The War on Bacteria

Key Stage 4 Programme – 2016/2017

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Pupil Name:_____

Timetable and Assignment Submission

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Course Rationale

Antibiotic resistance remains a global health concern with deaths attributed to resistance due to outnumber those caused by cancer in 2050. There is a growing concern that without an increase in new treatment methods or a decline in the spread of resistance there will be a return to the 'dark age' of medicine where diseases that were previously treatable become untreatable once more and procedures that are currently routine will once again become impossible. This course is aimed at students who are interested in biology and chemistry and will look at the development of resistance and the future of drug development within these fields focussing specifically on *Mycobacterium tuberculosis* (the causative agent of tuberculosis). Tuberculosis is often thought of being an 'old' illness but is once more on the rise with a large spread in drug resistant strains.

This course gives students the key background biological knowledge to understand the basics behind antibiotic resistance before going on to examine some cutting edge future treatments that are being developed. The final assignment, entitled 'Why haven't we won the war on tuberculosis?' will require students to research and analyse current treatments available and potential future treatments before concluding on a treatment pathway they see as being the 'future' in the fight to provide new effective drugs. They will be required to put forward a logical argument as to why their drug pathway is more effective than others they have mentioned and what advantages/disadvantages it has over current treatments. Students will be expected to engage in university style tutorials and will be exposed to critical thinking and reasoning.

Tutorial 1 – Sources of Disease

Today's Key Questions:

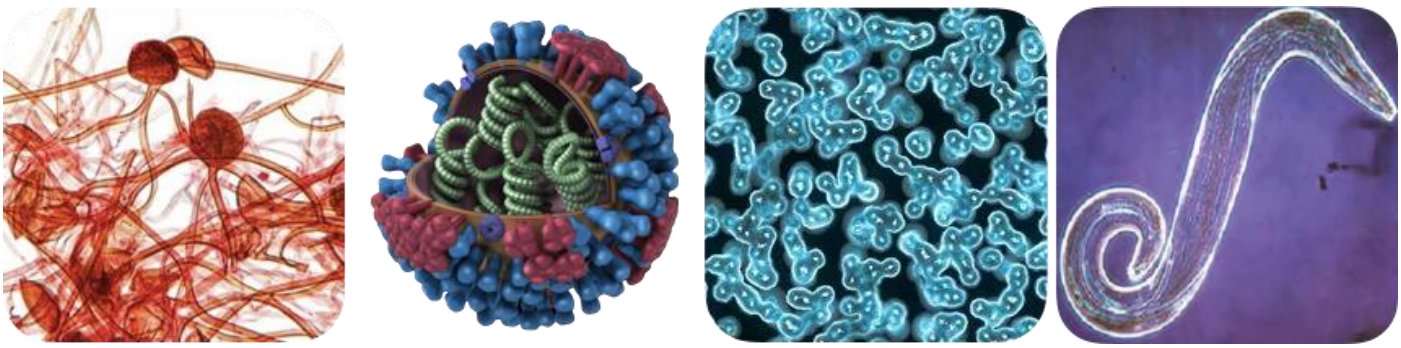
- What are the four causes of disease?
- How can disease be spread?
- What are the key structures of a bacterial cell?
- How do bacteria differ fro animal or plant cells?

What is the Purpose of Tutorial 1?

- Recall sources of disease
- Identify mechanisms for the spread of disease
- Develop an understanding of the basic bacterial cell structure.

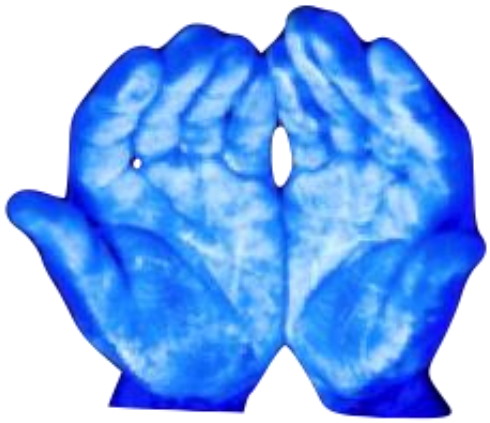
Causes of disease-

There are 4 main factors that result in disease in humans: these are bacteria, fungi, viruses and parasites (see Figure 1). All of these can cause a variety of illnesses.



Disease transmission-

There are six key mechanisms, through which disease can be transmitted, label the following:



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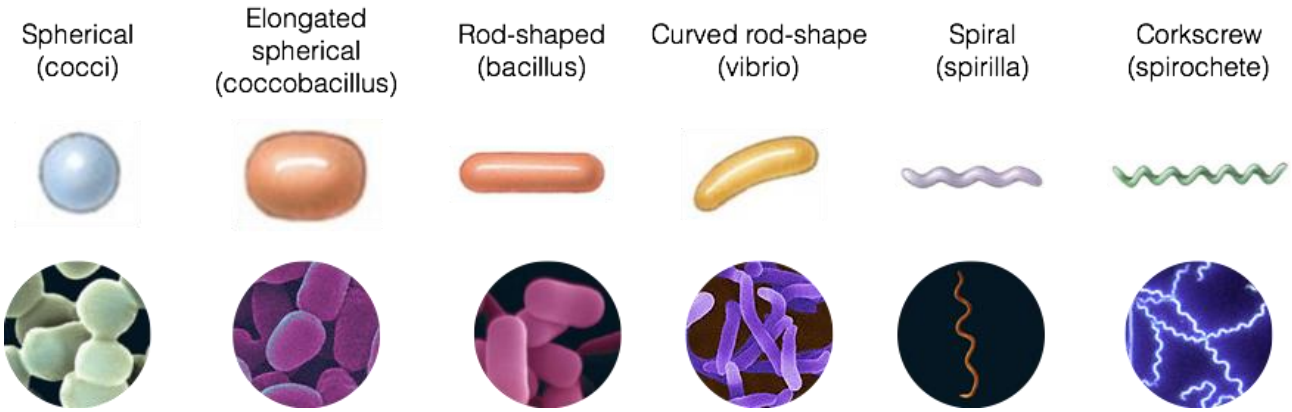
Bacterial cells-

Bacteria are one of the divisions of prokaryotic organisms, this means that they don't have a 'true' nucleus which contains all of their genetic information. They are typically a few micrometres in length and come in a variety of shapes including rods, spheres and spirals.

Some intermediary shapes also exist and these are known as coccobacillus (an elongated spherical form), vibrio (a curved rod-shaped form) and spirochete (a corkscrew structure).

They were thought to be one of the first forms of life to exist and have adapted to exist in almost all environments including the deepest part of the ocean (the Marianna Trench).



Exercise: many bacterial names indicate their shape, see if you can identify which bacteria is which based on shape alone!

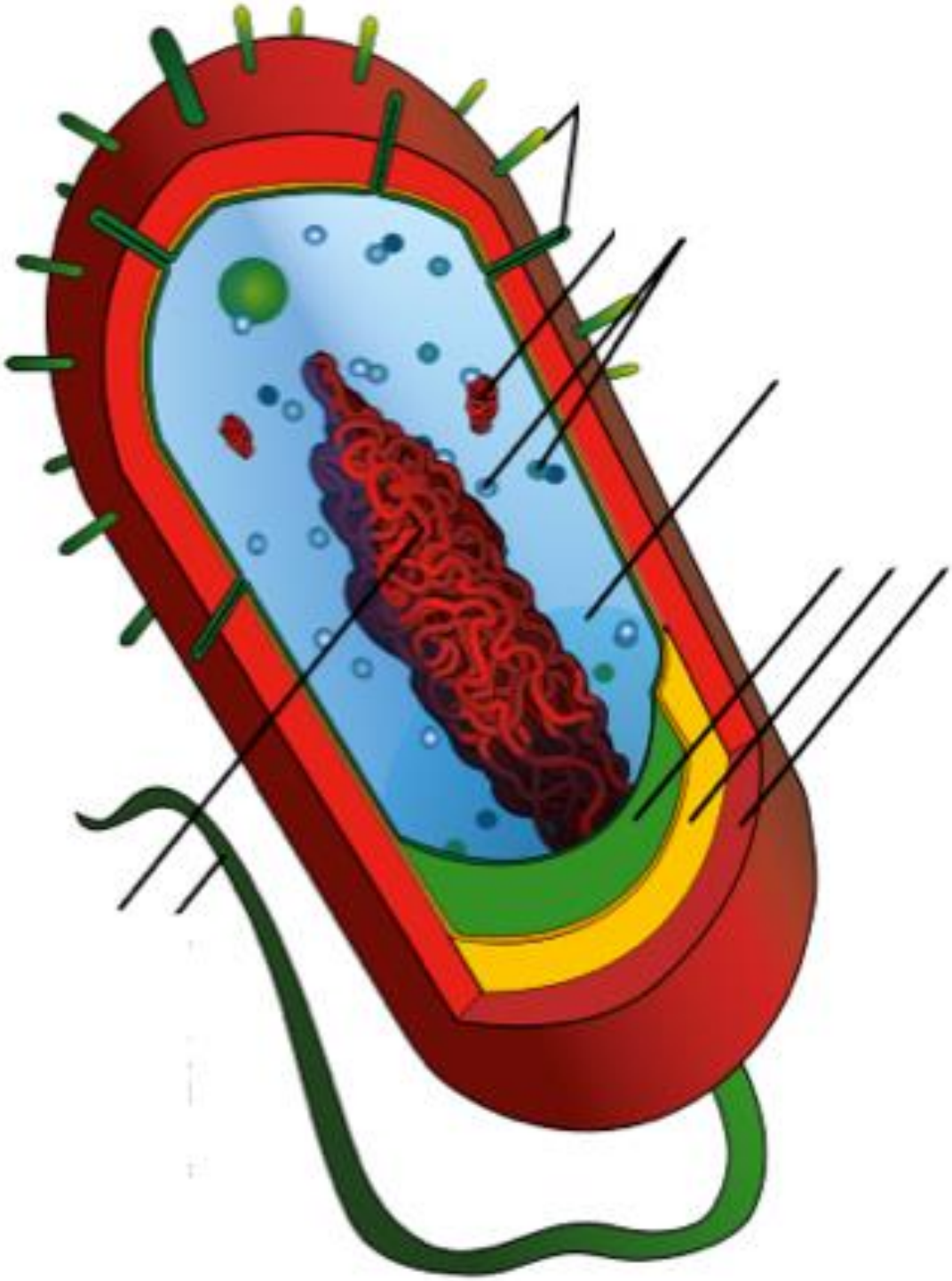
Streptococcus pneumoniae

Vibrio cholerae

Bacillus subtilis

NB all bacterial names are written with the first letter of the first word capitalised and both parts written in italics and so you should write it like this in all of your work too!

