns this card can be used (mostly just one).

> A special card is the AUTOIMMUNE card. This card means your patient's body's immune system has over-reacted and is attacking their body. Remove half the neutrophils and half the T-cells from your patient.

TREATMENT: Each card indicates what types of disease (pathogens or cancer) it is valid against, and what kind of treatment the card gives. The blue circle on the left indicates how many microbes are killed on each turn by this treatment, and the lighter circle on the right indicates how many turns this card can be used.

Returning cards to their piles

- When cards are returned to their piles, you can reshuffle the pile or place the returned card at the bottom of the pile.
- Yellow (DEFENDER) cards are returned to their pile as soon as they are used except antibodies, which are retained for the duration of the current disease, returned to the yellow pile at the end of the disease.
- Blue (TREATMENT) cards are returned to the blue pile when they are used, at the end of their number of turns or at the end of the disease in which they are used. ONLY 1 TREATMENT CARD can be held at a time by the team. If the players decide a treatment card held is not helpful (i.e., antibiotic when the current disease is viral), the player can return the TREATMENT card to the blue deck and hope to draw a better card on the next TREATMENT draw.
- Green (PREVENTION) cards are retained for the duration of the game except **washing hands** and **vegetables** cards.
- Red (DISEASE) cards are not returned to the red pile. When a disease is defeated, red cards are placed face-up on your Victory Pile

neutrophil

The game vs reality

There are two major parts of the immune system, the innate immune system (neutrophils, macrophages, dendritic cells in the game) and the adaptive immune system (antibodies, T-cells). We have blurred those two together for simplicity, showing the adaptive immune system only in the activation of this system by dendritic cells (illustrated in the Antibody Memory Bank graphic) and in the simplistic use of antibodies to increase immune system effectiveness.

We have greatly simplified a critical and really cool part of the adaptive immune system, the B-cells that store memory of past infections and manufacture antibodies. These are found in the lymph nodes, thymus, and spleen, and we use the **Antibody Memory Bank** to represent that system. The Antibody Memory Bank diagram on the board shows an outline of how it works:

1. A dendritic cell or macrophage eats a microbe, breaks it into protein bits, and puts these bits (antigens) on their cell surface.
2. The dendritic or macrophage carries the antigens to T-cells and/or B-cells.
3. If a T-cell 'recognizes' one of the antigens, it goes out hunting to find and kill the microbes (this step is not shown in the diagram).
4. If the T-cell does not recognize the antigen, it takes the antigen to the B-cells and tries every B-cell until it finds some that recognize the antigen, and then the T-cell activates those B-cells.
5. Some activated or 'matured' B-cells become 'memory' cells (high alert, respond faster next time) and others go into the blood as plasma cells (antibody factories), and spit out millions of antibodies. Some memory cells can live for a lifetime, some less.

Dendritic cells in your immune system destroy microbes, much like macrophages, but their activation of the adaptive immune system (through release of cytokines and presenting antigens to the T-cell or B-cell) is of such critical importance in mobilizing the adaptive immune system that we have chosen to emphasize that role in the game and use only macrophages and neutrophils and T-cells for the direct attacks.

Dendritic cells are important signalers for alerting other parts of the immune system, particularly T-cells and B-cells. In our game, we have made them necessary signalers for all cells including macrophages and neutrophils, and this is a simplification. Dendritic cells are not necessary to alert macrophages and neutrophils, though they do increase the activation of these other cells. Macrophages also alert other parts of the immune system.

Natural Killer Cells (NK) are a key part of the innate immune system that we have left out of the game because of the confusion with killer T-cells (also called Cytotoxic T Lymphocytes or CTLs, also called CD8+). NK and activated killer T-cells behave similarly in the body once they find infected cells. NK do not need to be activated as T-cells do (by antigen-presenting cells such as dendritic cells), but kill infected cells by patrolling and simpler assessments of 'normal'. They are very effective against virus-infected cells and sometimes against cancer cells. A current hot area of immunotherapy research is attempting to use NK more effectively against cancer.

Killer T-cells do activate neutrophils to attack infected and cancer cells, and we have created a simplified version of that in the game, by having them more effective when they work together.

Bacteriophages are not part of our immune system, but they are symbiotic partners in defending our health. They are viruses that specifically kill bacteria and are found in our nose, mouth, and the lining of our gut. We included them just because their beauty and injection mechanism (injecting their RNA or DNA into the bacteria) make them a favorite with my grandson and me. Bacteriophage infusions into patients are a new treatment under trial for fighting antibiotic-resistant bacteria. (There is a wonderful Kurtzgesagt 'In a Nutshell' video on this.)

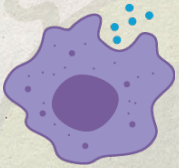
Antibodies in the game are effective by increasing the effectiveness of the DEFENDER cells. Although antibodies sometimes kill microbes directly, their usual action is to bind to the microbe and signal to a DEFENDER (or also bind to the DEFENDER) to come and kill the microbe, helping the DEFENDER locate the problem. General increased effectiveness is what we have modeled in the game.

