

Antibiotic Resistance

Module 2



Oregon
Health
Authority

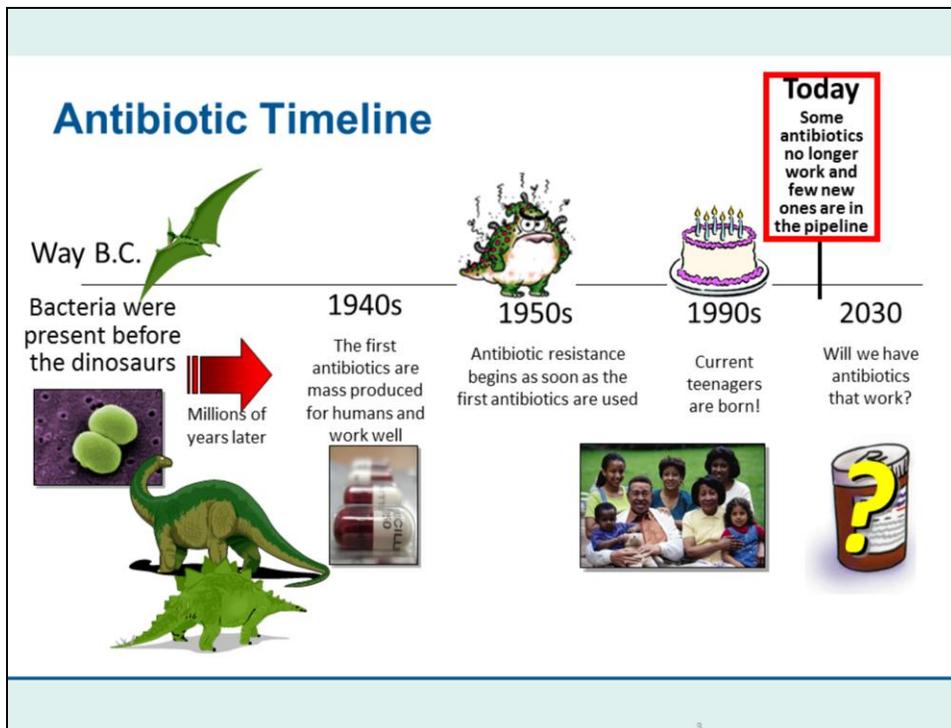
 **AWARE**
Oregon Alliance Working for
Antibiotic Resistance Education

Yesterday we learned about what bacteria are, how some are good and some can make us sick. We also learned about antibiotics and how they can help to cure bacterial infections. Today we are going to learn all about a problem known as antibiotic resistance and what we can all do to help stop it.

Overview: What Will We Learn?



- What is the history of antibiotic use and resistance?
- What is meant by spectrum of antibiotic activity?
- How do bacteria acquire resistance?
- How do bacteria become resistant?
- What has led us to the problem of antibiotic resistance?
- How do we prevent and combat resistance?



Key points:

Bacteria have been around for millions of years, surviving the ice age and the dinosaurs.

In the 1940s, antibiotics were mass produced and first used by humans to treat infections in people.

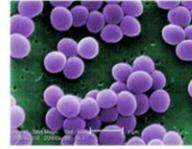
Before antibiotics were discovered and made available for physicians to prescribe, there was no effective treatment for bacterial infections. People often died from these infections. In 1924, President Calvin Coolidge's 16-year old son, who had the best treatment available, died from an infected blister on his foot.

Bacteria have continued to develop new resistance, outsmarting our antibiotics. If we don't use antibiotics properly, they may not work in the future. Today, microbiologists and researchers are discovering strains of bacteria that are resistant to multiple types of antibiotics. We even have some pathogenic bacteria that do not appear to respond to any of the antibiotics currently available.