Exercise: label the following bacterial cell



Function of organelles-

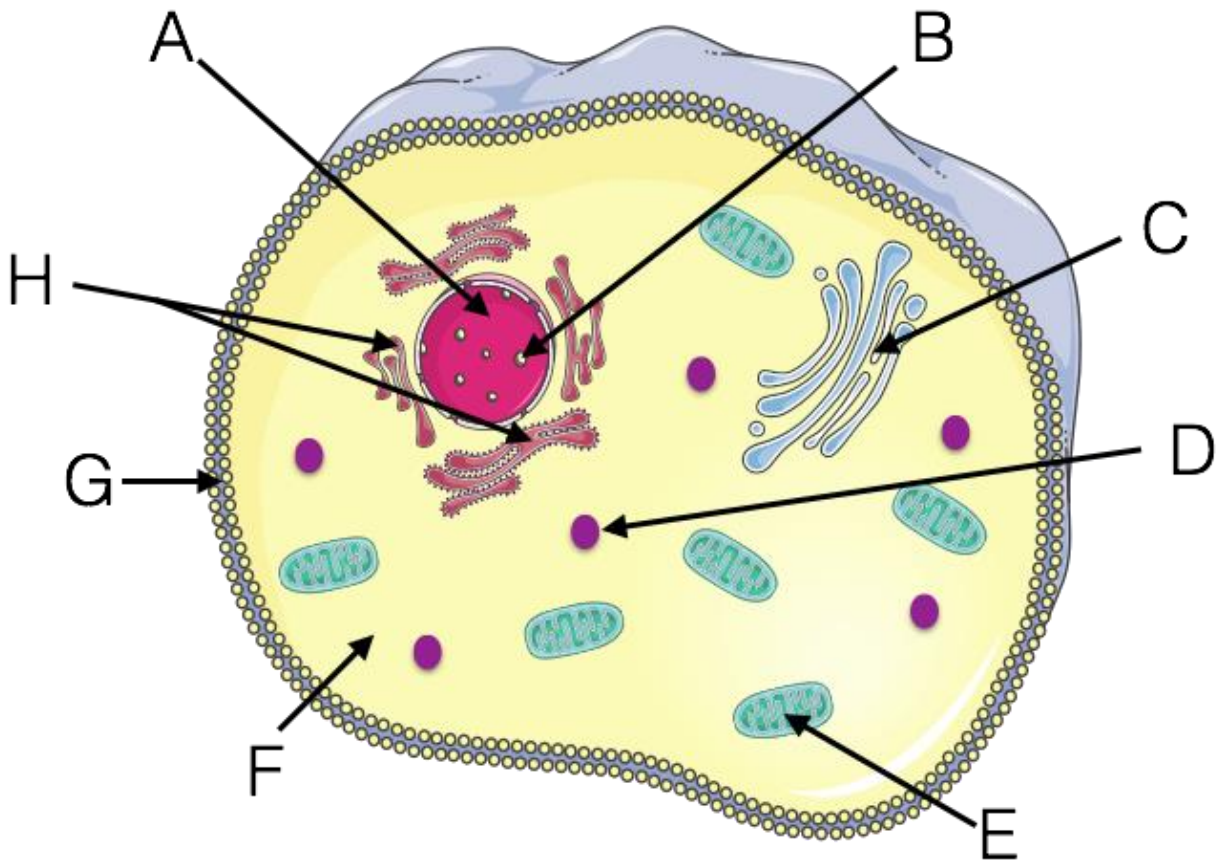
Name	Definition
Organelle	
	Protects all the components inside the cell
Cell wall	
	Separates the inside of the cell from the outside.
Cytoplasm	
Nucleoid	
	A small circular DNA molecule that is separate from the rest of the cells DNA.
Pilli	
	The protein builders of protein synthesisers in the cell.
Flagellum	

Homework 1- Worksheet

The homework assignment for the first tutorial is a baseline test to see your initial level of attainment in this subject area. The assignment will test for some or all of the subject specific skills that are required later in the final assignment. However, it is shorter than the final assignment and is will be an introduction to the subject as well as a challenge!

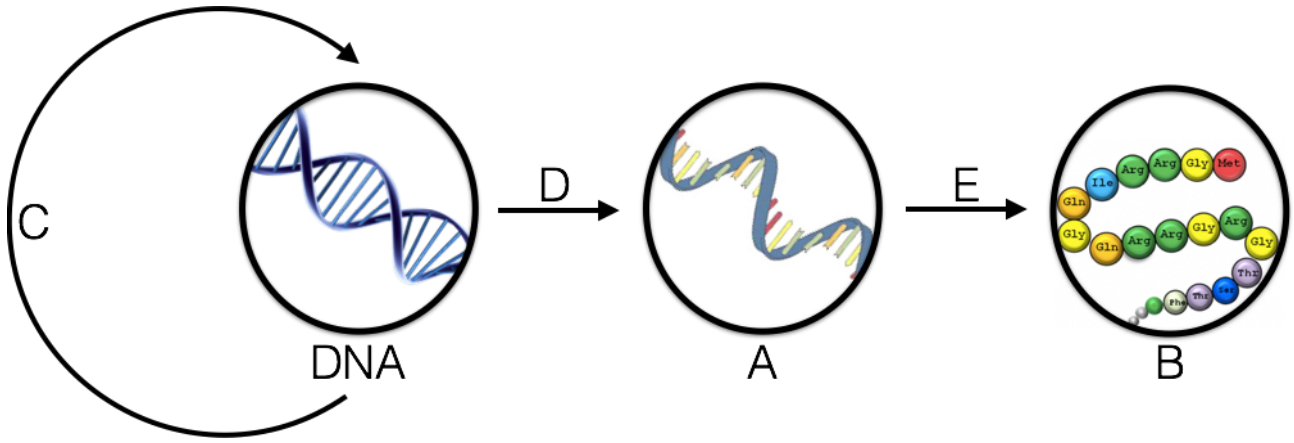
Do not worry too much about doing 'well' or 'badly' on the baseline test, it takes into account the fact that you may not be familiar with the subject area. It is designed to help you and your PhD tutor identify where you are at the start of the programme and to help you measure your progress along the way.

Question 1:



a) Name the labelled mammalian cell components.
b) State two differences between the structure of a plant cell and a mammalian cell.
c) State the function of E.

Question 2:



a) Name compounds A and B and processes C, D and E.
b) Name the enzymes involved in processes C and D.
c) State two key differences between DNA and compound A.

Question 3:

Answer the following questions after researching tuberculosis.

a) What causes tuberculosis?
b) How many people are affected worldwide?
c) What is the difference between active and latent tuberculosis (200 words)?
d) What is the current treatment?

Make sure to include any references you use in a list at the end of the work and within the text (see appendix 1 for examples).

Question 4:

The graphs shown below show the relative distribution of wealth (Figure 1) and the incidence of tuberculosis (Figure 2). **Discuss** the relationship between the two and give reasons for why you think this is (300 words).

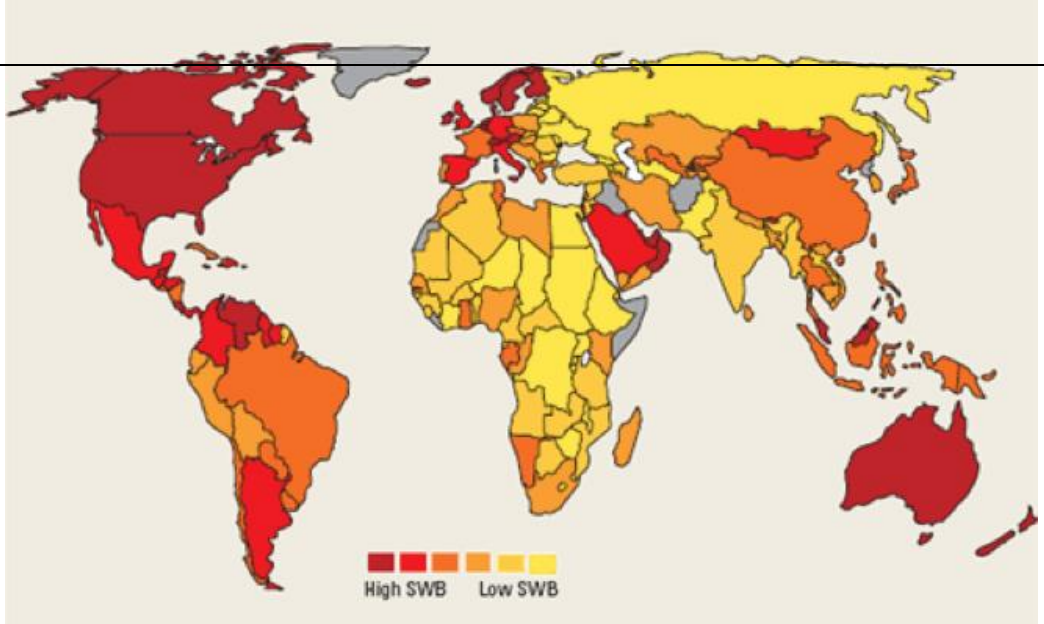


Figure 1: Relative distribution of wealth worldwide. In this image, high SWB indicates wealthy countries and low SWB indicates poor countries.

