Lecture 7
The diversity of infectious disease agents
Vertebrate immunity
Major killers: influenza virus

- Influenza is caused by a virus that attacks mainly the upper respiratory tract – the nose, throat and bronchi and rarely also the lungs.

- The virus has a single-stranded negative-sense RNA genome in several segments

- The infection usually lasts for about a week. It is characterized by sudden onset of high fever, headache and severe malaise, non-productive cough, sore throat, and rhinitis.

- Most people recover within one to two weeks without requiring any medical treatment.

- In the very young, the elderly and people suffering from medical conditions such as lung diseases, diabetes, cancer, kidney or heart problems, influenza poses a serious risk. In these people, the infection may lead to severe complications of underlying diseases, pneumonia and death.
Major killers: influenza virus

- rapidly spreads around the world in seasonal epidemics and imposes a considerable economic burden in the form of hospital and other health care costs and lost productivity.

- In annual influenza epidemics 5-15% of the population are affected with upper respiratory tract infections (i.e. 100s of millions of cases)

- Hospitalization and deaths mainly occur in high-risk groups (elderly, chronically ill).

- Although difficult to assess, these annual epidemics are thought to result in between three and five million cases of severe illness and between 250,000 and 500,000 deaths every year around the world. Most deaths currently associated with influenza in industrialized countries occur among the elderly over 65 years of age. (about 36,000 in the USA every year)

- Much less is known about the impact of influenza in the developing world.
Major killers: influenza virus

- The currently circulating influenza viruses that cause human disease are divided into two groups: A and B.

- Influenza A has 2 subtypes which are important for humans: A(H3N2) and A(H1N1), of which the former is currently associated with most deaths.

- Influenza viruses are defined by 2 different protein components, known as antigens, on the surface of the virus. They are spike-like features called haemagglutinin (H) and neuraminidase (N) components.

- The genetic makeup of influenza viruses allows frequent minor genetic changes, known as **antigenic drift**, and these changes require annual reformulation of influenza vaccines.
Major killers: influenza virus

- Three times in the last century, the influenza A viruses have undergone major genetic changes (antigenic shift), resulting in global pandemics and large tolls in terms of both disease and deaths.

- The most infamous pandemic was “Spanish Flu” which affected large parts of the world population and is thought to have killed at least 40 million people in 1918-1919.

- And maybe up to 100 million, at a time when the population of the Earth was around 1.8 billion.
Major killers: influenza virus

- More recently, two other influenza A pandemics occurred in 1957 (“Asian influenza”) and 1968 (“Hong Kong influenza”) and caused significant morbidity and mortality globally.

- In contrast to current influenza epidemics, these pandemics were associated with severe outcomes also among healthy younger persons, albeit not on such a dramatic scale as the “Spanish flu” where the death rate was highest among healthy young adults.

- Most recently, outbreaks of a new influenza subtype A(H5N1) directly transmitted from birds to humans have occurred
Major killers: influenza virus

• Vaccination is the principal measure for preventing influenza and reducing the impact of epidemics.

• Various types of influenza vaccines have been available and used for more than 60 years. They are safe and effective in preventing both mild and severe outcomes of influenza.

• Constant genetic changes in influenza viruses mean that the vaccines' virus composition must be adjusted annually to include the most recent circulating influenza A(H3N2), A(H1N1) and influenza B viruses.

• The WHO's Global Influenza Surveillance Network writes the annual vaccine recipe. The network, a partnership of 112 National Influenza Centres in 83 countries, is responsible for monitoring the influenza viruses circulating in humans and rapidly identifying new strains. Based on information collected by the Network, WHO recommends annually a vaccine that targets the 3 most virulent strains in circulation.
Major killers: influenza virus

- Antiviral drugs for influenza are an important adjunct to influenza vaccine for the treatment and prevention of influenza. However, they are not a substitute for vaccination.