Optional video: <https://www.youtube.com/watch?v=xZbcwi7SfZE>

Antibiotics and Resistance (CDC, 2013)

- Penicillin
 - Introduced (widespread use) in 1943
 - Resistance discovered in late 1940s (*Staphylococcus*)
- Tetracycline
 - Introduced in 1950
 - Resistance discovered in 1959 (*Shigella*)
- Methicillin
 - Introduced in 1960
 - Resistance discovered in 1962 (*Staphylococcus*, MRSA)

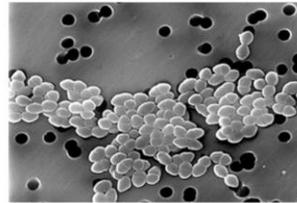
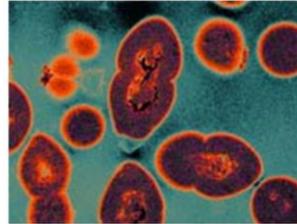


The most important point to make with this and the next slides that it is not IF resistance develops, but WHEN.

Methicillin is a modified form of penicillin that was created to circumvent penicillin resistance.

Antibiotics and Resistance (CDC, 2013)

- Vancomycin
 - Introduced 1972
 - Resistance discovered 1988 (*Enterococcus*, VRE)
 - Resistance discovered 2002 (*Staphylococcus*, VRSA)
- Linezolid
 - Introduced 2000
 - Resistance discovered 2001 (*Staphylococcus*)



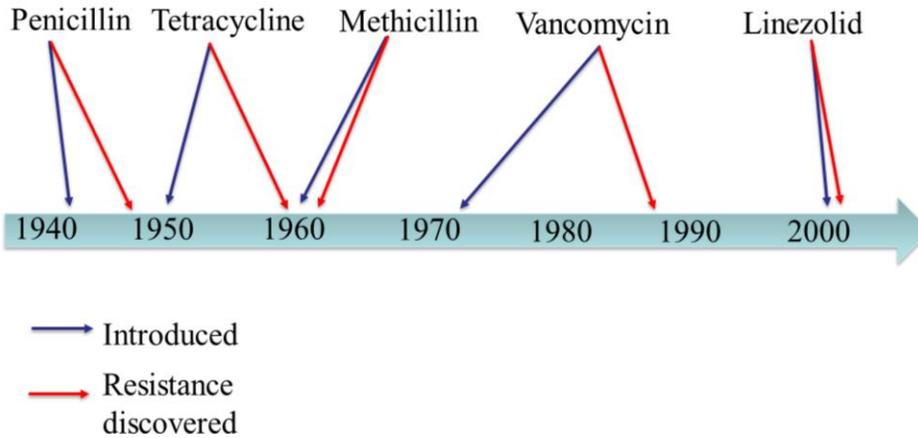
The most important point to make with these slides that it is not IF resistance develops, but WHEN.

Vancomycin has been the drug of choice to treat MRSA for some time.

Although scary, there have been very few cases of VRSA – vancomycin resistant *staphylococcus aureus*, infections. VREs - vancomycin resistant enterococci, are opportunistic pathogens in hospitals.

Linezolid is the drug used for MRSA, VRSA and others when vancomycin doesn't work.

Timeline of Resistance



Spectrum of Antibiotic Activity

- Spectrum of Activity
 - Describes how many types of bacteria the antibiotic is effective against
 - Narrow spectrum works on only one or a few types
 - Broad spectrum works on several types



This concept is important in that broad spectrum drugs are known to kill not only the target pathogenic bacteria, but beneficial bacteria as well.

This can lead to a secondary infection known as a superinfection. This is what typically occurs with *Clostridium difficile* in health care and long term care settings.

The ideal situation for antibiotic use is to know what type of bacterium is being targeted, then to use a narrow spectrum drug effective for that target.

(Question #1 from the student worksheet is answered on this slide)

Spectrum of Activity

Mycobacteria	Gram-negative bacteria	Gram-positive bacteria	Chlamydias, rickettsias
Isoniazid			
	Polymyxin		
		Penicillin	
Streptomycin			
	Erythromycin		
	Tetracycline		
		Sulfonamides	

Spectrum of Activity

- Broad-spectrum antibiotics are often used when the bacteria causing the infection is unknown
- Narrow-spectrum antibiotics are preferable for use, as they are less likely to harm beneficial bacteria



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Text:

Narrow-spectrum antibiotics are targeted for a limited group of bacterial species.