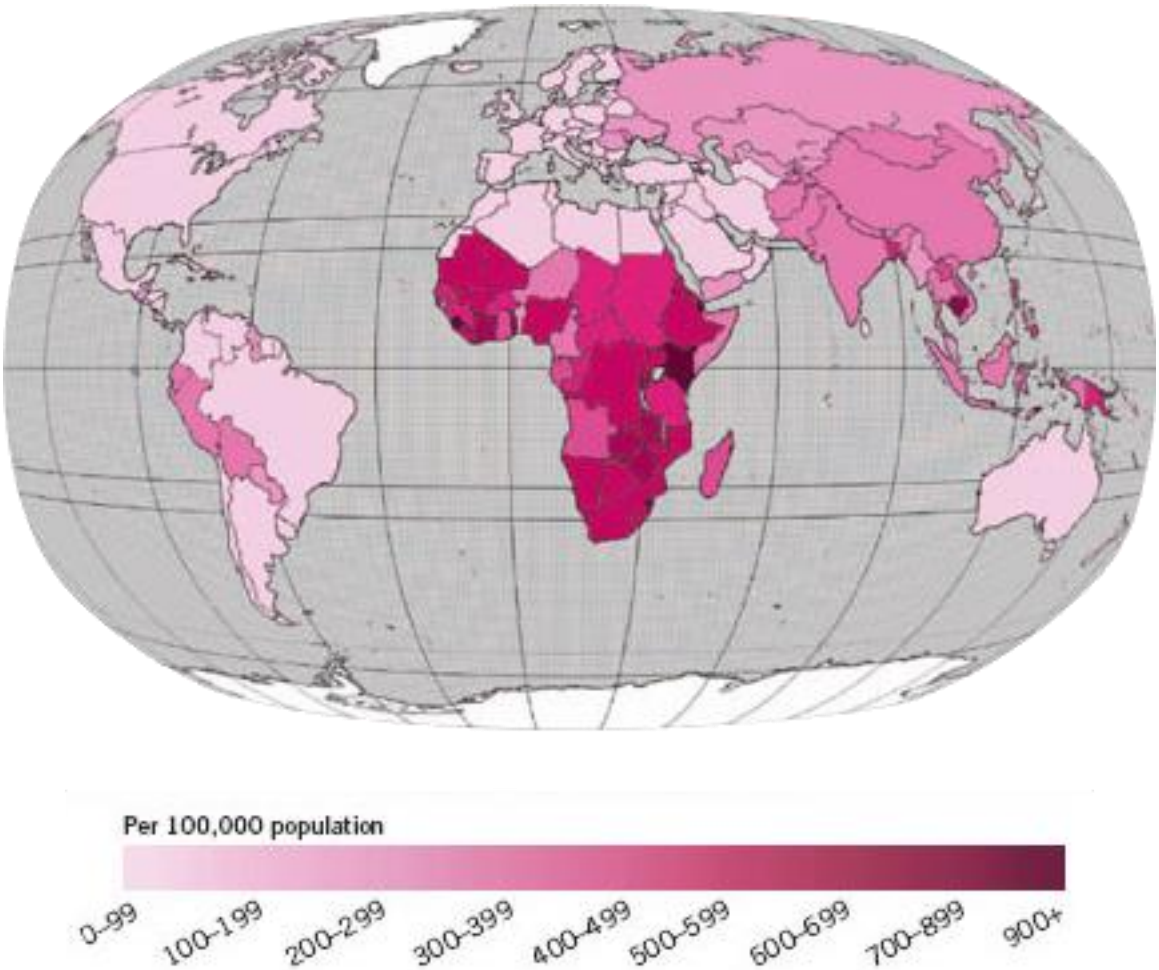
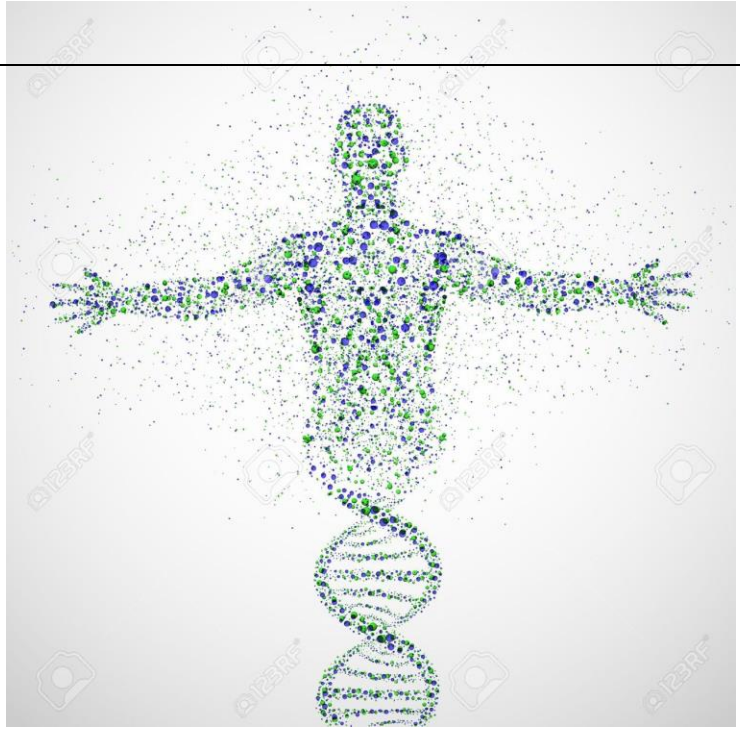


Figure 2: Worldwide incidence of tuberculosis per 100,000 people in different countries.

Tutorial 2 – DNA and mutations



Today's Key Questions:

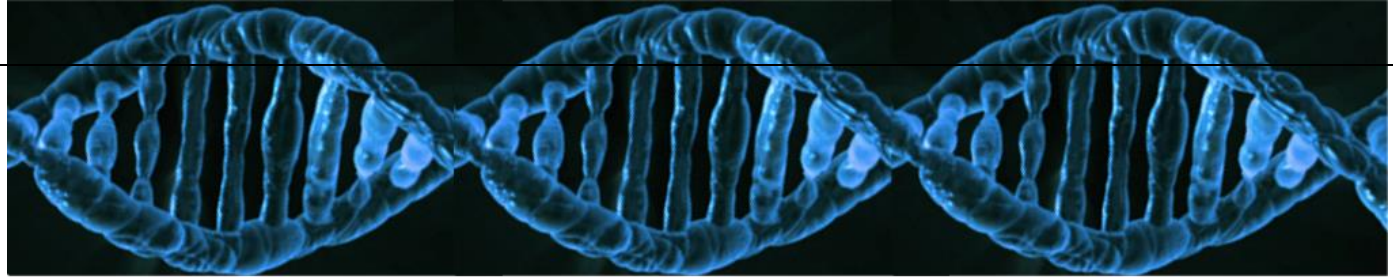
- What is the basic structure of DNA?
- How can a mutation occur?
- How can mutations at the DNA level impact on the protein level?
- How does the cell protect itself from mutations?

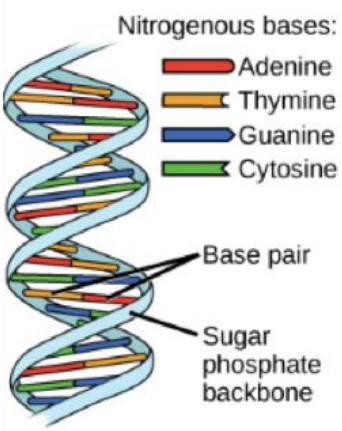
What is the Purpose of Tutorial 2?

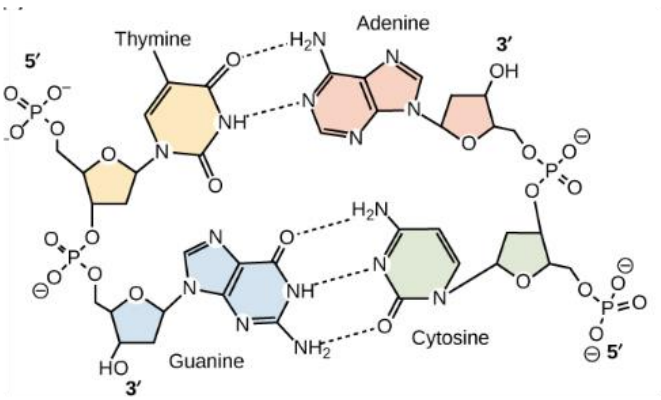
- Recall the basic structure and key process involved in the central dogma of molecular biology
- Identify the key process by which a mutation can occur
- Understand how a mutation at the DNA level impacts the cells phenotype.

DNA-

DNA (deoxyribonucleic acid) is the molecule that encodes the genetic information required in the development and functioning of all living organisms (and some viruses too). The information is encoded in the form of 4 bases: adenine (A), guanine (G), thymine (T) and cytosine (C). These are attached to a backbone of alternating sugar (deoxyribose) and phosphate groups. The whole molecule exists in double stranded form and forms a double helix structure.

