Introduction

Welcome to the Great Diseases Case Studies!

The case studies in this teacher manual cover a wide range of topics, including Infectious Disease, Neurological Disorders, Metabolic Disease, and Cancer. All of the cases are based on scientific data from primary papers, allowing students to work thought the processes and practices of biomedical research and scientific thinking in the context of topics that impact our everyday lives.

Structure of the cases

A case study tells a story. Sometimes this centers around a character, an event like a disease outbreak, or a scientific question. Students are given a parcel of information to use as they develop scientific questions, design experiments, analyze data, predict results, evaluate data, communicate, or develop models. After sharing their findings with the class, the next installment of information is given, moving the story forward and immersing the students in the iterative processes of research. Students will see that different methods are often required to answer a scientific question and that knowledge is revised as new findings are reported.

Teaching the cases

The case studies are based on actual data obtained from primary research papers. Using interrupted case studies based on primary scientific articles is a powerful way to engage high school students in real-life research. In part, this is because the topics and data are real so the findings may change how we chose to live our lives. In addition the scientific practices that student use mirror those that scientists use every day, making this experience both relevant and authentic.

When using these cases you may find that the life-relevant disease topics and authentic scientific reasoning makes students uncomfortable. It is important to keep in mind that these topics are engaging because they are not abstract — they impact our students directly or indirectly. This may also be the first time your students have been asked to use these scientific practices. They may be a bit apprehensive at first, but it is amazing to see how quickly they start thinking as scientists.

The Great Diseases case studies are divided into four groups, each supplementing a different module of the Great Diseases curriculum. Each case study can also be used as a 'stand-alone' lesson. Prerequisite concepts, if any, your students should be familiar with for a particular case study are described in the 'Student Prep' section of that case study's overview. Complete materials for each case study are available for **free download**[1] from the Great Diseases website.

Each case study includes:

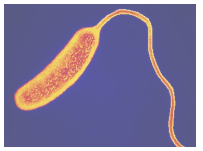
- Teacher background materials
- Teacher lesson plan
- Powerpoint teaching slides
- Student preparation materials (to assign at teacher's discretion)
- Student worksheet
- Student worksheet answers (for teacher)

1 *N.B. To restrict access to assessments, teacher downloads are password-protected; gaining a login requires a brief phone call.*

Available Case Studies

Infectious Disease (ID) Case Studies

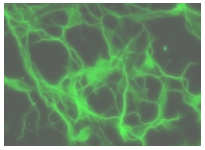
http://sites.tufts.edu/greatdiseases/modules/case-studies/cs-id/


Infectious Disease

- **ID CS 1:** What is this mysterious disease? *(Discusses the first reports of HIV infection)*
- **ID CS 2:** Do bacteria cause of stomach ulcers? Applying Koch's postulates
- **ID CS 3:** Where did HIV come from? Tracing the origin of disease
- **ID CS 4:** Antibiotic Resistance
- **ID CS 5:** How would you know if you were infected with HIV? *(Diagnosis and prevention)*

Neurological Disorders (ND) Case Studies

http://sites.tufts.edu/greatdiseases/modules/case-studies/cs-nd/


Neurological Disorders

- **ND CS 1**: The man with no memory
- **ND CS 2:** What causes Alzheimer's Disease?
- **ND CS 3:** How do placebos work?
- **ND CS 4:** What causes narcolepsy?
- **ND CS 5**: What role do cues play in addiction?

Metabolic Disease (MD) Case Studies

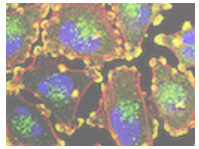
http://sites.tufts.edu/greatdiseases/modules/case-studies/cs-md/


Metabolic Disease

- **MD CS 1:** Should we say no to GMOs?
- **MD CS 2:** Do gut bacteria play a role in obesity?
- **MD CS 3:** What makes *trans*-fats so bad?
- **MD/ND CS 4:** How are the gut and brain connected?
- **MD CS 5:** Atkins vs Mediterranean diet—Which one is better?