Broad-spectrum antibiotics are effective against a wide range of bacterial species.

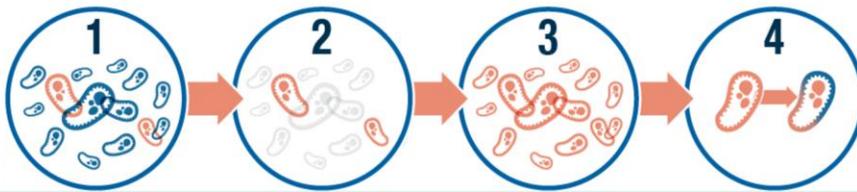
A narrow-spectrum antibiotic should be used, whenever possible, to target the specific bacterial infection. This preserves the colonizing bacteria in your body and avoids selection of resistance in these bacteria that might later cause an infection. A lab test will show the sensitivity (or susceptibility) of the bacteria to specific antibiotics. This is the most effective way to treat the bacterial infection and prevent the development of resistance.

Sometimes a laboratory sensitivity test cannot be done. In that case, a broad-spectrum antibiotic is often used. This may or may not be the most effective antibiotic for the bacteria.

(Question #3 from the student worksheet)

Selection for Resistance

- Example of Natural Selection
 - Bacteria either have gene or do not have gene for antibiotic resistance
 - Bacteria are exposed to drug; susceptible bacteria (no resistance gene) die, while resistant bacteria (the ones with a resistance gene) survive
 - Over time, resistant bacteria multiply, and the infection becomes resistant to that drug



Bacteria do not ‘become’ resistant in response to the presence of drug. Those that have the correct genes are selected for in the presence of drug, then those survivors reproduce to create a resistant population.

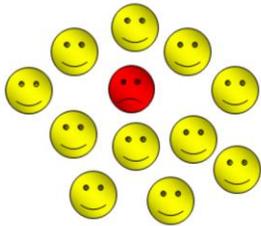
So, bottom line, any time a drug is used, it has the potential to select for those bacteria that have resistance genes.

Once again, not a matter of ‘if’, but ‘when’

(Question #2 from the student worksheet)

Drug Use Selects for Resistance

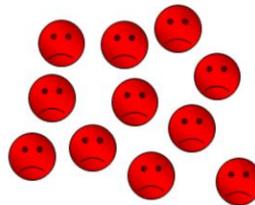
Sensitive and resistant bacteria live together.



Antibiotics kill sensitive bacteria.



The resistant bacteria are left to multiply.



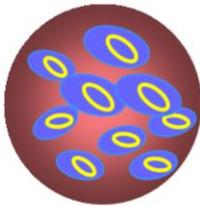
Text:

An antibiotic kills the susceptible bacteria but the resistant bacteria stay in the body and multiply.

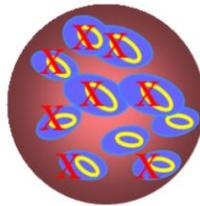
When a person develops resistant bacteria, other antibiotics that have disadvantages (such as toxicity, less convenient administration, or greater cost) may be required. Some resistant bacterial infections become resistant to multiple classes of antibiotics or cannot be treated at all.

Every time you take an antibiotic, even when there is a good reason and the antibiotic is appropriate, you subject the bacteria to this selection process.

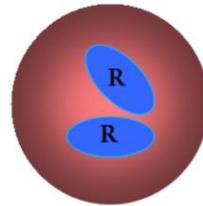
Unnecessary Antibiotics Cause Resistance



Jane takes penicillin.



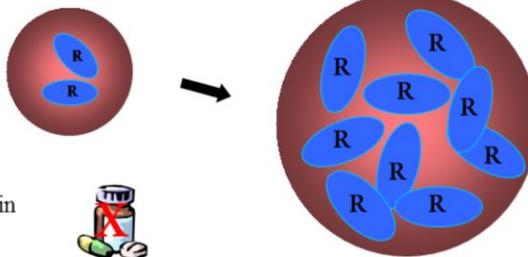
Susceptible bacteria are killed off.
A few hardy survivors are left behind.



The survivors can withstand penicillin.

