Week 7: Antibiotic Resistance

700,000 people per year die from antibiotic resistant pathogen and may reach over 10 million by 2050 ⇒ $100 trillion

What is Antibiotic Resistance

A big threat to global health, animal and food security.

It occurs naturally, through the use of antibiotics in human and animal (which accelerates the process).

E.g.) Tuberculosis, pneumonia, gonorrhea are becoming harder to treat as antibiotics are becoming less effective

⇒ Higher mortality, longer hospital stays, high costs.

WHO response to antibiotic resistance

- Improve awareness
- Strengthen surveillance and research
- Reduce infection incidence
- Optimise the use of antimicrobial medicines
- Ensure sustainable investment in countering antimicrobial resistance

Antibiotics History

- Ancient Cultures: Mold, plant materials to treat infections.
- 1874, Sir William Roberts noticed bacteria cannot grow in the presence of Penicillium Notatum
- 1897 Ernest Duchesne showed that E.coli can be eliminated by fungus Penicillium glaucum
- 1880's Paul Ehrlich used dyes that can colour bacterial cells to screen dyes and produce antibacterial drug in 1907 (salvarsan)
- 1928 Sir Alexander Fleming identified penicillin as an active ingredient that can block bacterial replication
- 1942 Ernst Chain and Howard florey purified the first penicillin

Antibiotics - side effects

70 billions clinical doses for 6 billion population (36% increase from 2000 to 2010)

- Diarrhea: Kills relationship with intestinal flora
- Overgrowth of yeast in vaginal area: antibiotic kills symbiotic bacteria needed to prevent overgrowth of yeast
- Obesity and Weight gain: Important for agriculture, cows.
- Might impact efficiency of birth control pills

Transfer of Antibiotic Resistance Genes

Plasmids

DNA circular molecule that replicates independently of chromosomal DNA, in a suitable host.
Allows for horizontal(neighborhood) and vertical(mother to daughter) gene transfer

Horizontal is a problem as a bad gene can be passed on to a community

Can vary from 1-200kilo bp (for research purposes we only use 15 kbp)

Implication

Used a route for transferring drug resistance genes among bacteria
The drug resistance gene may integrate into the genome of the bacteria host

Antibiotics: Mechanisms of Action and Drug Resistance

How antibiotics work
B-lactams: Inhibition of cell wall synthesis or disruption of cell membrane
Aminoglycosides: Inhibition of ribosome
Sulfonamides: Disruption of single-carbon metabolism
Quinolones: Disruption of DNA replication and integrity

How antibiotic resistant genes bypass this effect
Enzymatic degradation or modification
Alteration of antibiotic target
Active ejection of antibiotic from the cell
Reduce the cell's permeability

Chemical Structure of selected antibiotics

B-lactamase all have similar chemical structures, what we do is we alter them all a little bit so that it can bind differently.

Development of Antibiotics

There has been no new lead class of antibiotics in the last 30 years.
Antibiotics have been developed based on the effects of two microbes, whether the presence of one inhibits the other, which genes are essential players for these. From this the chemistry tried to be exploited and modified for use.
Problem: Many of them are ineffective due to overuse.

Global Spread of plasmid-borne resistance

Plasmid-borne resistance has been spreading globally.
Colistin and Vancomycin are some of the last resort of antibiotics

Antibiotic Stewardship

Infection prevention requires

- a collaborative approach that optimize the use of antibiotics
- Global coordination to overcome the different guidelines for different countries

This requires

- Government advocacy
- Collaborative research
- International guidelines
- Online training programs/mentoring programs
- Social media

South Africa is doing a much better job at doing this because they have a tighter policy in regulated antibiotic control (because of the high infection rates), compared to USA.

Co-localization of resistance genes, mobility elements and resistance regulatory elements.

When things get transferred from one organism to another, the mobility element can help deliver a genetic material and integrate it to a different system, supported by the resistance regulatory element

Next Generation Sequencing

By using NextGen sequencing, we are able to get data about origin of drug resistant genes and how they are being transferred.

Drug Development

- Informing combination therapies
- Risk prediction for new antibiotics
- Informing Resistance Inhibitors

Resistance Surveillance

- Identification of new resistance genes
- Risk assessment and prediction
- Improvement of bioinformatics

First Gen: Capillary sequencer (takes ages)

Classes of bacteria developing resistance

→ Due to influence of veterinary antimicrobial drugs. A view on the usage and consequences.

Target Pathogen → Efficacy in animal (farm)→ Animal Health Issue

Zoonotic → Efficacy in man (food chain) → Individual Health Issue

Commensal → Global ecological problem (environment) → collective issue

Treating animals with antibiotics in the early stage can increase weight gain → Economically great, but poses a problem for resistance.

They use sub-therapeutic concentrations of antibiotics to promote animal protein production (growth). These antibiotic resistant microbes can develop within the animal, or when the drug is released (excreted) by the animal, may be picked up by microbes within the environment.

Impact of AMD on Gastrointestinal microbiota after administration

The antibiotic would affect the microbiota → resistant bacteria development.

Antibiotic Adjuvants

Adjuvants in a vaccine setting, enhances immune response against antigens
Adjuvants are given with antibiotics to make them more effective and last longer

- Class I: Inhibit active or intrinsic (passive) antibiotic resistance in bacteria
- Class II: Enhance host ability to kill bacteria

You need to know what drug resistance mechanisms the bacteria has, as the adjuvants are used to counteract these genes. → Where next generation sequencing comes in

Antivirulence drug development

Antibiotics are more broad that can kill most microbes (unless they have drug resistant genes). But why not develop a drug that is more specific to the infecting pathogen? By doing so, you will be able to handle the pathogen infections without affecting other microbes, whose within the scope of antibiotics.

The challenge is: For each pathogen → you need specific drugs → Increased cost

Advantage	Disadvantage
-Little impact on host commensal flora -Can inactivate target rapidly -Improve less evolutionary pressure of microbes to adapt to drugs (hence resistance) than antibiotics -Can supplement antibiotics to increase efficacy -Protect immunocompromised/unvaccinated individuals	-Might require combination therapy to account for multiple, strain variable virulence factors -May not be effect for all forms of disease by the same pathogen -Have reduced therapeutic effects than antibiotics -Require identification of bacterial pathogen -Bacteria may persist and cause damage after therapy is withdrawn

Bacteriophages as means to control bacteria

Viruses for bacteria to control bacterial populations, since they are specific to bacteria and have relatively little harm to us.
Challenge: You need to select the right bacteriophage, grow them and amplify them.
Replication cycle of Bacteriophage
Attach to bacteria surface and inject its genome inside.

- Lytic cycle: Phage DNA replication, synthesis, phage assembly, host cell lysis, escape
- Lysogenic cycle: DNA of phage integrated into host genome before entering lytic cycle.