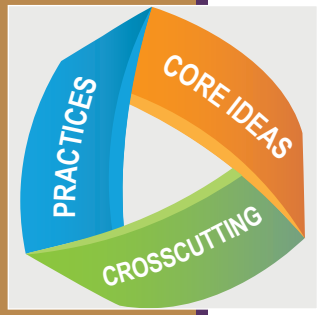
Cancer (CA) Case Studies

http://sites.tufts.edu/greatdiseases/modules/case-studies/cs-ca/


Cancer

- **CA CS 1:** Barbara's dilemma: radiation therapy
- **CA CS 2:** Fighting brain cancer with polio virus
- **CA CS 3:** Human papilloma virus (HPV) and cancer
- **CA CS 4:** Smoking and cancer

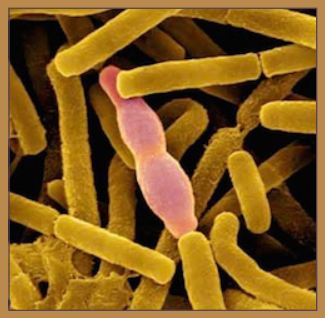
CASE STUDIES - NEXT GENERATION SCIENCE STANDARDS



NGSS Alignment

	Infectious					Neurological					Metabolic					Cancer			
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4
Cross-Cutting Concepts																			
1- Patterns	■														■				
2- Cause & Effect		■		■			■	■	■	■		■	■						■
3- Scale, Proportion & Quantity												■							
4- Systems & System Models								■				■		■					
5- Energy & Matter																			
6- Structure & Function						■	■												
7- Stability & Change																			
Disciplinary Core Ideas																			
LS1A- Structure & Function							■		■				■		■				
LS1B- Growth & Development												■				■			
LS1C- Organization in Organisms						■	■	■	■	■									
LS1D- Information Processing						■	■	■	■	■				■					
LS2A- Relationships in Ecosystems			■	■								■							
LS2C- Ecosystem Dynamics																			
LS2D- Social Interaction & Behavior					■														
LS3A- Inheritance of Traits																			
LS3B- Variation of Traits			■																
LS4A- Evidence of Common Ancestry			■																
LS4B- Natural Selection				■															
LS4C- Adaptation			■	■															
LS4D- Biodiversity & Humans																			
ETS1B- Developing Possible Solutions		■															■		
ETS1C- Optimizing the Design Solution																			
ETS2B- Influence of Science on Society	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
PS1A- Structures & Properties of Matter													■						
PS3B- Conservation of Energy and Energy Transfer																			
PS3D- Energy in Chemical Processes													■						
PS4B- Electromagnetic Radiation																			
Practices																			
1- Asking Questions & Defining Problems	■												■	■					
2- Developing & Using Models	■	■	■	■					■							■			
3- Planning & Carrying Out Investigations		■															■		■
4- Analyzing & Interpreting Data		■	■		■			■	■	■			■	■	■		■	■	
5- Mathematics & Computational Thinking																		■	
6- Construct Explanations & Design Solutions		■				■	■											■	
7- Engaging In Arguments From Evidence		■				■	■				■	■							
8- Obtain, Evaluate, Communicate Information											■			■	■	■			■

http://www.nextgenscience.org/



Teacher background can be found in the Teacher Prep folder for this lesson.

See the Great Diseases website page to download this and other materials:

https://sites.tufts.edu/greatdiseases/modules/case-studies/cs-id/cs-id4/

CASE STUDY

ID 4

OVERVIEW

Setting the Stage:
In this study, students synthesize information from different studies to arrive at a model (**P2**) to explain how human antibiotic resistant infections may be linked to antibiotic use on farms. Importantly, the evidence does not prove causation (**CCC2**), but conveys to students how an *accumulation* of evidence compels us to adopt a particular model. The concept of selective pressure is reviewed.

Recommended Integration: Between Infectious Disease (ID) Lessons 4.3 and 4.4.

Objectives:

- Describe the effect of selection pressure on antibiotic resistance (**LS4B, LS4C**).
- Distinguish between antibiotic resistance and an antibiotic-resistant infection.
- Develop a model to explain how human antibiotic resistant infections may be linked to antibiotic use on farms (**P2**).

Next Generation Science Standards:

Disciplinary Core Ideas

LS4B Natural Selection and LS4C Adaptation: We discuss how the selective pressure of antibiotics promotes natural selection of those bacteria that are resistant. Over time, with continued pressure, the population becomes resistant.