Resistant Bacteria Can Multiply and Spread

The resistant survivors multiply.



Treatment with penicillin has no effect.



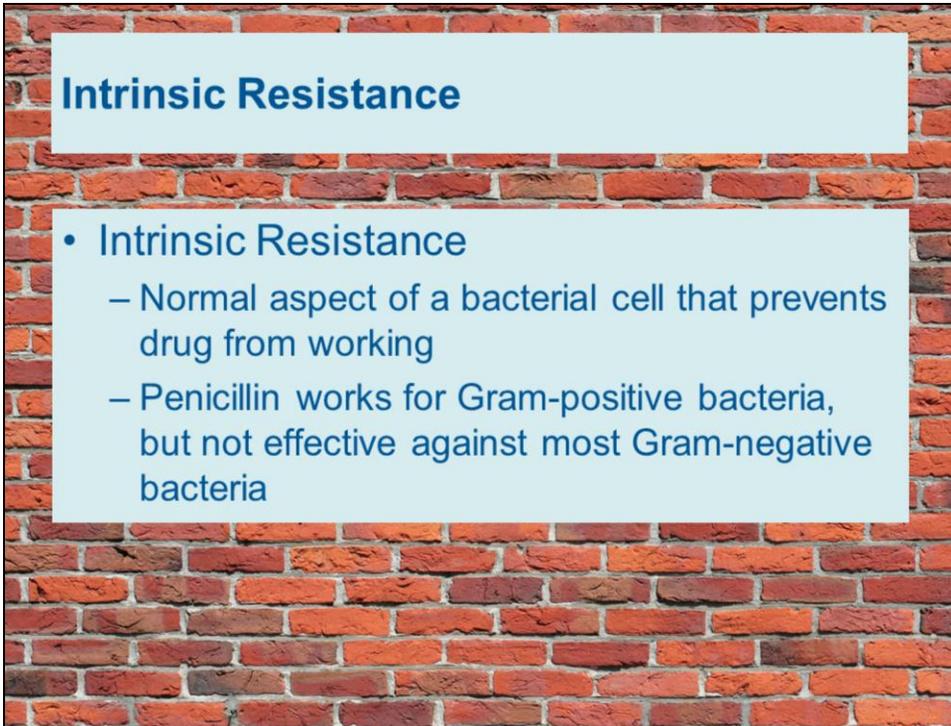
Jane is now a carrier of penicillin-resistant bacteria.

Now that Jane is a carrier of resistant bacteria, she can spread resistant infections to others in her family and community.

Types of Antibiotic Resistance

- Two main types of resistance
 - Intrinsic Resistance
 - Acquired Resistance
- Acquired resistance is the most problematic form





Intrinsic Resistance

- Intrinsic Resistance
 - Normal aspect of a bacterial cell that prevents drug from working
 - Penicillin works for Gram-positive bacteria, but not effective against most Gram-negative bacteria

Not all drugs are effective against all types of bacteria – intrinsic resistance.

Acquired Resistance

- Acquired resistance can arise in two ways
 - Novel mutations in the DNA of a bacterial cell that lead to mechanism that counteracts effects of drug, OR
 - Acquisition of new genes via sharing of DNA from other bacteria
 - Transformation
 - Conjugation



It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

There are two ways novel resistance genes are acquired by a susceptible bacterium.

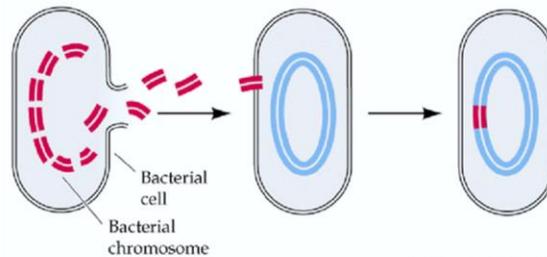
The first is that a spontaneous mutation occurs that alters the gene that leads to resistance. An excellent example is resistance to ciprofloxacin in *Campylobacter jejuni*, a leading cause of self-limiting diarrhea. Ciprofloxacin binds to DNA gyrase, a key enzyme in DNA replication. In some resistant strains of *C. jejuni*, a single substitution mutation leads to a single amino acid difference in the DNA gyrase enzyme. This single change prevents ciprofloxacin from binding.