- For several years, four antiviral drugs that act by preventing influenza virus replication have been available. They differ in terms of their pharmacokinetics, side effects, routes of administration, target age groups, dosages, and costs.
ssRNA: negative strand RNA viruses

Influenza A virus

Measles virus

Ebola virus
Major killers: measles virus and other “childhood” diseases

- Measles is an infectious viral disease that occurs most often in the late winter and spring. It begins with a fever that lasts for a couple of days, followed by a cough, runny nose, and conjunctivitis (pink eye). A rash starts on the face and upper neck, spreads down the back and trunk, then extends to the arms and hands, as well as the legs and feet. After about five days, the rash fades the same order it appeared.

- Measles is highly contagious. Infected people are usually contagious from about 4 days before their rash starts to 4 days afterwards. The measles virus resides in the mucus in the nose and throat of infected people. When they sneeze or cough, droplets spray into the air and the droplets remain active and contagious on infected surfaces for up to two hours.
Major killers: measles virus and other “childhood” diseases

- Measles itself is unpleasant, but the complications are dangerous.

- Six to 20 percent of the people who get the disease will get an ear infection, diarrhea, or even pneumonia.

- One out of 1000 people with measles will develop inflammation of the brain, and about one out of 1000 will die.

- Measles kills about 1 million children every year in spite of the availability of a safe and effective vaccine.
Measles is a crowd disease that probably could not have maintained itself until recently in human populations.

Related viruses are found in a range of mammals. Most closely related is Rinderpest, from bovids.

Did we acquire measles after settling down and domesticating cattle?

Major killers: measles virus and other "childhood" diseases
ssRNA: negative strand RNA viruses

Rabies virus

Mumps virus

Hanta viruses

Human respiratory syncytial virus
Major killers: other respiratory infections

- Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia among infants and children under 1 year of age.

- The majority of children hospitalized for RSV infection are under 6 months of age. RSV also causes repeated infections throughout life, usually associated with moderate-to-severe cold-like symptoms.

- However, severe lower respiratory tract disease may occur at any age, especially among the elderly or among those with compromised cardiac, pulmonary, or immune systems.

- RSV is a single-stranded negative-sense, enveloped RNA virus. The virion is variable in shape and size (average diameter of between 120 and 300 nm), is unstable in the environment (surviving only a few hours on environmental surfaces), and is readily inactivated with soap and water and disinfectants.
Major killers: respiratory infections

• RSV is spread from respiratory secretions through close contact with infected persons or contact with contaminated surfaces or objects. Infection can occur when infectious material contacts mucous membranes of the eyes, mouth, or nose, and possibly through the inhalation of droplets generated by a sneeze or cough.

• In temperate climates, RSV infections usually occur during annual community outbreaks, often lasting 4 to 6 months, during the late fall, winter, or early spring months.

• Development of an RSV vaccine is a high research priority, but none is yet available.
Major killers: respiratory infections

- Human parainfluenza viruses (HPIVs) are second to respiratory syncytial virus (RSV) as a common cause of lower respiratory tract disease in young children.

- Similar to RSV, HPIVs can cause repeated infections throughout life, usually manifested by an upper respiratory tract illness (e.g., a cold and/or sore throat).

- HPIVs can also cause serious lower respiratory tract disease with repeat infection (e.g., pneumonia, bronchitis, and bronchiolitis), especially among the elderly, and among patients with compromised immune systems.
HPIVs are negative-sense, single-stranded RNA viruses that possess fusion and hemagglutinin-neuraminidase glycoprotein "spikes" on their surface. There are four serotypes types of HPIV (1 through 4) and two subtypes (4a and 4b).

- unstable in the environment (surviving a few hours on environmental surfaces), and readily inactivated with soap and water.