Practices

P2 Developing and Using Models: Students synthesize information from different studies to arrive at a model to explain how human antibiotic resistant infections may be linked to antibiotic use on farms.

The Lesson Plan

ID Case Study 4: Antibiotic Resistance

Student prep for Case Study 4:

Students should be familiar with selective pressure and natural selection.

- ID CS4 Handout reading (read part 1 prior to class).

1. Do Now:

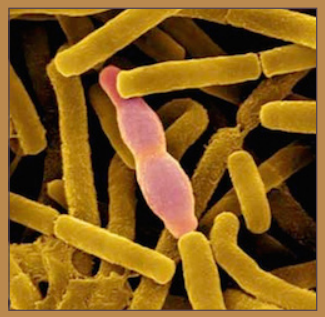
What is "selection pressure" in the context of antibiotic resistance?

2. Activities:

Analyze and interpret multiple pieces of data pertaining to antibiotic resistance.

3. Wrap Up:

Provide a model to link antibiotic use on farms with human infections.



CASE STUDY

ID 4

I. DO NOW

Learning Objectives

At the end of today's lesson, you will be able to:

- Describe the effect of selection pressure on antibiotic resistance.
- Distinguish between antibiotic resistance and an antibiotic-resistant infection.
- Develop a model to explain how human antibiotic resistant infections may be linked to antibiotic use on farms.

Slide 2

Denmark 1988

- There were 25 cases of food poisoning.
- All were infected with a strain of *Salmonella* that is usually treated with cipro antibiotic.
- The antibiotic wasn't effective and two patients died.

How did the *Salmonella* strain become resistant to the Cipro antibiotic?

Source: Molbak et al. (1999) New England Journal of Medicine 341:1420-1425.

Slide 3

Students should have read the background reading Part I prior to class. The case described in the reading refers to one of these twenty-five cases of food poisoning in Denmark, 1988.

Ask the students: If this strain of *Salmonella* had always been killed by cipro antibiotic, why wasn't it killing this strain?

- The simple answer is that the strain had become resistant to ciprofloxacin (cipro). But the bigger question is how and why did it become resistant?
- For this lesson, it is not necessary for students to understand the underlying genetics of antibiotic resistance (see background below). The point is to provide a context for students to consider selective pressure as it pertains to antibiotic resistance.

INSTRUCTOR BACKGROUND:

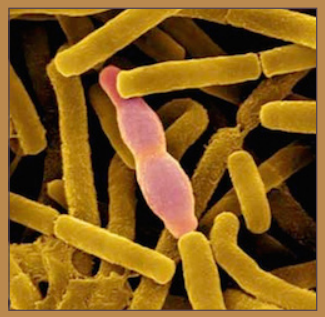
There are two classes of changes to the bacterial genome that result in antibiotic resistance.

- In the first, a random mutation alters the DNA sequence in a way that results in change to structure of an antibiotic target. The antibiotic can no longer bind to the new structure, so it is ineffective at killing the bacterium.
- In the second, a bacterial cell can acquire a large chunk of DNA from another bacterial cell. This chunk of DNA encodes several genes that promote resistance (for example, a pump that exports the antibiotic as soon as it enters the bacterial cell, keeping the cellular concentration too low to kill the cell).

Do now

- What is 'selection pressure' in the context of antibiotic resistance?
- Choose the correct scenario from the options on the worksheet.