Mutations do not have to be dramatic to cause resistance.

(Question #4 from the student worksheet)

Transformation

- Some bacterial cells can take up pieces of DNA from environment
- This DNA could contain a gene (or genes) for antibiotic resistance



Transformation is the uptake and incorporation of a piece of DNA from the environment. Often, the source of this DNA are dead bacteria that release their contents upon lysis.

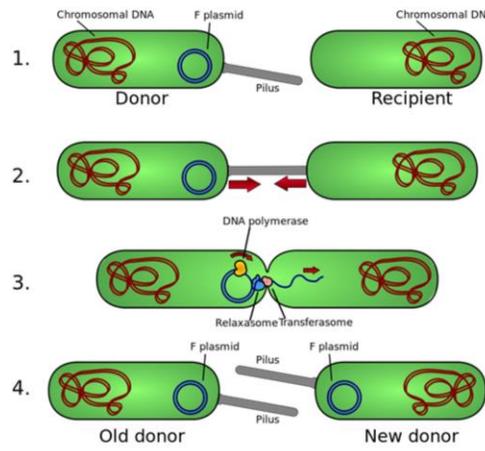
In the spread of antibiotic resistance, this commonly happens in the intestines of the host organism.

Conjugation

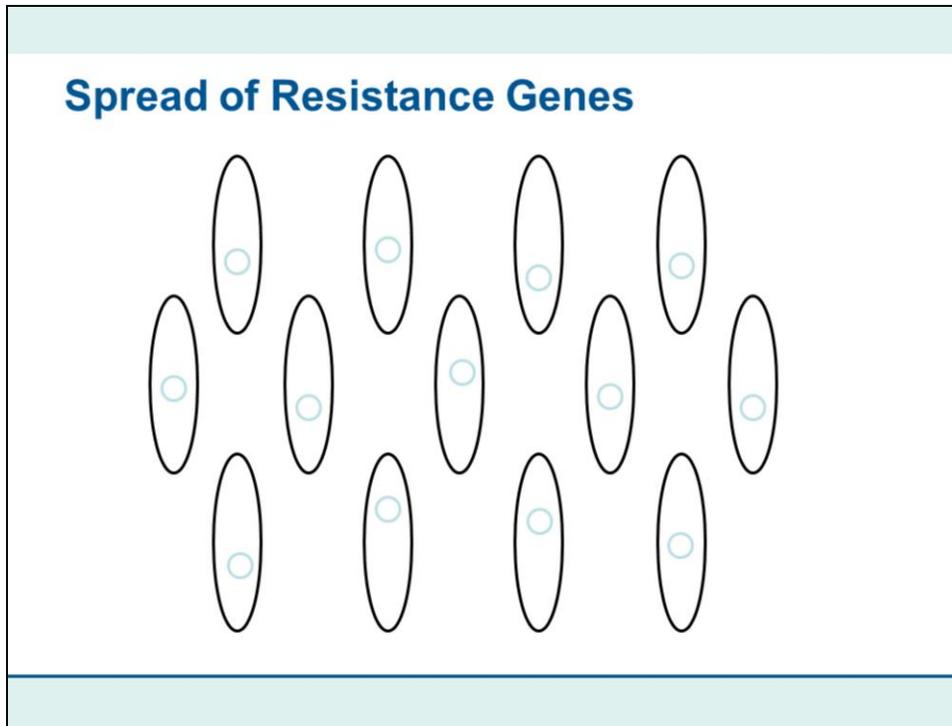
- Transfer of a copy of a plasmid, a small, circular piece of DNA, from one bacterium to another
- Plasmids often contain antibiotic resistance genes
- Entire populations of bacteria can share resistance genes very quickly