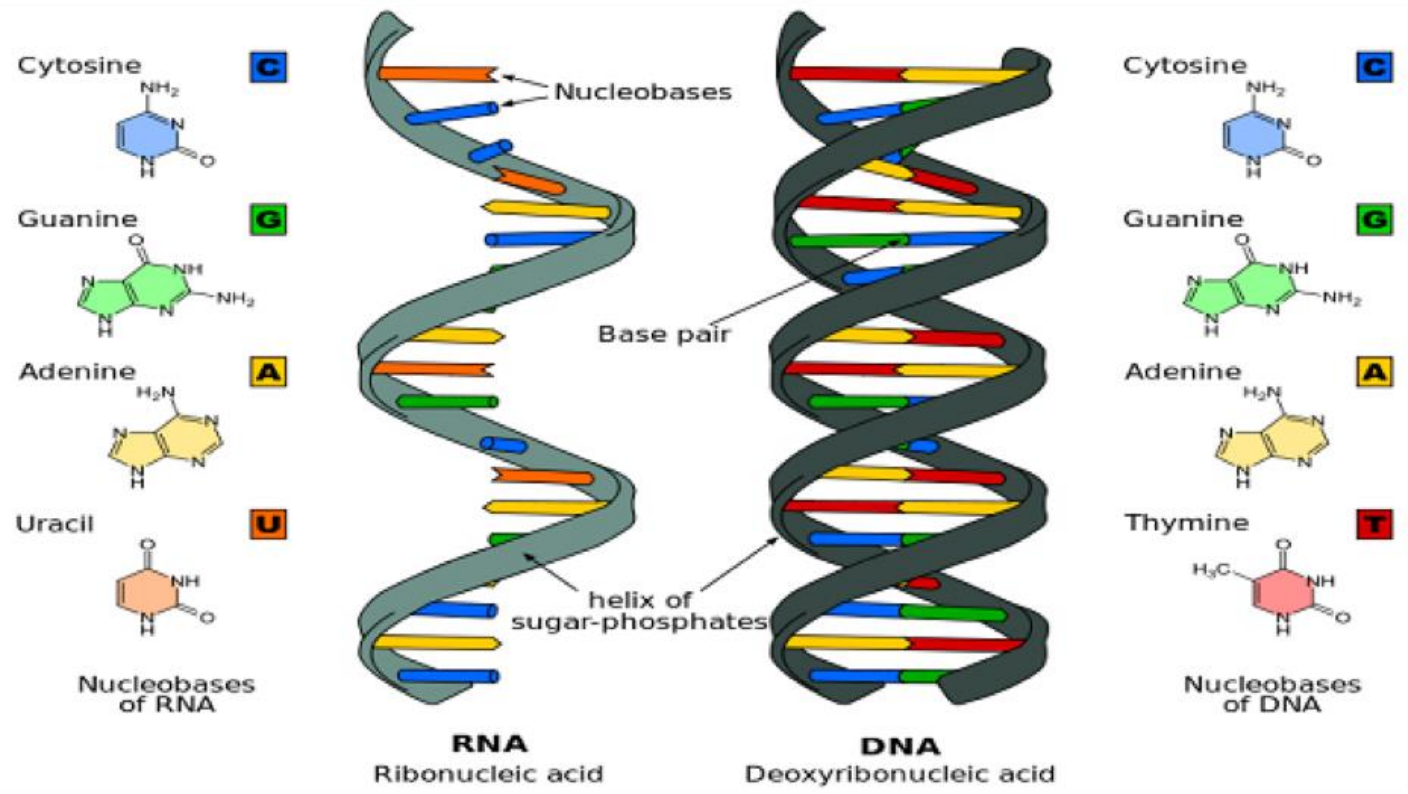




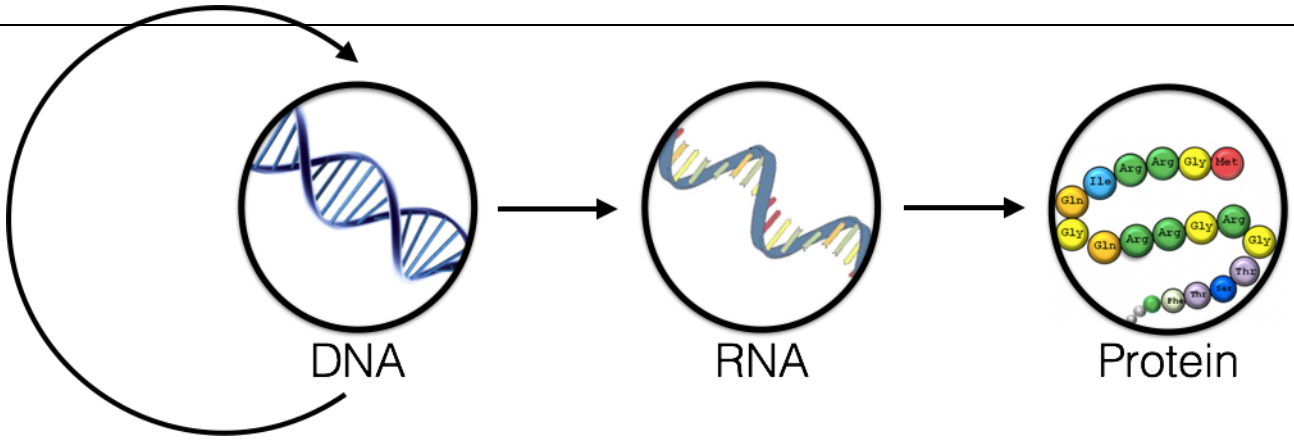


RNA-

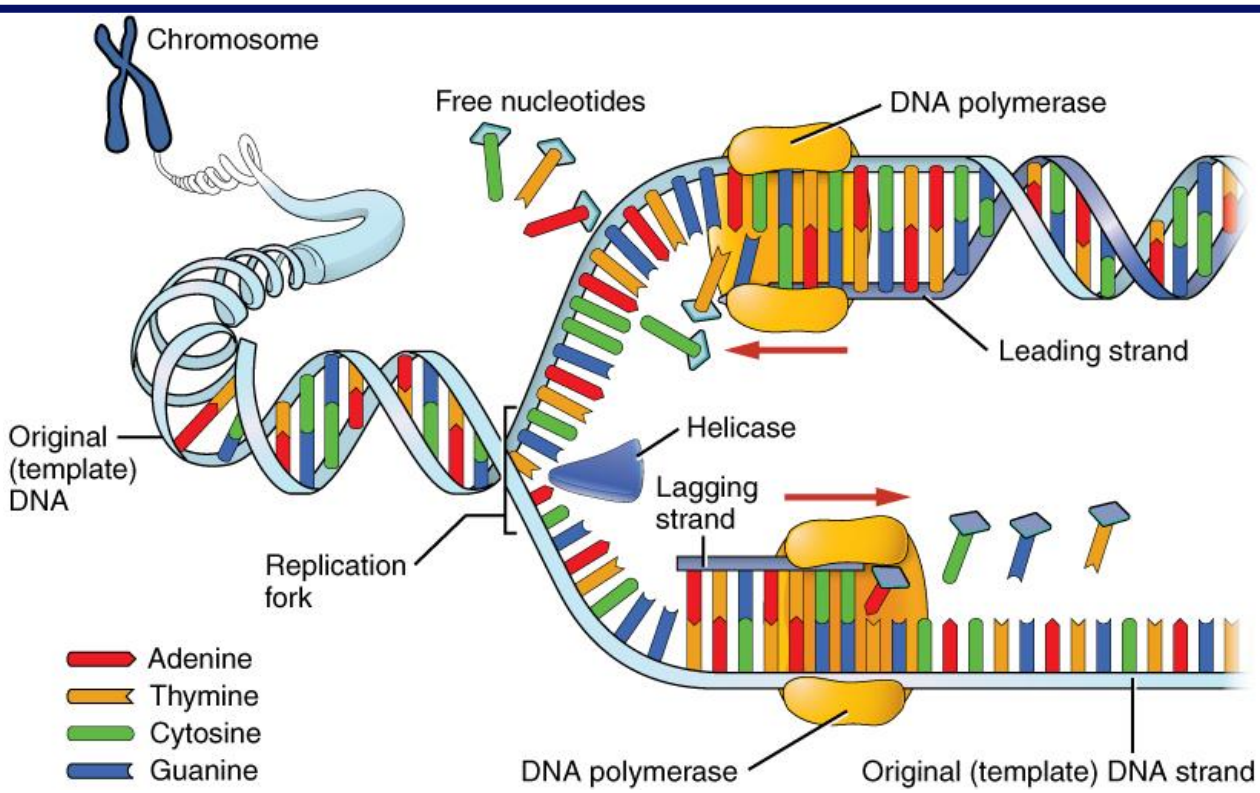
RNA (ribonucleic acid) is different from DNA in that it is only single stranded. The base thymine does not exist in RNA and instead is replaced by uracil (U) and a slightly different sugar (ribose, it has one less hydroxyl group than deoxyribose which makes the whole structure less stable) is used to make up the sugar phosphate backbone.



Central dogma of molecular biology-



DNA replication-



Task: you have 30 seconds to copy as much of the DNA strand as possible to produce the copy strand (NB A becomes T in the copy strand and G becomes C and vice versa)

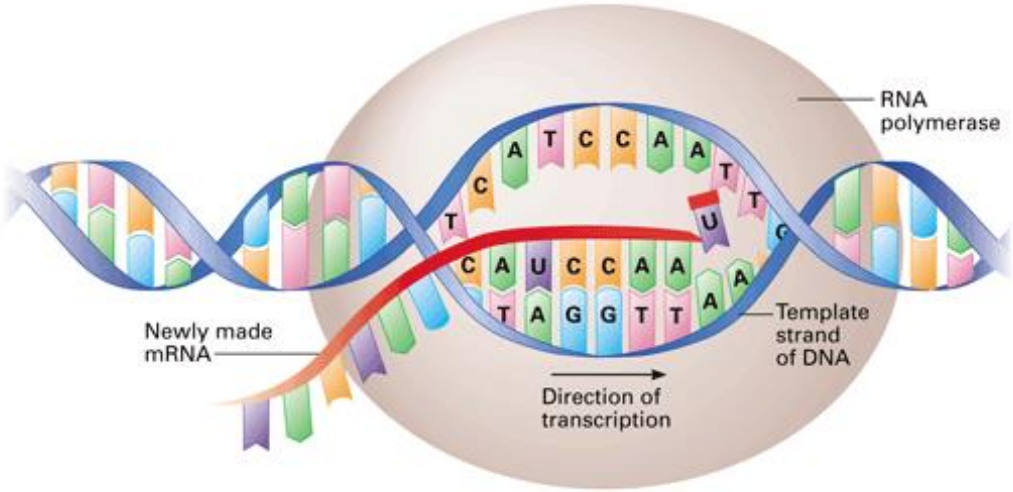
DNA strand:

ATGCAGTACGATGACTGACTAGATACTATCGCTACGACAATCGCATCGA

Copied DNA strand:

A single molecule of DNA polymerase can copy 50 bases in a single second!

Transcription-



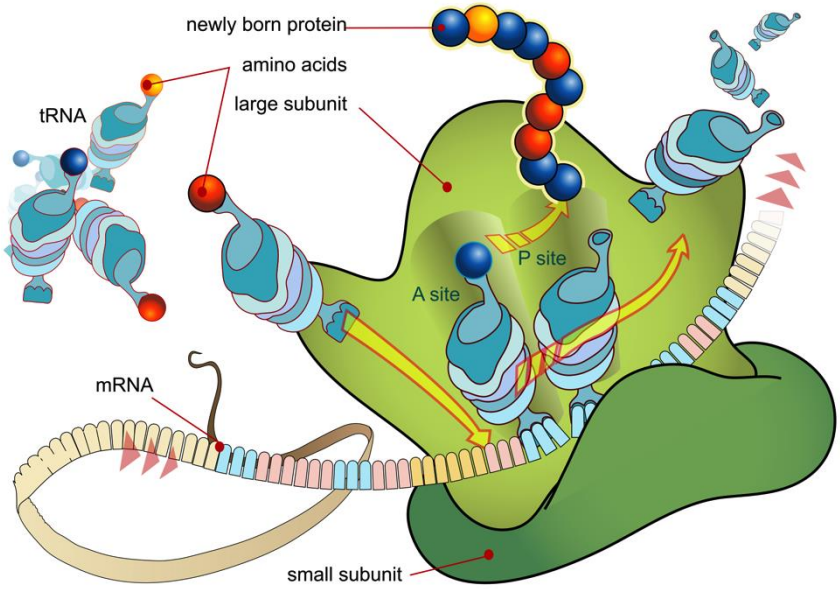
Task: produce the complementary mRNA strand for the following molecule (NB T becomes A in the complementary strand and G becomes C and vice versa but there is <u>no T in mRNA</u> and instead you have the <u>base U</u>)

DNA strand:

ATGCAGTACGATGACTGACTAGATACTATCGCTACGACAATCGCATCGA

Complementary mRNA strand:

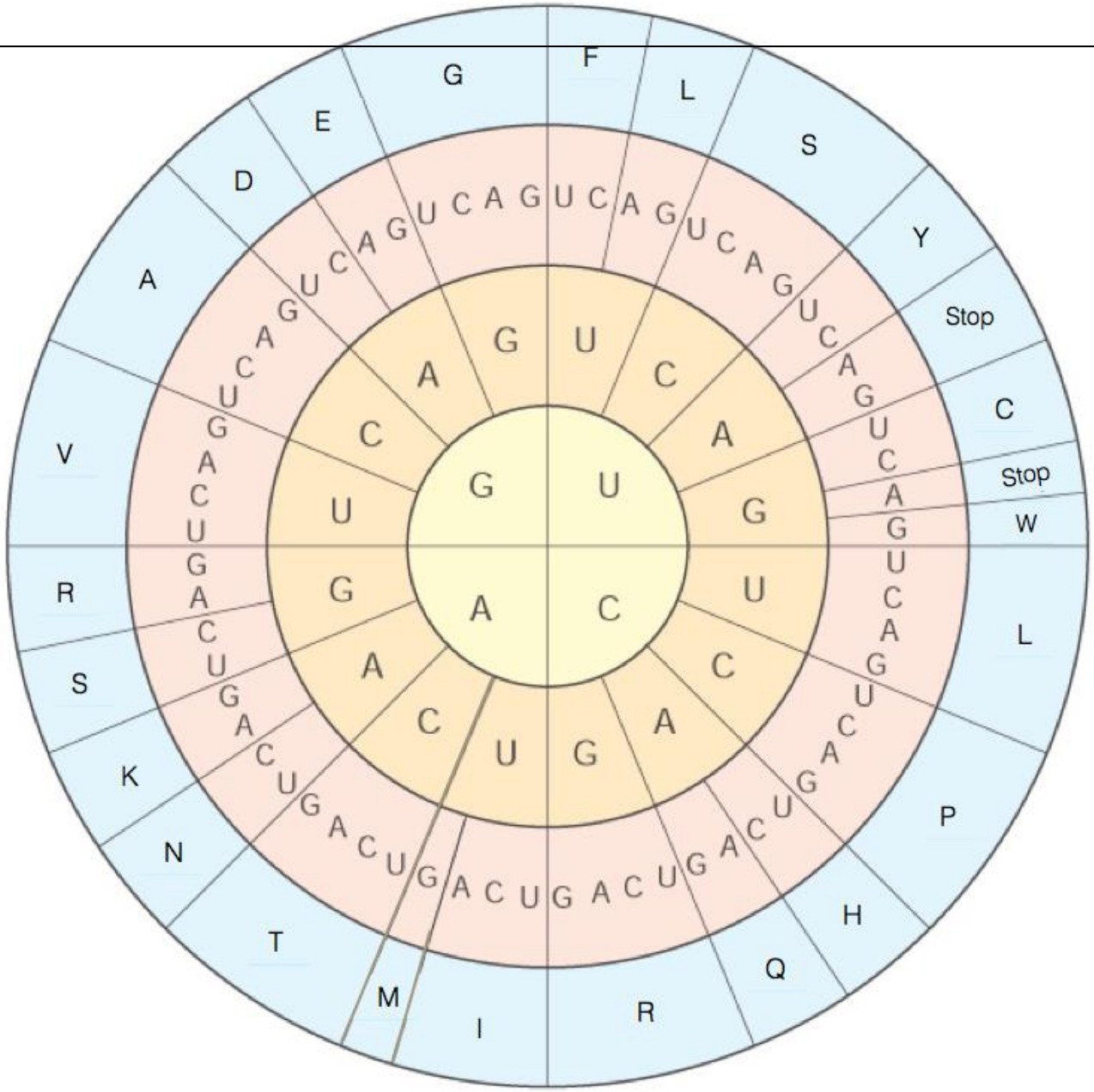
Translation-



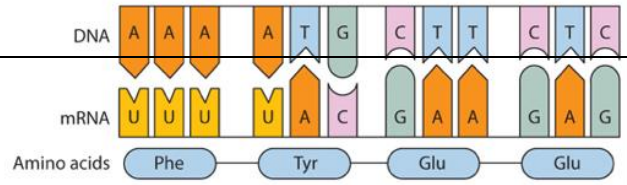
Every 3 bases in a DNA strand codes for a single amino acid, which can be depicted as a single letter. Using the translation wheel (Figure 5) depict the following sequences:

i) GAC AAT GCA

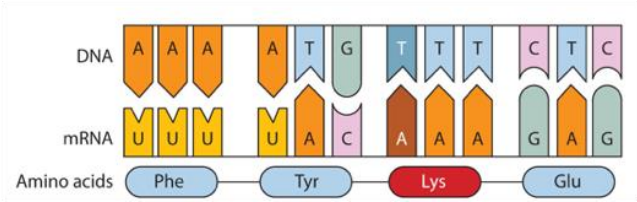
ii) GGG GAG AAC GAA TCT


G
F
L
S
Y
Stop
C
Stop
W
L
P
H
Q
R
I
M
T
N
K
S
R
V
A
D
E
U C A G U C A G U C A G U C A G
G U C A G U C A G U C A G U C A
A C U G A C U G A C U G A C U G
G A C U G A C U G A C U G A C U
G U A C G U A C G U A C G U A C
A G U C A G U C A G U C A G U C
U C A G U C A G U C A G U C A G

Wild type

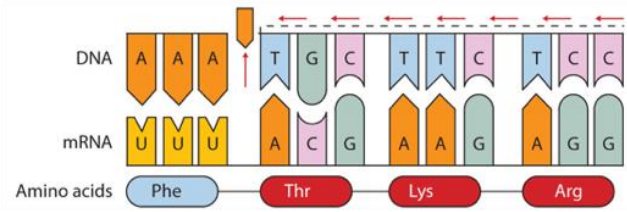


Substitution

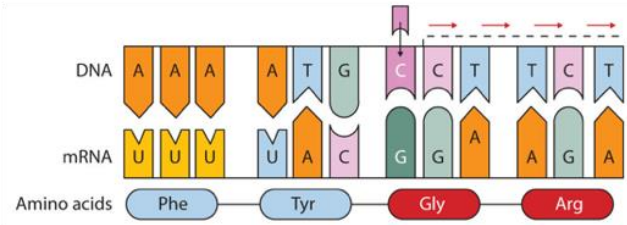


However, if we consider a base deletion or a base insertion then the impact of this is much more serious as every amino acid downstream from that point can be affected. This is a lot more likely to result in malformed proteins that are then ineffective.

Deletion



Insertion



Causes of mutations-

Not all DNA mutations are ‘dangerous’. Many mutations will occur in the non-coding region of DNA known as junk DNA, mutations here are very unlikely to effect coding regions of DNA and as only coding regions determine final amino acid sequences there is unlikely to be any change in protein or cell phenotype. Another mechanism of protection is known as genetic redundancy.

Genetic Redundancy-

	DNA sequence	mRNA	Amino acid sequence
Example	GTCAAG	CAGUUC	QF
Person 1	TTTAAA		
Person 2	TTCAAA		
Person 3	TTGAAA		

What observation can you make about the DNA sequence that codes for an amino acid sequence?

Fill in the blanks using the words below:

Genetic _____ is the process by which _____ than one sequence of bases can encode for the same amino acid. A _____ in the DNA would alter the _____ but this mutation might not affect the amino acid sequence and so won't have an affect on the _____.

More **Phenotype** **Mutation** **Genotype** **Redundancy**

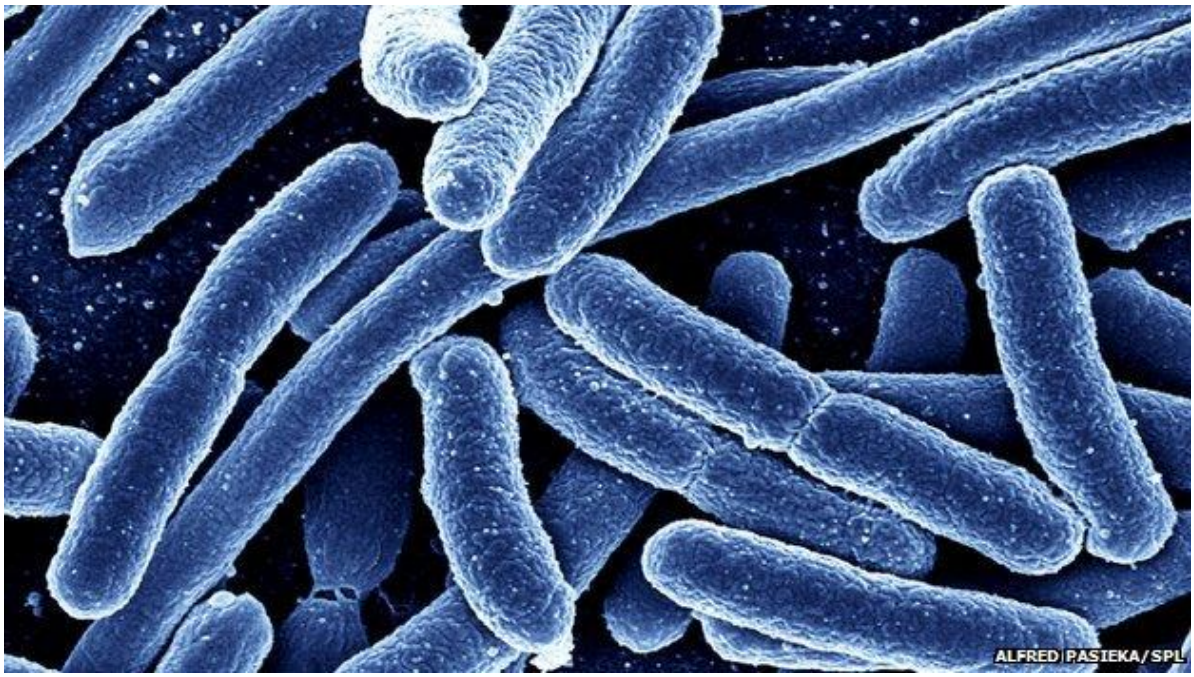
Homework 2- Superbug presentation

Each person will be given a single article to summarise (all of the articles are included). The summary should cover all of the key points of the article and you need to produce a one minute presentation of the key points to be presented in the next tutorial.

Article Notes:

Article 1

Superbugs to kill 'more than cancer' by 2050



Drug resistant *E.coli* bacteria are already a significant problem in Europe

Drug resistant infections will kill an extra 10 million people a year worldwide - more than currently die from cancer - by 2050 unless action is taken, a study says.

They are currently implicated in 700,000 deaths each year.

The analysis, presented by the economist Jim O'Neill, said the costs would spiral to $100tn (£63tn).

He was appointed by Prime Minister David Cameron in July to head a review of antimicrobial resistance.

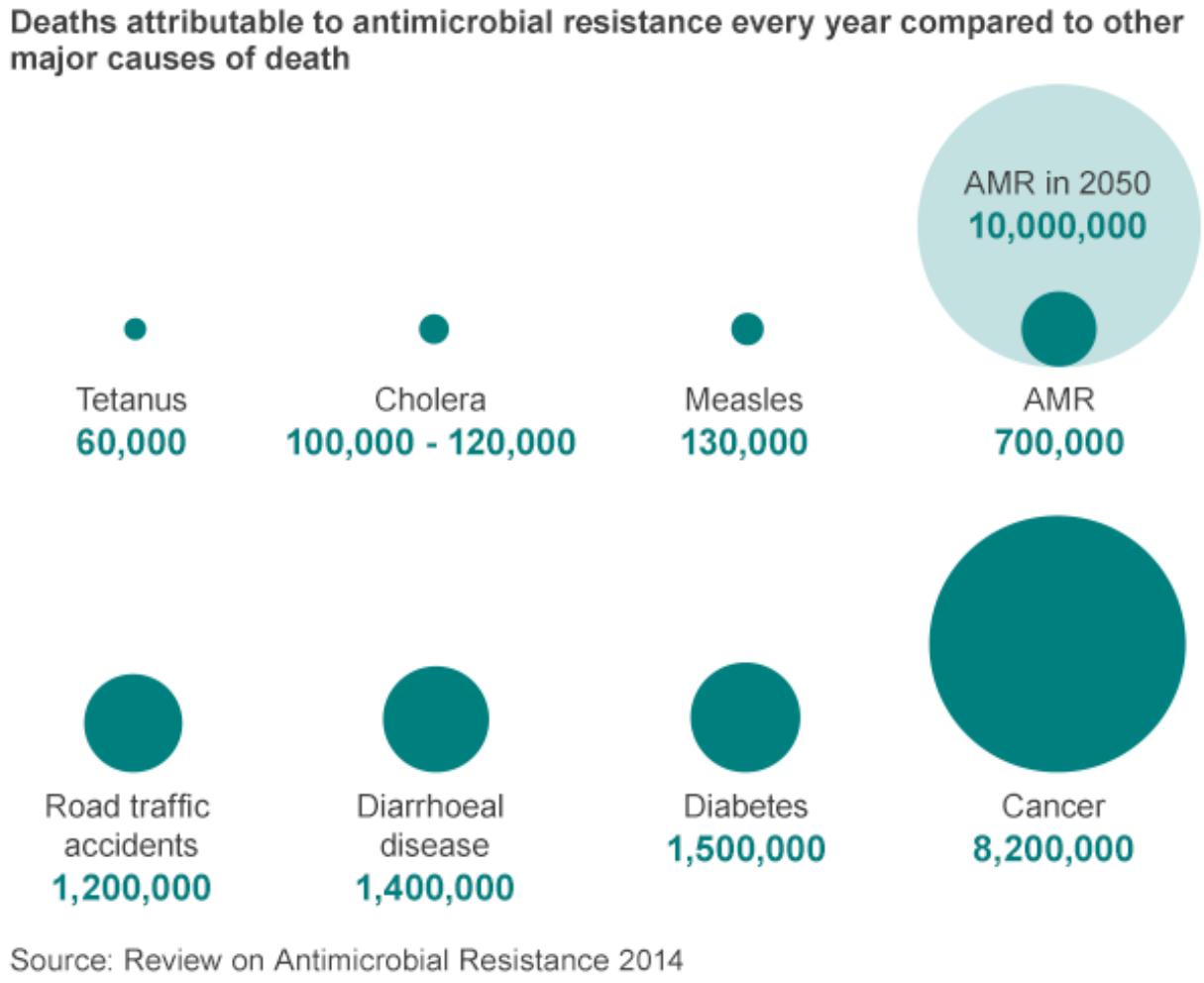
Mr O'Neill told the BBC: "To put that in context, the annual GDP [gross domestic product] of the UK is about $3tn, so this would be the equivalent of around 35 years without the UK contribution to the global economy."