Slide 4

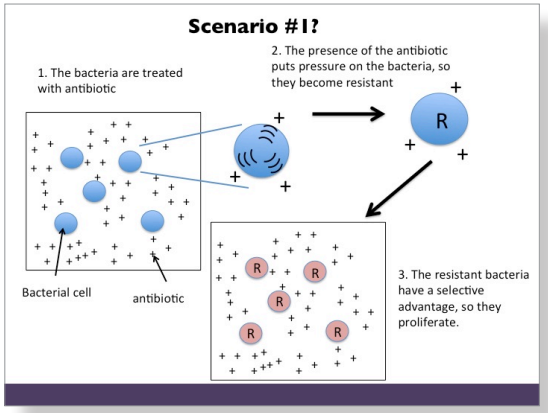


CASE STUDY

ID 4

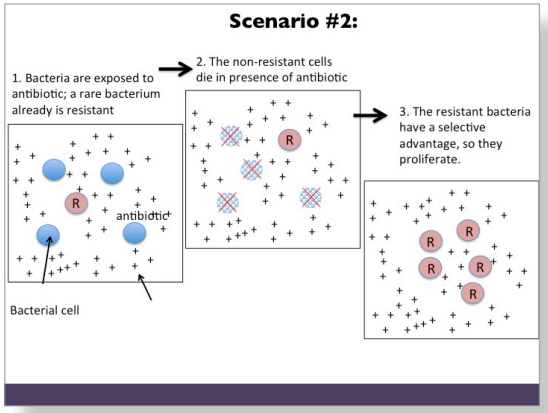
2.

Have the students choose the best scenario from the worksheet.

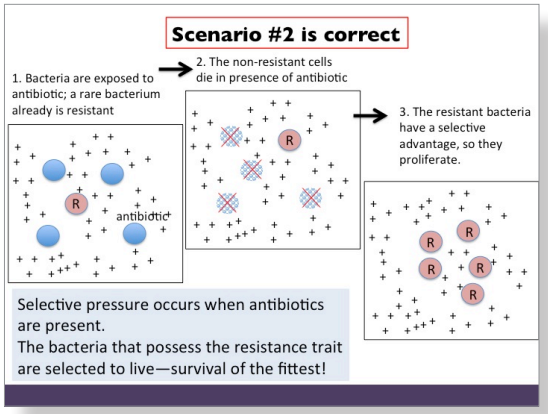


Slide 5

- Slide #1 portrays a common misconception in evolution. Heritable changes (like that needed for antibiotic resistance) do not occur in response to the environment.

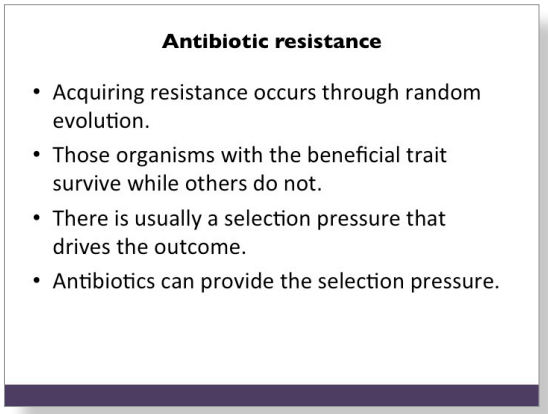


Slide 6

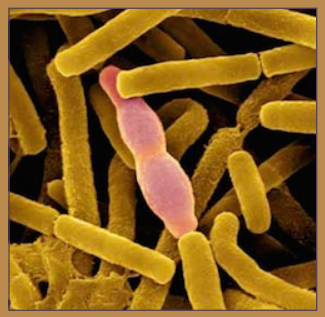


Slide 7

- Scenario #2 describes how selective pressure leads to adaptation of a population. Natural selection is at play—only those cells that already had the ability to survive in the presence of antibiotic will be able to survive and replicate. Evolutionary adaptation always refers to populations, not individuals.
- The term adaptation in the context of evolution can be confusing to students because in other contexts it can refer to change of an individual organism (*e.g.* one can adapt to living in a colder environment by wearing warmer clothes). However, adaptation in evolution refers to the ability of a population to change over time—in our example, an individual cell was able to survive the antibiotic; it passed its favorable genes onto subsequent generations so that, over time, the entire population becomes resistant.



Slide 8



CASE STUDY

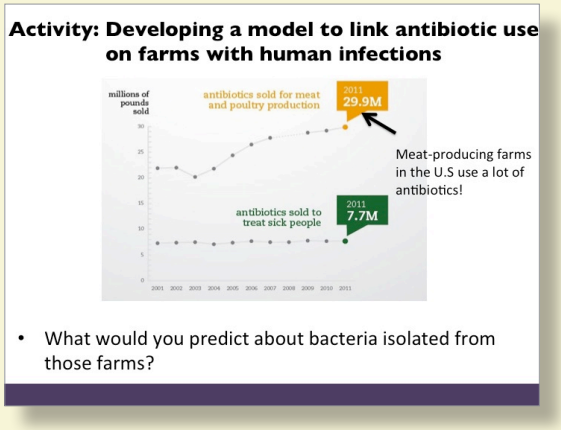
ID 4

- Acquiring resistance occurs through random evolution.
- Those organisms with the beneficial trait survive while others do not.
- There is usually a selection pressure that drives the outcome.
- Antibiotics can provide the selection pressure.