- No vaccine is currently available to protect against infection caused by any of the HPIVs
Table 2.2 Some diseases spread by the respiratory route

<table>
<thead>
<tr>
<th>Pathogen/disease</th>
<th>Type of organism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus</td>
<td>Bacterium</td>
<td>Common cause of pneumonia</td>
</tr>
<tr>
<td><em>Haemophilus</em></td>
<td>*</td>
<td>Common cause of pneumonia</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>*</td>
<td>May spread to other organs</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>*</td>
<td>Laryngitis</td>
</tr>
<tr>
<td>Anthrax</td>
<td>*</td>
<td>More usually via skin</td>
</tr>
<tr>
<td>Plague (‘pneumonic’)</td>
<td>*</td>
<td>Also via skin (‘bubonic’)</td>
</tr>
<tr>
<td>Common cold</td>
<td>Viruses</td>
<td>Usually self-limited</td>
</tr>
<tr>
<td>Influenza</td>
<td>Virus</td>
<td>May spread to lung (pneumonia)</td>
</tr>
<tr>
<td>Measles</td>
<td>*</td>
<td>Also skin rash</td>
</tr>
<tr>
<td>Mumps</td>
<td>*</td>
<td>Also salivary glands</td>
</tr>
<tr>
<td>Chickenpox</td>
<td>*</td>
<td>Rash; may recur as shingles</td>
</tr>
<tr>
<td>Rubella</td>
<td>*</td>
<td>May affect fetus</td>
</tr>
<tr>
<td><em>Aspergillus</em></td>
<td>Fungus</td>
<td>May cause allergy</td>
</tr>
<tr>
<td>Histoplasma</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>
ssRNA: positive strand RNA viruses

Poliovirus (poliomyelitis)

Rhinovirus (common cold)

Hepatitis A virus

Dengue virus

West Nile virus

Hepatitis C virus

Foot-and-mouth disease virus

SARS
ssRNA: positive strand RNA viruses

• Hepatitis C infects an estimated 170 million people worldwide and 4 million in the United States.

• There are about 35,000 to 185,000 new cases a year in the United States. Co-infection with HIV is common and rates among HIV positive populations are higher.

• 10,000-20,000 deaths a year in the United States are from HCV; expectations are that this will increase, as those who were infected by transfusion before HCV testing are expected to become apparent.

• A survey conducted in California showed prevalence of up to 34% among prison inmates;[10] 82% of subjects diagnosed with hepatitis C have previously been in jail,[11] and transmission while in prison is well described.[12]

• Egypt has the highest seroprevalence for HCV, up to 20% in some areas. This was linked, in 2000, to a mass-treatment campaign for schistosomiasis, which is endemic in that country.
Noroviruses are a group of viruses that cause the “stomach flu,” or gastroenteritis in people.

Enveloped, single-stranded positive-sense RNA virus

The term norovirus was recently approved as the official name for this group of viruses. Several other names have been used for noroviruses, including:

- Norwalk-like viruses (NLVs)
- Caliciviruses (because they belong to the virus family *Caliciviridae*)
• The symptoms of norovirus illness usually include nausea, vomiting, diarrhea, and some stomach cramping.

• The illness is usually brief and milder than rotaviral infection, with symptoms lasting only about 1 or 2 days.

• Also known as…
• * stomach flu – this “stomach flu” is not related to the flu (or influenza), which is a respiratory illness caused by influenza virus.
• * viral gastroenteritis – the most common name for illness caused by norovirus. Gastroenteritis refers to an inflammation of the stomach and intestines.
• * food poisoning (although there are other causes of food poisoning)
## Vectored diseases

<table>
<thead>
<tr>
<th>Pathogen/disease</th>
<th>Type of organism</th>
<th>Vector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plague</td>
<td>Bacterium</td>
<td>Flea (from rats)</td>
</tr>
<tr>
<td>Tularaemia</td>
<td>&quot;</td>
<td>Flea, tick, louse</td>
</tr>
<tr>
<td>Relapsing fever</td>
<td>&quot;</td>
<td>Louse</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>&quot;</td>
<td>Tick</td>
</tr>
<tr>
<td>Typhus</td>
<td>Rickettsia</td>
<td>Flea, louse</td>
</tr>
<tr>
<td>Dengue</td>
<td>Virus</td>
<td>Mosquito</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Malaria</td>
<td>Protozoan</td>
<td>&quot;</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>&quot;</td>
<td>Sandfly</td>
</tr>
<tr>
<td>Sleeping sickness</td>
<td>&quot;</td>
<td>Tsetse fly</td>
</tr>
<tr>
<td>Chagas’ disease</td>
<td>&quot;</td>
<td>Reduviid bug</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>Worm</td>
<td>Blackfly</td>
</tr>
<tr>
<td>Filariasis</td>
<td>&quot;</td>
<td>Mosquito</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>&quot;</td>
<td>Snail</td>
</tr>
</tbody>
</table>
# Zoonoses:

## Table 2.5 Major diseases caught from animals (zoonoses)

<table>
<thead>
<tr>
<th>Pathogen/disease</th>
<th>Type of organism</th>
<th>Animal reservoir/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine tuberculosis</td>
<td>Bacterium</td>
<td>Cattle; rare since pasteurization</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>&quot;</td>
<td>Cattle, goat, dog</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>&quot;</td>
<td>Horse, cattle, dog</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>&quot;</td>
<td>Deer</td>
</tr>
<tr>
<td>Plague</td>
<td>&quot;</td>
<td>Rat</td>
</tr>
<tr>
<td>Tularaemia</td>
<td>&quot;</td>
<td>Rat</td>
</tr>
<tr>
<td>Anthrax</td>
<td>&quot;</td>
<td>Farm animals</td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>&quot;</td>
<td>Farm and dairy products</td>
</tr>
<tr>
<td>Psittacosis</td>
<td>Chlamydia</td>
<td>Birds</td>
</tr>
<tr>
<td>Rabies</td>
<td>Virus</td>
<td>Bat, dog, fox, racoon</td>
</tr>
<tr>
<td>Influenza</td>
<td>&quot;</td>
<td>Birds, pig</td>
</tr>
<tr>
<td>Lassa fever</td>
<td>&quot;</td>
<td>Rodents</td>
</tr>
<tr>
<td>Ebola, Marburg</td>
<td>&quot;</td>
<td>Monkeys</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>&quot;</td>
<td>Chimpanzees; monkeys (originally, now human → human)</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>Fungus</td>
<td>Birds</td>
</tr>
<tr>
<td>Toxoplasma</td>
<td>Protozoan</td>
<td>Cat</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>&quot;</td>
<td>Birds, mammals</td>
</tr>
<tr>
<td>Echinococcus</td>
<td>Worm</td>
<td>Dog</td>
</tr>
<tr>
<td>Tapeworms(s)</td>
<td>&quot;</td>
<td>Pig, cattle</td>
</tr>
<tr>
<td>Toxocara</td>
<td>&quot;</td>
<td>Dog</td>
</tr>
</tbody>
</table>
Brief history of immunology

• Relatively new science; origin usually attributed to Edward Jenner, but has deep roots in folk medicine
• Jenner discovered in 1796 that cowpox (vaccinia) induced protection against smallpox
• Jenner called his procedure “vaccination”
It took almost two centuries for smallpox vaccination to become universal.

Vaccination enabled the WHO to announce in 1979 that smallpox had been eradicated, arguably the greatest triumph in modern medicine.
**Brief history of immunology**

- Jenner knew nothing of the infectious agents which caused disease.

- It wasn’t until the late 19th century that Robert Koch proved that infectious diseases are caused by microorganisms, each one responsible for a particular disease, or pathology.

- Broad categories of pathogen: viruses, bacteria, eukaryotes (includes pathogenic fungi, and other relatively large and complex eukaryotic organisms often just called parasites).
Brief history of immunology

- Discoveries of Koch and others stimulated the extension of Jenner’s strategy of vaccination.
- In the 1880s, Louis Pasteur devised a vaccine against cholera in chickens and developed a rabies vaccine that proved a spectacular success upon its first use in a boy bitten by a rabid dog.
- These practical triumphs led to a search for the mechanisms of protection and the development of the science of immunology.
- In 1890 Emil von Behring and Shibasaburo Kitasato discovered that the serum of vaccinated individuals contained “antibodies” that specifically bound to the relevant pathogen.
Brief history of immunology

- Meanwhile the Russian zoologist Ilya Metchnikoff showed that cells could be protective too, by engulfing and digesting foreign material, including pathogens.

- He called these cells phagocytes ("eating cells").