The AUTOIMMUNE card represents a pathological condition where the body's immune system attacks parts of the body. There are autoimmune diseases such as lupus, rheumatoid arthritis, type1 diabetes, but autoimmune syndromes can also be triggered by some viral diseases and by immunotherapies. One treatment for immunotherapy-induced autoimmunity is corticosteroids which shut down or calm down neutrophils and T-cells, reducing their attacks on body tissues. We have simplified this for the game, but autoimmunity is real and very dangerous.

The most common opportunistic disease is pneumonia, often contracted by people whose immune system is overwhelmed fighting another serious disease. Pneumonia is often the final cause of death in such individuals, particularly the elderly. Pneumocystis pneumonia (PCP) is generally rare but an opportunistic pneumonia, frequently with late-stage AIDS and other serious illnesses.

In our game, all viruses have a vaccine. Although they are not all tested and ready for medicine, there are vaccines in development for these, so the promise is there. More importantly, some viruses are retroviruses (most flu, dengue fever, west Nile fever, Hanta, HIV) or RNA viruses (ebola, some flu) and mutate quickly, so the immunizations are neither 100% effective nor permanent, which is why you need a flu shot every year. We have modeled this in a simple way by having vaccines for those viruses only 1/2 effective.

There is an important part of the innate immune system that we have left out, the 'complement system', starting with the C3 protein and including B, D, C5, C6, C7, C8, and C9 proteins that together in a series of steps build a **membrane attack complex** that ends up drilling a hole in bacteria! Cool, but fairly complex and beyond the scope of this game. They are passive in that they are just proteins with no active movement, but are spread all over tissues, and activated by three different activation pathways.


macrophage

Cell types and terms in the Immune System

WBC: Most of the cells in the immune system are white blood cells, all created in the bone marrow. There are two groups, leucocytes (in the blood), and lymphocytes (in the lymphatic system which includes the thymus and spleen).

Microbe: A microbe is a microscopic organism, typically one cell, but can be a few cells.

Pathogen: A pathogen is a microbe that is unfriendly (most microbes are not), that causes disease or 'pathology'.

Antigen: An antigen is a piece of organic matter, usually a protein or part of a protein, that elicits or could or should elicit a "not us" reaction from the immune system. When a pathogen is first attacked, often by a macrophage or dendritic cell, it is broken into bits and those bits are pushed to the surface of the ingesting cell and shown around to T-cells and B-cells to find one that recognizes it and knows how to create antibodies for it. All living cells and viruses have many different proteins all over their surface, and each of these is a potential antigen.

Antibody: An antibody is a protein that very specifically binds to one other protein, the antigen. Typically it then attracts or grabs an immune cell to attack what it is holding, sometimes it kills directly. Antibodies are made by B-cells, and can be made in the laboratory with cultures of B-cells. A monoclonal antibody is a laboratory-made antibody that was made from a single cell cloned into a culture of millions of identical cells making the same antibody. Drugs that end in '-mab' are usually monoclonal antibodies. Monoclonal antibodies can be made for many different mechanisms, sometimes to grab onto a cell to prevent an action, sometimes to grab onto a cell to attract other (killer) cells, sometimes to deliver a protein or chemical or protein to a cell that might directly kill the cell. Antibodies carrying markers (often radioactive) can help count or locate cells.

Cytokines: Cytokine is the name of a broad category of small proteins used by cells of the immune system for signaling to each other (usually activating or shutting down).They include interleukins, interferon, growth factors, and many other types. Some used by T-cells and NK cells are specialized to kill infected cells.

Innate Immune System

Neutrophils: These leucocytes are the most numerous white blood cells, found in blood and all tissues, and are first responders. They are the primary bacteria killers. Because they can go crazy killing when they are turned on, they also have a short life span. They can be mobilized by T-cells to kill cancer and other infected body cells. Overactive neutrophils are often part of auto-immune syndromes. Auto-immune is when the immune system attacks healthy parts of the body (eg, rheumatoid arthritis, lupus, type 1 diabetes).

Macrophages: These leucocytes are the clean-up crew. The are the largest white blood cells ('macro') and on patrol all over the body, cleaning up (eating, or 'phaging') bits of organic matter. They will recognize and eat bacteria and viruses, and can present antigens from those invaders to the adaptive immune system. In a rare abnormal condition, macrophages can turn on the body and 'clean up' normal red blood cells. Macrophages also release cytokines to alert NK and other immune system cells when they find pathogens.

Dendritic cells: Dendritic cells are leucocytes found all over the body. They are front-line defenders, first-responders, but especially they are the key antigen-presenting cells (APC). They will eat pathogens, and then are the primary cells to present to the T-cells and B-cells all of the antigens they find on those pathogens. They also release cytokines that alert NK and other cells in the immune system of an invasion.