At this point, students should be able to meet Learning Objective #1.

2.

Activity



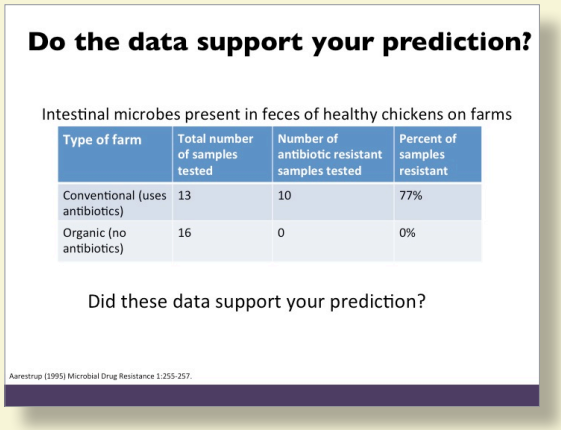
Slide 9

Ask the students: What is represented on this graph?

- The graph shows the amount of antibiotics (vertical axis) sold over time (plotted on the horizontal axis). Students may be surprised to see that the amount of antibiotics used for meat and poultry production far exceeds that used to treat sick people.

Have the students write what they predict about bacteria isolated from farms where antibiotics are used.

Have the students complete the table in the worksheet by dividing the number of antibiotic-resistant infections by the total number. They should analyze the data and determine if the results support their prediction.

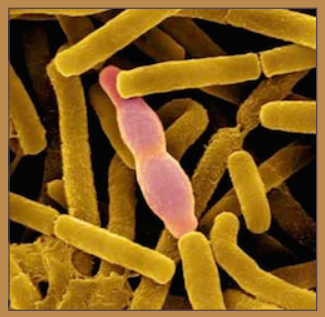


Slide 10

- Students just learned that the presence of antibiotics creates selective pressure. Based on this, one would expect that levels of antibiotic resistant microbes would be higher on farms where antibiotics are used, compared to other sites.
  - The data support the hypothesis/prediction that farms using antibiotics have higher levels of resistant microbes compared to farms that don't.
  - Many other studies in other countries and/or with different animals show the same association.

INSTRUCTOR BACKGROUND:

- The practice of providing antibiotics to healthy animals has been a widespread practice. Low levels of antibiotic (non-therapeutic levels) in feed are associated with greater animal weight gain (and therefore, more profit).
- In the experiment, researchers tested samples of a common intestinal bacterium called *Enterococcus faecium* isolated from the intestinal tract of chickens.



CASE STUDY

ID 4

2.

- This organism doesn't usually cause disease.
- The chickens were not necessarily sick; they simply had a resistant version of the organism.
- A problem arises IF someone gets sick with a resistant version; it will resist treatment by those antibiotics.

- The data show that there is an association between antibiotic use on farms and the presence of resistant bacteria in animals on those farms.
- What does this mean for human health?

Slide 11

Ask the students: What does this mean for human health?

- It is important to indicate to students that none of this data links the presence of resistant bacteria on farms with risk to humans. It is important not to jump to conclusions about effects on human health without adequate evidence.

Reason for concern?

A groundbreaking study in 1976:

Part 1
- Investigated a farm that did not use antibiotics. Took stool samples from family members and neighbors as well as chickens from the farm.

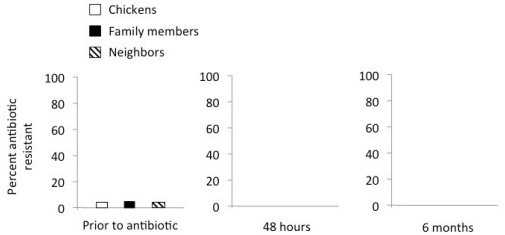
Part 2
- Added tetracycline (antibiotic) to the chicken feed.
- Over time, measured levels of tetracycline-resistant bacteria in the stool samples from family members, neighbors and chickens from the farm.

Source: Levy et al. (1976) New England Journal of Medicine 295:583-588.