The reduction in population and the impact on ill-health would reduce world economic output by between 2% and 3.5%.

The analysis was based on scenarios modelled by researchers Rand Europe and auditors KPMG.

They found that drug resistant *E. coli,* malaria and tuberculosis (TB) would have the biggest impact.

In Europe and the United States, antimicrobial resistance causes at least 50,000 deaths each year, they said. And left unchecked, deaths would rise more than 10-fold by 2050.

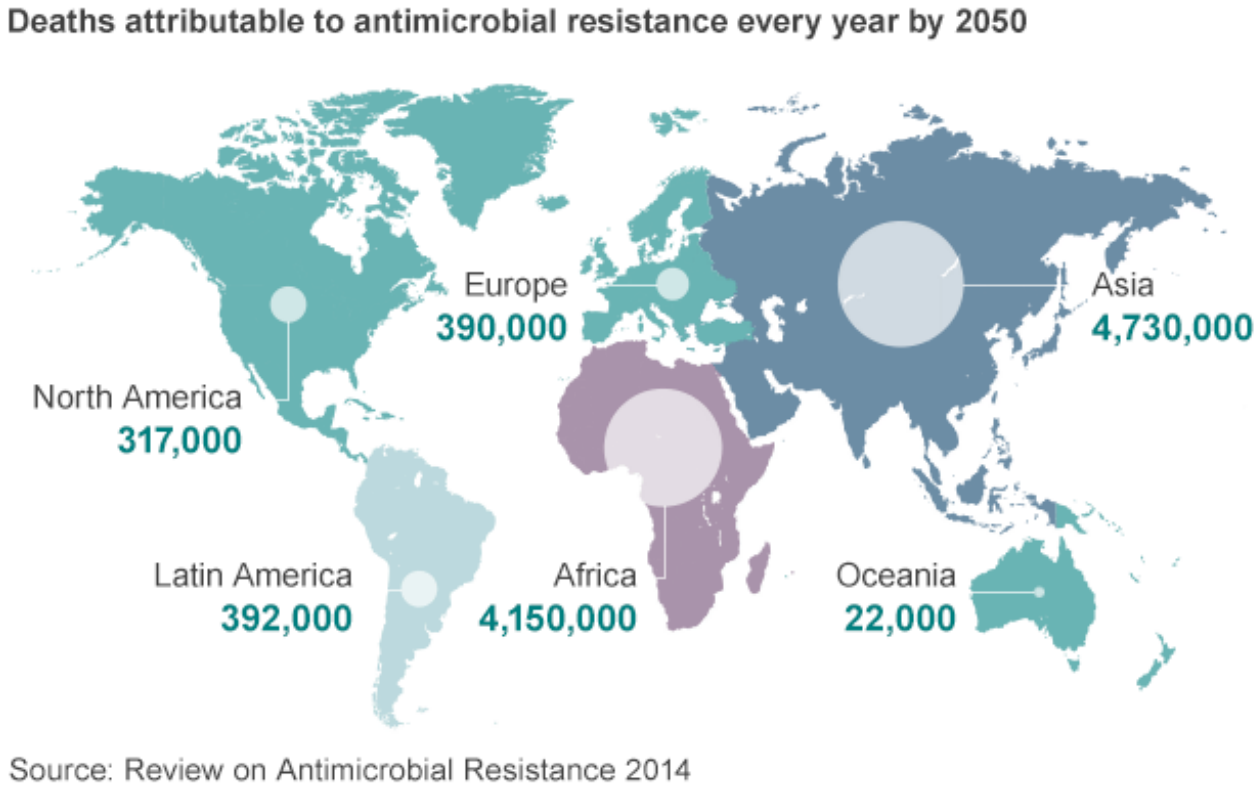


Mr O'Neill is best known for his economic analysis of developing nations and their growing importance in global trade.

He coined the acronyms Bric (Brazil, Russia, India and China) and more recently Mint (Mexico, Indonesia, Nigeria and Turkey).

He said the impact of them would be mostly keenly felt in these countries.

"In Nigeria, by 2050, more than one in four deaths would be attributable to drug resistant infections, while India would see an additional two million lives lost every year."



The review team believes its analysis represents a significant underestimate of the potential impact of failing to tackle drug resistance, as it did not include the effects on healthcare of a world in which antibiotics no longer worked.

Joint replacements, Caesarean sections, chemotherapy and transplant surgery are among many treatments that depend on antibiotics being available to prevent infections.

The review team estimates that Caesarean sections currently contribute 2% to world GDP, joint replacements 0.65%, cancer drugs 0.75% and organ transplants 0.1%.

This is based on the number of lives saved, and ill-health prevented in people of working age.

Without effective antibiotics, these procedures would become much riskier and in many cases impossible.

The review team concludes that this would cost a further $100tn by 2050.

Mr O'Neill said his team would now be exploring what action could be taken to avert this looming crisis.

This would include looking at:

- how drug use could be changed to reduce the rise of resistance
- how to boost the development of new drugs
- the need for coherent international action concerning drug use in humans and animals

Mr O'Neill said the support of the Bric and Mint nations was vital.

He noted that China would be hosting the G20 summit in 2016 and said he hoped this issue would be a focus of discussion.

'Compelling'
He said scientists seemed more certain that drug resistance would be a major problem in the short term, than they were over climate change.

Dr Jeremy Farrar, the director the Wellcome Trust, said: "By highlighting the vast financial and human costs that unchecked drug resistance will have, this important research underlines that this is not just a medical problem, but an economic and social one too."

Prof Dame Sally Davies, chief medical officer for England, said: "This is a compelling piece of work, which takes us a step forward in understanding the true gravity of the threat."

The review team concludes that solving the problem of drug resistance will be far cheaper than doing nothing and there was "cause for optimism" that the right steps could be taken.

This included university researchers and biotech entrepreneurs "teeming with ideas" including new drugs, vaccines and alternative therapies such as antibodies.

Investment
Laura Piddock, professor of microbiology at the University of Birmingham, is focusing her research on bacteria such as *E. coli* and salmonella, which are responsible for a growing level of drug resistant infections.

Both are so-called gram-negative bacteria, which have a complex cell wall that acts as a barrier to drugs. If they do penetrate the wall, they are "vacuumed out" by the cell.

She said: "My team is looking at what are the switches in those bacteria which turn that vacuum cleaner off, and at molecules which would have the same effect. If we can do that, we can make the bacteria sensitive to antibiotics."

Prof Piddock said there had not been enough global investment in finding new drugs.

She said: "It is very difficult to find drugs against bacteria like *E.coli* because they are so naturally resistant.

"We need more investment and new business models to ensure the pipeline is filled with promising molecules, to ensure that we can solve this problem, and make sure the drugs are there when patients need them."

Article 2

'Superbugs could erase a century of medical advances,' experts warn

Doctors issue new warning of devastating effect of over-prescribing antibiotics for trivial ailments

Drug-resistant "superbugs" represent one of the gravest threats in the history of medicine, leading experts have warned.

Routine operations could become deadly "in the very near future" as bacteria evolve to resist the drugs we use to combat them. This process could erase a century of medical advances, say government doctors in a special editorial in *The Lancet* health journal.

Although the looming threat of antibiotic, or anti-microbial, resistance has been known about for years, the new warning reflects growing concern that the NHS and other national health systems, already under pressure from ageing populations, will struggle to cope with the rising cost of caring for people in the "post-antibiotic era".

In a stark reflection of the seriousness of the threat, England's deputy chief medical officer, Professor John Watson, said: "I am concerned that in 20 years, if I go into hospital for a hip replacement, I could get an infection leading to major complications and possible death, simply because antibiotics no longer work as they do now."

About 35 million antibiotics are prescribed by GPs in England every year. The more the drugs circulate, the more bacteria are able to evolve to resist them. In the past, drug development kept pace with evolving microbes, with a constant production line of new classes of antibiotics. But the drugs have ceased to be profitable and a new class has not been created since 1987.

Writing in *The Lancet*, experts, including England's chief medical officer, Dame Sally Davies, warn that death rates from bacterial infections "might return to those of the early 20th century". They write: "Rarely has modern medicine faced such a grave threat. Without antibiotics, treatments from minor surgery to major transplants could become impossible, and health-care costs are likely to spiral as we resort to newer, more expensive antibiotics and sustain longer hospital admissions."

Strategies to combat the rise in resistance include cutting the amount of antibiotics prescribed, improving hospital hygiene and incentivising the pharmaceutical industry to work on novel antibiotics and antibiotic alternatives.

However, a leading GP told *The Independent on Sunday* that the time had come for the general public to take responsibility. "The change needs to come in patient expectation. We need public education: that not every ill needs a pill," said Dr Peter Swinyard, chairman of the Family Doctor Association.

"We try hard not to prescribe, but it's difficult in practice. The patient will be dissatisfied with your consultation, and is likely to vote with their feet, register somewhere else or go to the walk-in centre and get antibiotics from the nurse.

"But if we go into a post-antibiotic phase, we may find that people with pneumonia will not be treatable with an antibiotic, and will die, whereas at the moment they would live.

"People need to realise the link. If you treat little Johnny's ear infection with antibiotics, his mummy may end up dying of pneumonia. It's stark and it's, of course, not direct, but on a population-wide level, that's the kind of link we're talking about."

There are no reliable estimates of what resistance could cost health systems in the future, but the European Centre for Disease Prevention and Control believes that €1.5bn (£1.2bn) a year is already being spent on health problems associated with antibiotic resistance in Europe.

Joanna Coast, professor of health economics at the University of Birmingham, said that the problem of resistance had the potential to "affect how entire health systems work".

Professor Coast added: "We don't know how big this is going to be. It's like the problems with planning for global warming. We know what the costs are now but we don't know what the costs will be into the future.