Conjugation



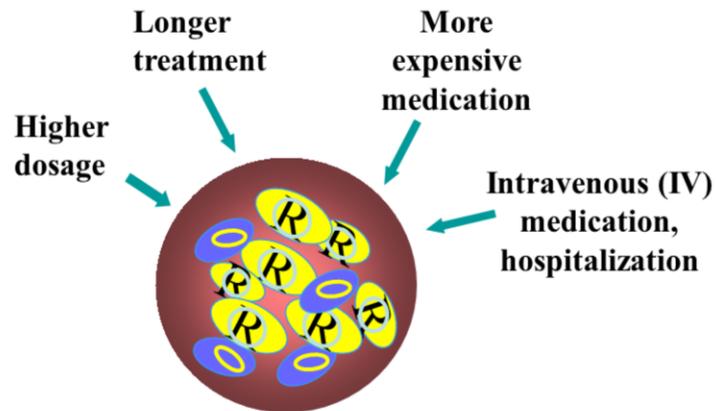
By Adenosine (Own work) [CC BY-SA 3.0 (<http://creativecommons.org/licenses/by-sa/3.0/>)], via Wikimedia Commons



A good exercise to complement this slide is to have students play a game of ‘tag’. Start with one student who is resistant – they ‘tag’ one other student, now there are two that are resistant. These two ‘resistant’ students then ‘tag’ one more student each, and so on.

This shows the exponential spread of the resistance genes in a population, and is a good way of showing just how fast the genes can spread.

Resistant Infections Require Special Treatment



Treatments for resistant infections are more dangerous and expensive.

(Question #5 from the student worksheet)

Scenario 3

- Amy has strep throat and has been given penicillin
- She feels better after a couple of days, and her parents decide she no longer needs the medicine
- A few days later, her grandmother comes down with strep throat
- The doctor prescribes penicillin, but it is ineffective



Scenario 3

- How did Amy's grandmother acquire strep throat?
- Why did the penicillin not work for Amy's grandmother?
- What mistake did Amy's parents make regarding her penicillin usage?
- What was the ultimate cause of penicillin resistance in the strep bacteria?

Mechanisms of Resistance

- Bacterial genes produce different mechanisms of resistance
- For example:
 - Produce enzymes that inactivate the antibiotic
 - Pump the drug out of the cell before it gets a chance to work
 - Alter the target site where the drug usually binds to the bacteria, so it can't bind anymore

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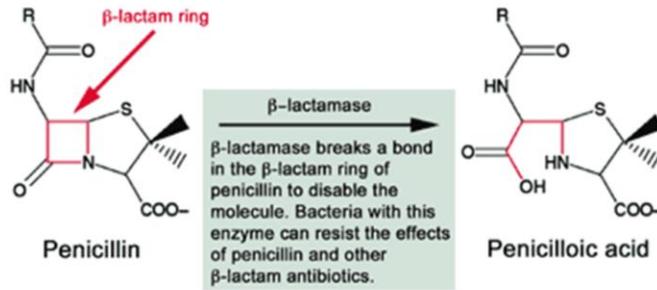
Bacteria are clever! Bacteria become resistant to antibiotics by mutations in their bacterial genes preventing susceptibility to current antibiotics. Such bacterial gene mutations include:

- Changing the bacterial cell wall so it is less permeable and prevents the antibiotic from entering the cell
- Producing enzymes that inactivate the antibiotic
- Pumping the antibiotic out of the cell before it gets a chance to work
- Altering the target site where the antibiotic usually binds to the bacteria, preventing the antibiotic from binding to the site where it has its effect

(Question #6 from the student worksheet)

Antibiotic Inactivation

Penicillin Resistance



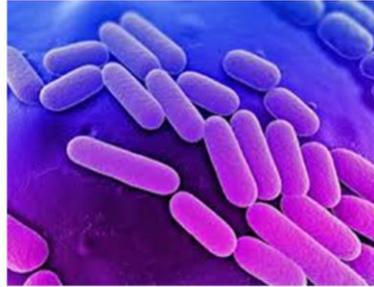
The Problem of Antibiotic Resistance

- The misuse and overuse of antibiotic drugs in food production and health care has led to the current state of widespread antibiotic resistance at both national and global levels



The Problem of Antibiotic Resistance

- Resistance rates in bacteria are still increasing
- For example, rates of resistance to Carbapenem (similar to penicillin) among *Klebsiella* samples (a common hospital acquired bacterium) increased from 1.6 % to 10.4% from 2001 to 2011 (MMWR, 2013, 62:9)



CRE – Carbapenem Resistant Enterobacteriaceae are a growing concern in hospitals and other health care facilities.