Slide 12

Predict the results

Draw a graph of the percentage of bacteria in the stool samples that were tetracycline resistant 48 hours and 6 months after adding tetracycline to the chicken feed.



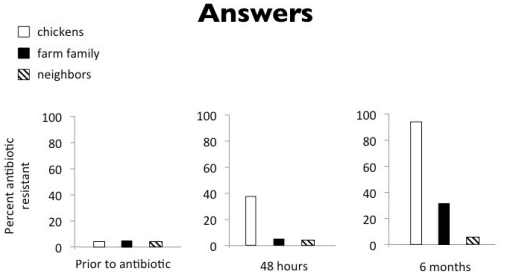
Adapted from results in Levy et al. (1976) New England Journal of Medicine 295:583-588.

Slide 13

The first graph shows the results of the control ("prior to antibiotic").

Have students draw their predictions on the graphs on their worksheets.

Answers

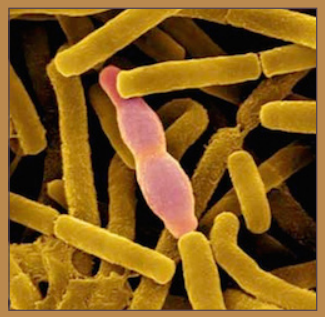


Interpret the results

Adapted from results in Levy et al. (1976) New England Journal of Medicine 295:583-588.

Slide 14

- Students will likely predict an increase in resistant bacteria in the two groups over time. In the actual experiment, an increase in resistant microbes occurred within 48 hours in the chickens, but took longer in the family members living on the farm.
- The point is that after introduction of antibiotics, people and animals in contact with those antibiotics carried resistant bacteria in their stools. These resistant bacteria were not observed in the control population (neighbors).



CASE STUDY

ID 4

2.

- There were two main controls in this study (the "prior to antibiotic" testing and the "neighbors").

- Treating the chickens on the farms with antibiotics was associated with an increase in antibiotic resistant bacteria in both the chickens and in the humans who live on and around those farms.
- This study has now been repeated many times.

Slide 15

- Treating the chickens on the farms with antibiotics was associated with an increase in antibiotic resistant bacteria in both the chickens and in the humans who live on and around those farms.
- This study has now been repeated many times.

- Does having antibiotic-resistant bacteria on your skin or in your intestinal tract mean you are sick?

Slide 16

What would be the result of having tetracycline-resistant bacteria in/on your body?

A. You would be sick and treating you with tetracycline won't cure the infection.
B. You would be sick, but treating you with tetracycline should clear the infection.
C. You are not necessarily going to get sick.
D. You would not get sick because you are resistant to tetracycline infections.

Slide 17

Have the students answer the multiple-choice question on their worksheet and then to explain their answer.

A. You would be sick and treating you with tetracycline won't cure the infection.

B. You would be sick, but treating you with tetracycline should clear the infection.

C. You are not necessarily going to get sick.

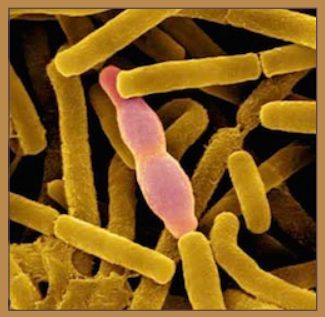
D. You would not get sick because you are resistant to tetracycline infections.

What would be the result of having tetracycline-resistant bacteria in/on your body?

A. You would be sick and treating you with tetracycline won't cure the infection.
B. You would be sick, but treating you with tetracycline should clear the infection.
C. You are not necessarily going to get sick.
D. You would not get sick because you are resistant to tetracycline infections.
- Explain your answer

Slide 18

The correct answer is C.



CASE STUDY

ID 4

2.

Just because a bacterial strain is resistant to antibiotics doesn't mean it will cause disease. It does mean that it may be harder to treat if it does result in infection. It would not be killed by treating with tetracycline.

Which is an accurate statement?

A) Humans can become resistant to antibiotics.
B) Humans can get infected with bacteria that are resistant to antibiotics.
C) Both are true.
D) Neither is true.

Slide 19

Have the students answer the multiple-choice question on their worksheet.