"Much of what we do in modern health system relies on us having antibiotics. We need them for prophylaxis for surgery, for people having chemotherapy for cancer. The worry is that it might make big changes to how we run our health system."

Antibiotics are also used in vast quantities in agriculture, fisheries and by vets, the resulting environmental exposure adding to bacterial resistance, with further consequences for human health.

Experts say that to meet demand without increasing resistance, drug companies will

need to find new ways of financing antibiotic development that are not linked to expectations of large volume sales. Global health authorities such as the World Health Organisation have also warned that global drives to reduce antibiotic use must not harm access to life-saving drugs in poorer countries.

Writing in The Lancet, Professor Otto Cars of Uppsala University in Sweden, and one of the world's leading experts on antibiotic resistance, said: "Antibiotic resistance is a complex ecological problem which doesn't just affect people, but is also intimately connected with agriculture and the environment.

"We need to move on from 'blaming and shaming' among the many stakeholders who have all contributed to the problem, towards concrete political action and commitment to address this threat."

Article 3

NATURE | NEWS

Totally drug-resistant TB emerges in India

Discovery of a deadly form of TB highlights crisis of 'mismanagement'.

Katherine Rowland

13 January 2012

Physicians in India have identified a form of incurable tuberculosis there, raising further concerns over increasing drug resistance to the disease[1]. Although reports call this latest form a “new entity”, researchers suggest that it is instead another development in a long-standing problem.

The discovery makes India the third country in which a completely drug-resistant form of the disease has emerged, following cases documented in Italy in 2007[2] and Iran in 2009[3].

However, data on the disease, dubbed totally drug-resistant tuberculosis (TDR-TB), are sparse, and official accounts may not provide an adequate indication of its prevalence. Giovanni Migliori, director of the World Health Organization (WHO) Collaborating Centre for Tuberculosis and Lung Diseases in Tradate, Italy, suggests that TDR-TB is a deadlier iteration of the highly resistant forms of TB that have been increasingly reported over the past decade. “Totally resistant TB is not new at all,” he says.

An untreatable form of tuberculosis has been found in India.

ATUL LOKE/PANOS

Since the 1960s, two drugs — isoniazid and rifampicin — have been the standard TB treatment. Although episodes of resistance cropped up periodically, during the 1990s the incidence of multiple drug resistance grew significantly, leading researchers in 2006 to refer to it as extensively drug-resistant tuberculosis (XDR-TB). Surveillance data from the WHO indicate that XDR-TB is present in at least in 58 countries, with an estimated 25,000 cases occurring each year.

Epidemiologist Carole Mitnick of Harvard Medical School in Boston, Massachusetts, agrees that TDR-TB is not new, and points to the history of XDR-TB. “When XDR-TB was first named, it was a phenomenon that had existed but hadn’t gotten much attention before. TB in general doesn’t receive a lot of attention,” she says.

Inadequate care

Part of the increase in drug resistance is related to complications that arise in treating patients who are also infected with HIV — 13% of TB cases, according to the WHO. However, the greatest part of the problem results from the management of the disease.

Related stories

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Although the WHO describes TB as a “disease of poverty”, drug-resistant varieties might best be understood as resulting from poor treatment. According to a 2011 WHO report, fewer than 5% of newly diagnosed or previously treated patients are tested for drug resistance. And it is estimated that just 16% of patients with drug-resistant TB are receiving appropriate treatment.

“The cases are a story of mismanagement,” says Migliori. “Resistance is man-made, caused by exposure to the wrong treatment, the wrong regimen, the wrong treatment duration.”

extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. (2010)

- Global Alliance for TB Drug Development. 2009 report on Tuberculosis research funding trends, 2005-2009. (2009).

In the management of TB, many factors affect whether the disease is cured or becomes resistant to treatment. Drug misuse or mismanagement can result if a patient does not follow a full course of treatment, or if the correct drugs are not available or patients with undiagnosed resistant TB receive inappropriate therapies.

Part of the problem also relates to TB testing. The WHO recommends sputum smear microscopy, a test developed more than one hundred years ago, as the standard diagnosis. Although inexpensive, this method is prone to false negatives, does not provide information on drug susceptibility, and test results can take several weeks — a large window of time for a patient to potentially receive the wrong drugs or transmit the infection. However in 2010, the WHO approved a new rapid and fully automated test, known as Xpert, which assesses resistance to the first-line drug rifampicin. As of July 2011, 26 countries are using Xpert and 145 are eligible to purchase kits at a reduced price.

Drug dearth

The fact that no new first-line TB drugs have been developed for half a century has probably contributed to the emergence of strains that are unresponsive to treatment, says Mitnick. “If you keep using the same drugs for that long, resistance is inevitable.”

Tuberculosis trails behind only HIV as the world’s leading cause of death from infectious disease. But in spite of its impact on human health and economic growth, it has not ranked among the pharmaceutical industry's priorities.

“The pharmaceutical industry had scant interest in TB for decades,” says Richard Chaisson, director of the Center for TB Research at the Johns Hopkins School of Public Health in Baltimore, Maryland. “The industry pretty much concluded it wasn’t an attractive market, there was not enough potential profit.”

But with a growing number of public–private partnerships in research, Chaisson says, industry interest is “an order of magnitude greater than it was a decade ago”.

As of 2011, there were 11 new or repurposed TB drugs in clinical trials that have the potential to either shorten treatment duration or improve therapy for resistant TB. Late-stage studies include a phase III trial by Bayer in

partnership with the Global Alliance for TB Drug Development (TB Alliance) to assess whether its antibiotic moxifloxacin can help to reduce the duration of standard therapy from 6 months to 4. Tibotec, also in partnership with the TB Alliance, is in phase II trials for a product that may be useful in treating drug-resistant forms.

Nature doi:10.1038/nature.2012.9797

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2. Migliori, G. B., De Iaco, G., Besozzi, G., Centis, R. & Cirillo, D. M. *Eurosurveillance* **12**, 3194 (2007).
   Show context
3. Velayati, A. A. *et al*. *Chest* **136**, 136–420 (2009).
   Show context Article

Bacteria that resist 'last antibiotic' found in UK

By James Gallagher

Bacteria that resist the most common antibiotic of last resort - colistin - have been discovered in the UK.

Officials say the threat to human health is low, but is under ongoing review.

Scientists warned the world was on the cusp of a post-antibiotic era when such resistance was **discovered in China last month**.

Now checks have discovered the same resistance on three farms and in samples of human infections.

When all other antibiotics fail then doctors turn to colistin - that's why it is so important.

Doctors in the UK thought they had three years before colistin-resistance would spread from China to the UK.

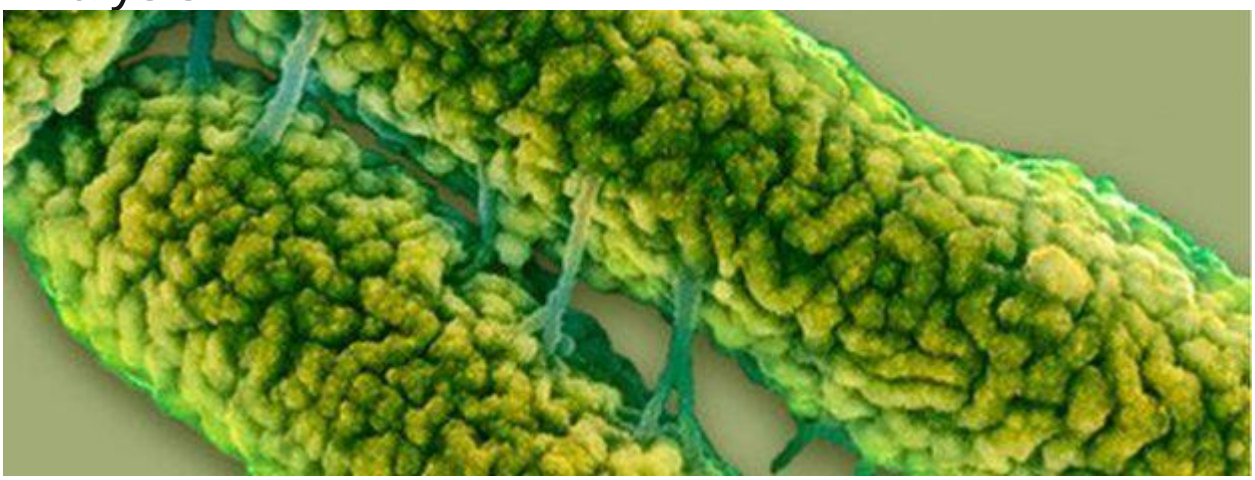
But Public Health England and the Animal and Plant Health Agency began testing for it.

Public Health England has gone through the 24,000 bacterial samples it keeps on record from cases between 2012 and 2015.

Colistin-resistance was discovered in fifteen of them, including samples of Salmonella and *E. coli.*

The Animal and Plant Health Agency has discovered colistin-resistant bacteria on three pig farms.

Analysis



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The news will not be a massive surprise after similar discoveries in parts of Europe, Asia and Africa.

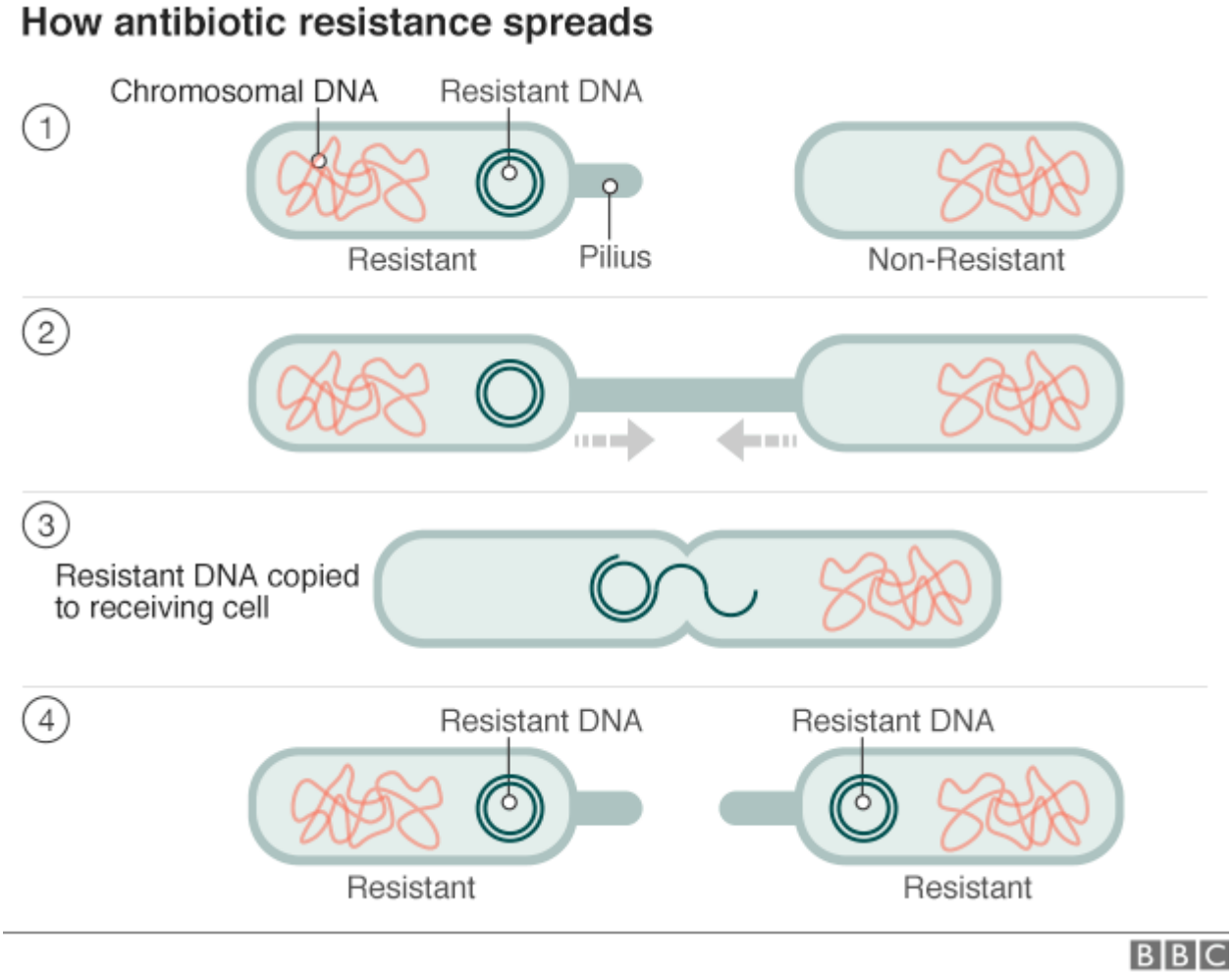
It raises the prospect of untreatable infections - what is known as the antibiotic apocalypse and threatens to plunge medicine back into the dark ages.