- Debate raged over whether antibodies or phagocytes were more important in defence.
Brief history of immunology

- By 1897 the German chemist Paul Ehrlich had started asking awkward questions like:

  How is it that antibodies and phagocytes can destroy foreign invaders but not the tissues of their host?

  How do they know what is foreign?

  What do you think?
Immunology overview

- A specific immune response, such as the production of antibodies to a particular pathogen, is known as an adaptive immune response, because it occurs during the lifetime of an individual as an adaptive response to that pathogen.
- In many cases, an adaptive immune response confers life-long protective immunity to re-infection.
- This distinguishes such responses from innate immunity, for instance many microorganisms can be engulfed and digested by phagocytes, termed macrophages.
- Macrophages are immediately available to combat a wide range of bacteria without requiring prior exposure and act the same way in all individuals.
Both innate and adaptive immunity depend upon the activities of white blood cells, or leukocytes.

Innate immunity is mediated mostly by granulocytes.

Adaptive immunity is mediated by lymphocytes.

These two main branches of the immune system together provide a remarkably effective defense system that ensures that, although we spend our lives surrounded by potentially pathogenic microorganisms, we become ill only rarely, and when infection occurs it is usually met successfully and followed by lasting immunity.
Innate immunity

Innate (aka natural, nonspecific) immunity.

- Responding to invasion requires three elements: Recognition, Disposal, Communication

- Imagine the innate immune system as police walking the beat

- Recognize villains and lock them up (or shoot, them, or disarm them…)

- E.g. phagocytes
**Innate immunity**

Innate (aka natural, nonspecific) immunity.

- Independent of *prior* contact with foreign agents
- Involves phagocytosis by macrophages responding to foreign, generic signals like bacterial cell wall constituents
- Involves inflammation reaction, cytokines, chemokines: triggers for cascades of reactions to destroy invaders
Innate immunity

- There are certain molecular patterns that are found in some pathogens and not at all in mammalian cells
  - E.g. lipopolysaccharide (LPS) in bacterial cell walls
  - Particular sugars like mannose
  - Double-stranded RNA in some viruses (which triggers release of interferon)
- These are PAMPs (pathogen-associated molecular patterns)
But what if you can’t latch on to a PAMP?

…call in the detectives…---Specific (aka adaptive, acquired) immunity.

- Recognizes small regions of particular parasite molecules
- May depend on just 5 or 10 amino acids
- Specific host immunity recognizes and bids to an epitope (a small molecular site within a larger parasite molecule)
- An antigen is a parasite molecular that stimulates a specific immune response because it contains one or more epitopes
Adaptive immunity

- Where most of the evolutionary action is
- Depends on contact between host cells and antigens (antibody generation)
- Two major categories of response: humoral immunity and cellular immunity
Adaptive immunity

Specific (aka adaptive, acquired) immunity.

• Roughly, these correspond to another way of characterizing the two branches of the adaptive immune system: **B-cell mediated** and **T-cell mediated**

• B-cell responses focus on pathogens outside of cells; T-cell responses focus on pathogens that are intracellular
Essential features of immunity

B-cell mediated immunity.

- Mediated by serum gamma globulins called **antibodies** (immunoglobulins)
- Immunoglobulins are synthesized by a class of white blood cells called **B-lymphocytes**, which originate from stem cells in bone marrow. “B” is for “bone” (or “bursa”)
- Each antibody immunoglobulin is **specific** for the antigen that induced it
**Essential features of immunity**

B-cell mediated immunity.

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T-cell mediated immunity.

- Mediated by another class of lymphocyte called **T-lymphocytes**, plus a class of phagocyte called **macrophages** (monocytes)
- T-lymphocytes also originate in bone marrow but differentiate in the thymus gland before emigrating to peripheral tissues. “T” is for “thymus”
Cytotoxic T cell recognizes complex of viral peptide with MHC class I and kills infected cell.
Essential features of immunity

Interaction of antigens with immune system cells:

1. **Inducer cells and T-lymphocytes**: most antigens interact first with inducer cells (macrophages, dendritic cells, Langerhans cells) and are presented to T-lymphocytes for initiation of immunity