Natural Killer Cells: Although they are part of the innate immune system (are not specific in the antigen they respond to), these 'NK' cells are lymphocytes, they mature in the spleen and lymph nodes. These cells are critical in distinguishing self from non-self cells, and recognizing stressed (eg, virus-infected or mutated) cells and releasing cytokines to kill them. They are important for tissue-rejection, and new research has shown that there are thousands of different kinds of NK cells. There is still much unknown, but also hope that NK cells may prove a new direction in attacking cancer.

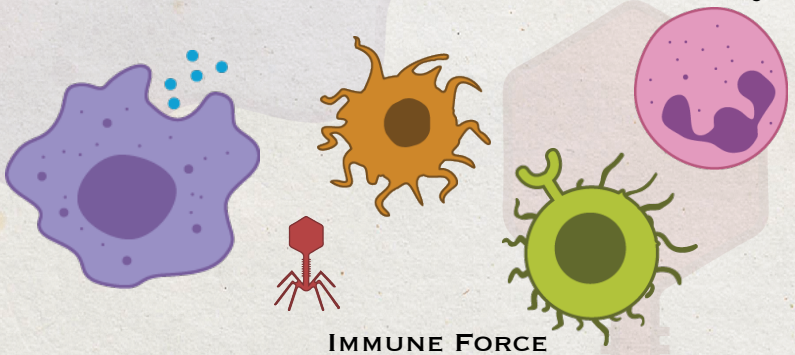
Adaptive Immune System

B-cells: Each B-cell can recognize one antigen and create one antibody specific for that antigen. Soon after conception, the embryo creates trillions of B-cell types, each with a randomly-different antibody. The mechanism is too complicated to explain here, but is truly wondrous. B-cells are lymphocytes.

T-cells: T-cells are the lymphocytes that are stored and matured in the thymus gland, the origin of their name. Like B-cells but unlike Natural Killer Cells, T-cells are created with randomly different antigen-recognition proteins. Each T-cell is matured to recognize a specific antigen and attack the host cell that has that antigen. Virus-infected cells present specific proteins on their surface (their call for help) that some T-cells recognize and attack.

There are many different kinds of T-cells, and 'T-cell profiling' is an emerging diagnostic that can predict the effectiveness of certain immunotherapies for cancer treatment. It appears that patients who are not helped by certain new immunotherapies do not have enough of a certain kind of T-cell.

Basophils and Mast Cells: These are important in allergies, they react to antigens by releasing cytokines, histamine, heparin and other chemicals that trigger allergic reactions. Basophils are found in the blood and mast cells in tissues, much the same kind of cell. These are not in the *Immune Force* game.



Learn more about the Immune System

The immune system is one of the most complicated yet fascinating systems in biology, having evolved (still evolving) as a life-critical arms race with many convoluted layers of 'patches' on older weapons. Beautiful, wondrous, fascinating, complex, but designed like a Rube-Goldberg cartoon.

All of the cell types and pathogens in this game are well described in Wikipedia pages. ("Killer T-cells" are called Cytotoxic T-cells in Wikipedia.) That is a good place to start, though a search on any term will show several excellent resources.

A good short introduction to the immune system is a UK government pamphlet that can be found online at http://www.imgt.org/IMGTeducation/Tutorials/ImmuneSystem/UK/the_immune_system.pdf

A pamphlet that my grandson and I read many times is *Understanding the Immune System* by Lydia Woods Schindler, Diane Publishing, published for NIH. Short, excellent diagrams and detail (p 12 is great). Though certainly dated (1991), it is free online in Google Books and contains the basics.

One textbook that is easy to read, current, and an excellent overview is *How the Immune System Works* (Sixth Edition, 2019) by Lauren Sompayrac. Though much more depth than casual readers might enjoy, I found this one of the best-written of the textbooks.

A bit more technical depth into the research and mechanisms of immunity, yet still readable for those with some biology background, are the excellent books by Daniel Davis (immunology research scientist), *The Compatibility Gene: How Our Bodies Fight Disease, Attract Others, and Define Our Selves* and especially *The Beautiful Cure: The Revolution in Immunology and What It Means for Your Health*. I couldn't put those books down.

My grandson and I watched a lot of videos about the immune system, and among our favorites were the ones by Kurzgesagt – 'In a Nutshell'. We also spent a lot of time with university textbooks on the immune system; he loved asking me to explain the pictures. I had to learn quickly. Thus the game to capture some of what we learned.

This game was made possible by a generous contribution from Rebecca and Shawn Scully.

25% of the profits from sales of this game through the year 2024 will be donated to the Benaroya Research Institute Virginia Mason in Seattle

https://www.benaroyaresearch.org/

Benaroya Institute is not associated with the product or its content.