These opportunistic pathogens are highly problematic with regard to immunocompromised patients.

Note - There was no graphic in the original paper.

Agriculture

- Bacteria with resistance can be transmitted to humans through animal products
- Two main factors are related to increased rates of resistance in bacteria
 - In-feed antibiotics given at low dosages (known to increase growth rate of animals)
 - Antibiotics added to water and feed as a preventative measure against common infections



Drugs are given to animals in feed and water to boost growth rate – this increases productivity and profit.

Some animals, such as chickens, are given drugs as prophylactics to prevent the acquisition of infection.

In each case, the dosages may not be high enough to kill bacteria, and over time, those bacteria with greater resistances are selected for.

(Question #7 from the student worksheet)

Health Care

- Antibiotic use in health care is problematic at many levels
 - Patient
 - Provider
 - Pharmaceutical Industry



Antibiotic resistance in the health care field is a multi-faceted problem.

Health Care

- Patient
 - Antibiotics not taken as directed
 - Skipping doses
 - Not taken for full length of prescribed time
 - Antibiotics asked for in cases of viral infection – cold, flu, sinusitis, etc.
 - Antibiotics not effective against viral infection



Antibiotics must be taken as directed. This is critical, as clinical dosages must be maintained within the patient. Additionally, if a prescription is ended early, it is very likely that only the most susceptible bacteria have been eliminated. Any bacteria remaining will multiply and there is a likelihood that resistance can develop.

Antibiotics are not effective against viral infections. Most cases of sinus infections (~90%) are viral. Many patients will demand antibiotics – puts provider under pressure to comply.

Health Care

- Patient
 - Self-prescribing
 - In some countries, do not need prescription for antibiotics
 - Some people will take old antibiotics if they think they have a new infection
 - Improper Disposal
 - Flushing drugs down the toilet or sink can lead to resistance in environmental bacteria



Self-prescribing – in some countries, you do not need a prescription to buy antibiotics at a drug store. In the US, people will take antibiotics they have at home as a form of treatment, whether appropriate or not.

Drugs that are flushed down the drain have an impact on the number of bacteria in the environment that develop resistance. These bacteria are then a potential source of infection, or at the least a potential source of new genes for other bacteria.

Health Care

- Provider
 - Prescribe antibiotics when not needed
 - Pressured by patient to prescribe antibiotics when ineffective
 - Incorrect diagnosis (viral v. bacterial sinusitis)
 - Broad spectrum drugs prescribed
 - May affect more than just infective bacteria
 - Can promote selection of resistance genes in otherwise harmless bacteria



Practitioners have become much better educated over the past decade, but instances of over-prescription overuse still exist.

Health Care

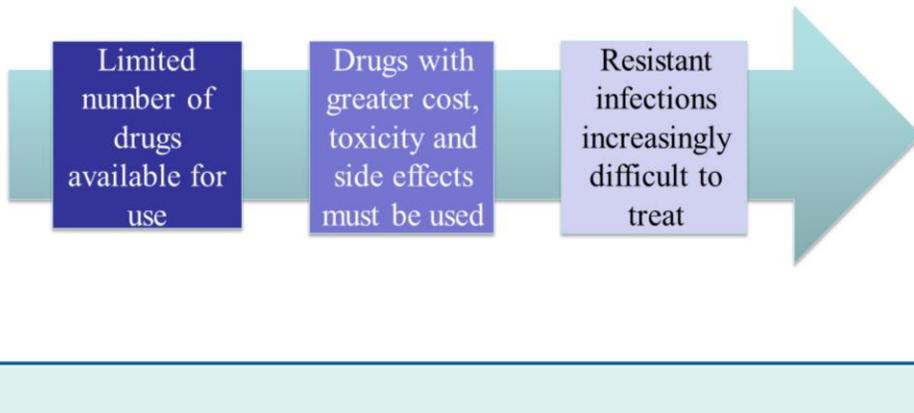
- Pharmaceutical Industry
 - Very little development of new antimicrobials over last three decades
 - Medications for chronic conditions such as high cholesterol, diabetes, etc. more profitable than antibiotics



Most research in to new antibiotics takes place in academia. Unfortunately, researchers do not have the means to follow through and develop a drug for commercial use. Over the past 30 or so years, the pharma industry has ignored antibiotics, as they do not provide the return on investment that life-long drugs do.