A. Humans can become resistant to antibiotics.

B. Humans can get infected with bacteria that are resistant to antibiotics.

C. Both are true.

D. Neither is true.

Which is an accurate statement?

A) Humans can become resistant to antibiotics.
B) Humans can get infected with bacteria that are resistant to antibiotics.
C) Both are true.
D) Neither is true.

- Animals do not become resistant to antibiotics, bacteria do.
- Some of the normal bacteria (flora) in or on our bodies may be resistant but we may never know it.
- We can become infected with resistant types of bacteria.

Slide 20

The correct answer is B.

This question addresses a common misconception—that we (humans) develop antibiotic resistance.

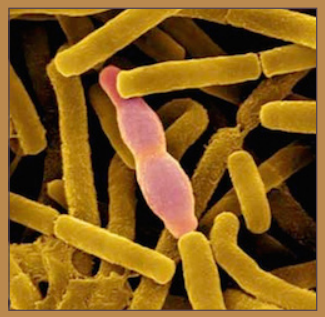
- Humans do not become resistant to antibiotics, but they can acquire bacteria that are resistant.
- Humans can harbor antibiotic-resistant bacteria as part of their normal flora (*e.g.* on skin or in their intestinal tract) and they may never become sick because of them.
- Or humans can acquire antibiotic-resistant bacteria through infection in which case the infection will not respond to treatment with that antibiotic.
- Antibiotics work by killing bacteria. They have no direct effect on human cells.

At this point, students should be able to meet the second learning objective

- What is the link between the antibiotic-resistant microbes that were found on the farm and the antibiotic-resistant human food poisoning outbreak?

Read part 2 of the background reading.

Slide 21



CASE STUDY

ID 4

2.

- Patients with the cipro-resistant infections were interviewed.
- Most had eaten pork, or had been in contact with the infected patients.
- The pork they had eaten was traced to a single herd of pigs.
- Pigs from that herd tested positive for the same strain of *Salmonella* as in the patients.

Source: Molbak et al. (1999) New England Journal of Medicine 341:1420-1425.

Slide 22

Have the students read the second part of the reading handout.

Up until this point, we haven't had any direct evidence to associate antibiotic resistant bacteria found on farms with risk to humans. But now students are presented with a strong association.

- The researchers used DNA matching to show that the strain found in the Danish *Salmonella* food poisoning victims was the same strain as that found in a pig herd.
- Those pigs had been treated with cipro.
- Most of the patients had eaten pork that could be traced to that herd (in fact the strain was isolated from frozen pork in a patient's freezer!).

Have the students answer questions 7-8 on the worksheet.

Does this story prove causation?

- This story is not proof that antibiotic use on farms causes resistant infections in humans.
- What would prove it?
- But an accumulating number of reports like this are creating consensus that the link is causative.
- In many areas of science, an *accumulation* of evidence compels us to adopt a particular model. For example:
  - Smoking and lung cancer
  - Human activity and global warming

Slide 23

- It is important to distinguish causation from correlation. However, causation is often difficult to prove.
- In many areas of science, an *accumulation* of evidence compels us to adopt a particular model. For example:
  - Smoking and lung cancer
  - Human activity and global warming

3.

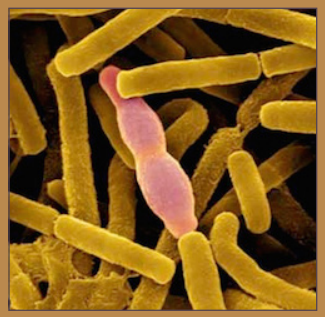
Wrap Up

Wrap Up

- Provide a model that explains how did the deadly *Salmonella* strain originally became resistant to the Cipro antibiotic?

Slide 24

Have students provide a model to explain: How did the deadly *Salmonella* strain originally became resistant to the Cipro antibiotic?



CASE STUDY

ID 4

3.

- Cipro or a related antibiotic could have been used on the farm.
- It would have provided selection pressure such that pigs carried *Salmonella* resistant to the antibiotic survived and replicated.
- The resistant bacteria remained on the pork product after slaughter and delivery to market.
- Patients ingested the *Salmonella* either through handling or consumption of raw pork.
- The strain is pathogenic and usually causes disease when ingested, but in this case wasn't treatable using the normal antibiotic prescribed.

At this point, the students should be able to meet the final learning objective.

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