2. **The macrophages**: play an important role as scavengers, taking up foreign antigen and degrading it. Some antigen is disposed of, remainder is expressed on cell surface
**Essential features of immunity**

Interaction of antigens with immune system cells:

3. **T-helper cells**: antigen on the surface of inducer cells is recognized by a subclass of T-lymphocytes called T-helper cells. They stimulate other T-lymphocytes…

4. **Cellular and humoral immunity**: various lymphocytes are stimulated including T-lymphocytes called **cytotoxic T-lymphocytes** (CTLs) that take part in cellular immunity, and B-lymphocytes that produce antibody

5. The response is **regulated** by feedback from antibodies and T suppressor cells, plus cytokines, hormone-like factors produced by immune cells
Lymphocytes, like wasps, are genetically programmed for exploration, but each of them seems to be permitted a different, solitary idea. They roam through the tissues, sensing and monitoring. Since there are so many of them, they can make collective guesses at almost anything antigenic on the surface of the earth, but they must do their work one notion at a time. They carry specific information in the surface receptors, presented in the form of a question: is there, anywhere out there, my particular molecular configuration?

Lewis Thomas, 1974
Lymphocytes

- The phenomena of antibody formation, immunological memory, and the success of vaccines were well known before 1900.
- It wasn’t until the 1950s that it became clear that they were all due to lymphocytes.
- Lymphocytes make up about a third of the white blood cells and are very different from other leukocytes like phagocytes.
- They are very long lived (years/decades).
- They recirculate from blood to tissues and back again.
Lymphocytes

- Each endlessly searches for its unique target
- When a new pathogen appears somewhere in the body, only one or a few out of the millions and millions of lymphocytes will be able to recognize it
- (Think Holmes and Moriarty)
Lymphocytes

- To increase the chance of “seeing” its nemesis, there are special locations where pathogens and lymphocytes are likely to meet.

- These are the lymphoid organs, most importantly the lymph nodes (or glands).

- When you have swollen glands, say in your throat, there’s a lot going on...

- Lymphocytes recognizing the invading virus or bacteria home in to do battle.
Lymphocytes

• Unless it takes extraordinary precautions, a pathogen cannot avoid coming into contact with the “right” lymphocyte sooner or later

• That marks the beginning of the end for most invaders

• At this point, via antibody production (B-cells) and/or various killing devices mediated (T-cells), the lymphocytes wage all out war on the pathogen

What is meant by the “right” lymphocyte?

How does a lymphocyte get to be “right”?

How many sorts of lymphocyte are there?
The “right” lymphocyte

- By “right” we’re talking about **receptors**

- Protein molecules on the surface of the lymphocytes that can bind tightly to suitably shapes molecules (think lock/key or cinderella’s slipper and foot)

- Slipper = receptor

- Foot = some tiny portion of the pathogen (**epitope**)

- Sort of similar to phagocytes, but with a crucial difference

*What?*
• The cells of innate immunity (like phagocytes) carry many different types of receptor

• All phagocytes carry the same set of 15 or more receptors of PAMPs

• Each lymphocyte carries thousands of copies of a single receptor

• It can recognize only one single shape, unique to that lymphocyte
The “right” lymphocyte

• Paul Ehrlich (1854-1915)

• Put forward the fundamental immunological idea of unique receptors on cells in 1890!

• 70 years before it was confirmed

• He thought the bonds would be chemical but they turned out to be physical--just like a slipper and foot.

“The indefatigable industry shown by Ehrlich throughout his life, his kindness and modesty, his lifelong habit of eating little and smoking incessantly 25 strong cigars a day, a box of which he frequently carried under one arm...have been vividly described.”
The “right” lymphocyte

• The lymphocyte type of recognition is often referred to as **specificity** (“specific” immunity and so on)

• To refer to the phagocyte type of innate immunity as “non-specific” is a bit unfair since they can distinguish perfectly well between most pathogens and normal body cells

• That’s actually more than lymphocytes can do: they have no way of knowing if the shape they bind to is part of a pathogen, a harmless symbiont, or one of the body’s own cells

• It is shape-directed: millions of shapes, millions of receptors

*So, where does the diversity come from?*