Consequences of Resistance

- Number of appropriate antibiotics decreasing



As the number of effective drugs decreases, those drugs that are more toxic, more expensive or with negative side effects must be used.

(Question #8 from the student worksheet)

Consequences of Resistance

- Number of infections that cannot be treated with known antibiotics increasing
 - Colistin resistance – drug of last resort, no way to treat infection



Colistin has been a useful drug because it has not been in use for some time. Recently, a patient with colistin resistant E. coli was found in the US. That means that this drug of last resort is already on its way out as a useful drug.

Combating Resistance

- Prevent Infection
 - Hand-washing and proper hygiene
 - Immunization
 - Healthy lifestyle: proper nutrition, exercise, regular sleep habits
 - Handle and prepare food properly



(Question #9 from the student worksheet)

Combating Resistance

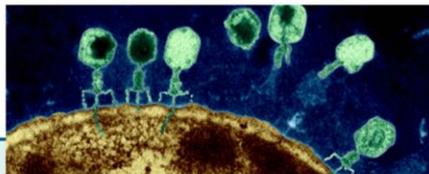
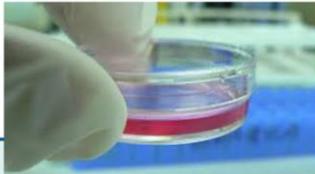
- Proper antibiotic use
 - Take for prescribed time and as directed
 - Do not share antibiotics
 - Dispose of properly
 - Only take for bacterial infection
 - Limit use in food animals
 - Use narrow spectrum drugs after infective agent has been identified



(Question #10 from the student worksheet)

Combating Resistance

- Drug and alternative treatment discovery
 - Support for new drug discovery
 - Lugdinin – substance produced by bacteria in nose that kills *Staphylococcus aureus* (MRSA)
 - Alternative therapies
 - Bacteriophage therapy
 - Bacterial viruses that are specific to certain types of bacteria
 - Bacterial viruses do not infect humans
 - Shown to be effective against skin and eye infections



Recently in the news, lugdinin is a protein produced by the bacterium *Staphylococcus lugdunensis*. This bacterium is a natural inhabitant of the nose and produces the protein lugdinin that kills the more harmful *Staphylococcus aureus*. Researchers wanted to know why some people did not harbor *S. aureus* in their noses, and it was found that they had *S. lugdunensis* in their noses. This is a great example of how new drugs can be discovered.

Bacteriophage therapy has been used for decades in Russia and other old Soviet Union countries. These viruses are specific to bacteria and do not infect humans. In addition, resistance is not likely, as the viruses themselves mutate to keep up with the bacteria. So far, their use has been limited in the US, but studies from Europe have suggested the treatment method works.

Combating Resistance

- National (USA) Initiatives
 - National Action Plan for Combating Antibiotic Resistant Bacteria – March 2015, Executive Order 13676
 - Antibiotic Resistance Solutions Initiative – CDC, 2016



Both national and international programs have been established to combat the growing problem of antibiotic resistance.



- Every time someone takes an antibiotic, resistant bacteria may be selected for and multiply
- Resistant bacteria may then spread to others, compromising the effectiveness of treatment for future infections
- Share what you have learned with your friends and family members



Another way you can make a difference is to share what you have learned about bacteria, appropriate antibiotic use, how resistance develops and how to prevent it. Share this information with your families, friends and other people in your community. Think twice about asking your care provider for an antibiotic. You can also consider how you can make a difference in the professional world when you graduate. There are many kinds of jobs in multiple fields that can help prevent antibiotic resistance including research, microbiology, animal husbandry, medicine, and health care administration to name a few. **YOU CAN MAKE A DIFFERENCE!**