The DNA that gives bacteria resistance to colistin - the mcr-1 gene - can spread rapidly between species.

The concern is that colistin-resistance will now find its way into other superbugs to create infections that doctors cannot treat.

Prof Alan Johnson, from Public Health England, said: "Our assessment is that the public health risk posed by this gene is currently considered very low, but is subject to ongoing review as more information becomes available.

"The organisms identified can be killed by cooking your food properly and all the bacteria we identified with this gene were responsive to other antibiotics, called carbapenems.
"We will monitor this closely, and will provide any further public advice as needed."



The Chinese resistance cases were down to overuse of antibiotics in agriculture.
Alliance to Save Our Antibiotics says 837kg of colistin was sold to British farms in 2014.
Coilin Nunan, from the Alliance to Save Our Antibiotics, said: "We need the government, the European Commission and regulatory bodies like the Veterinary Medicines Directorate to respond urgently.
"The routine preventative use in farming of colistin, and all antibiotics important in human medicine, needs to be banned immediately."
The Department for Environment, Food and Rural Affairs said colistin made up just 0.2% of the antibiotics used in livestock in the UK.
A spokesperson said: "We are enhancing our surveillance for colistin resistance, and veterinary prescribers have voluntarily updated prescribing guidelines to restrict use of colistin in animals."

Tutorial 3- What makes a superbug 'super'?

Today's Key Questions:

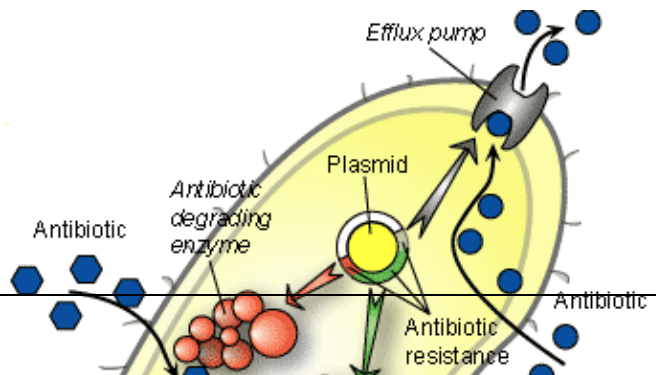
- What is a superbug?
- How does the survival of the fittest explain the spread of resistance?
- How can a bacterium be resistant to an antibiotic?
- How can this resistance be spread?

What is the Purpose of Tutorial 3?

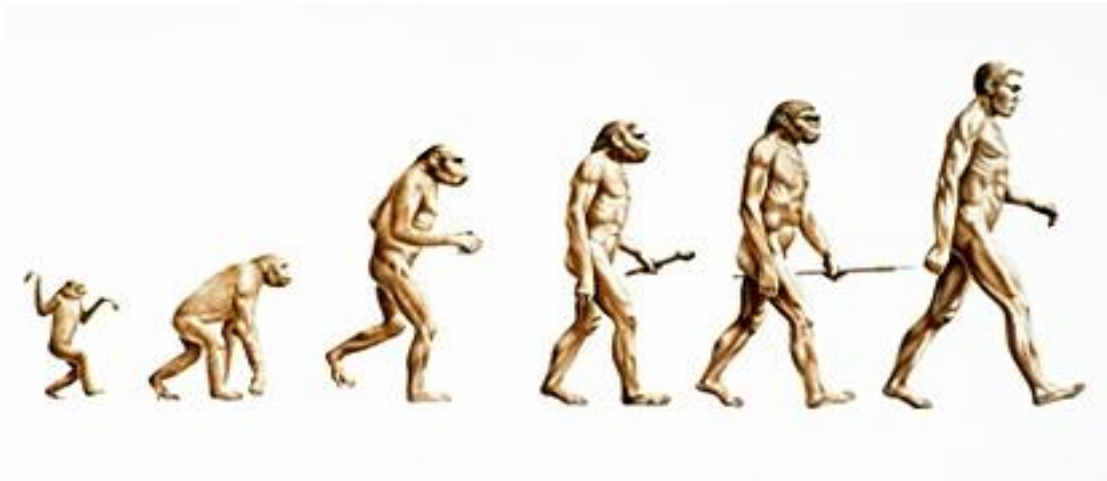
- Understand what a superbug is and how they occur
- Identify basic survival of the fittest concepts and how they relate to resistance
- Describe how antibiotic resistance can be transferred between bacteria.

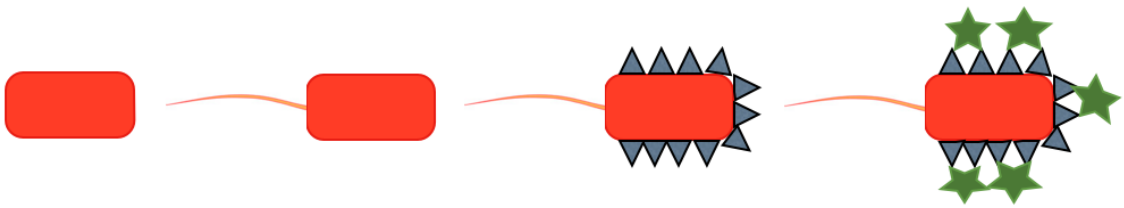
Resistance mechanisms-

Bacteria can develop resistance through a number of mechanisms including an efflux pump, an antibiotic degrading enzyme or an antibiotic altering enzyme. Whilst a bacterium can utilise any one of these pathways, each antibiotic within a specific class tends to be evaded in a similar manner. Any mechanism that a wild bacterium has is called **inherent** resistance.



Survival of the fittest-



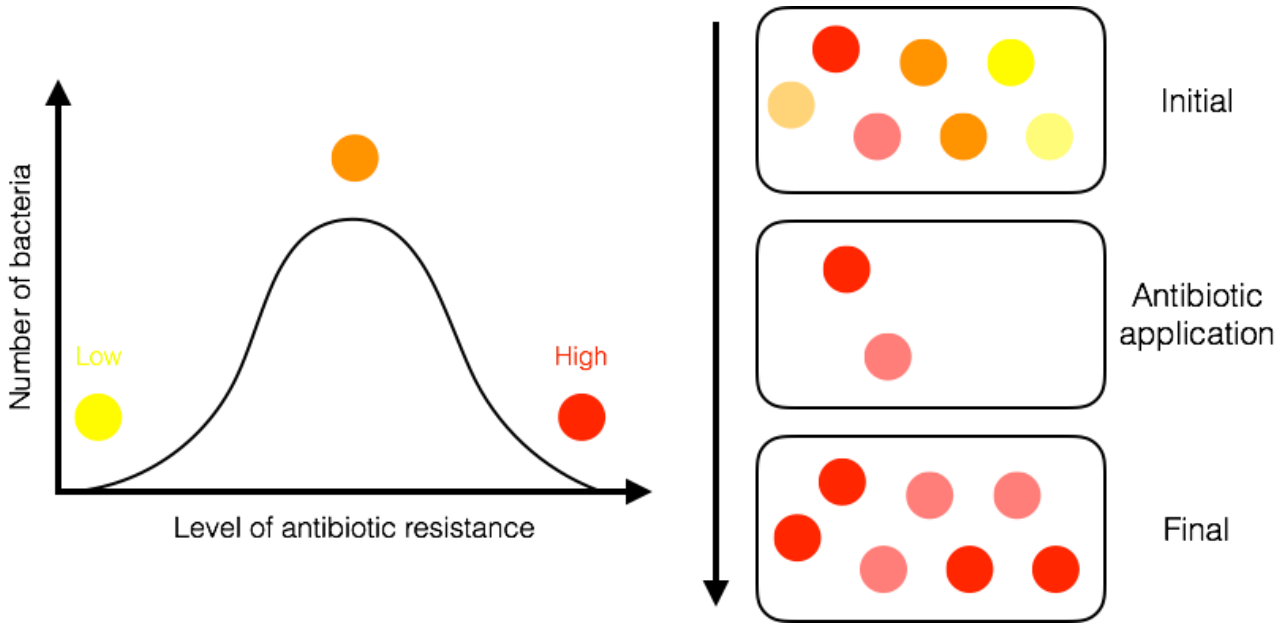


Genetic mutations occur in the population through various mechanisms. Not all mutations will have any effect and some will only have a small affect. A change of a single amino acid in the resulting protein can have devastating consequences, particularly if the nature of the amino acid changes (for example a different end group or if it is hydrophobic). Sometimes these changes will have very little effect until something in the environment changes, this could make one mutation significantly more/less favourable.

If the change is favourable then the organism will be more likely to survive and reproduce during which it could pass the mutation on to its offspring and thus increasing the occurrence of that mutation in the offspring.

Antibiotic resistance-

Bacteria form a heterogeneous population in which some bacteria will have mutations that give them mechanisms that allow them to be resistant to antibiotics. When the population is exposed to this antibiotic only those with the mutation survive. This remaining population can then rapidly increase as there is less competition for nutrients within the area of the infection. These remaining bacteria will also pass their beneficial mutation on to their offspring thus producing a resistant population (survival of the 'fittest').



After discovery of an antibiotic, resistance is soon discovered in the population. Indeed Alexander Fleming (who discovered penicillin) warned of such a phenomenon in his speech in 1945 upon receiving the Nobel prize for medicine.

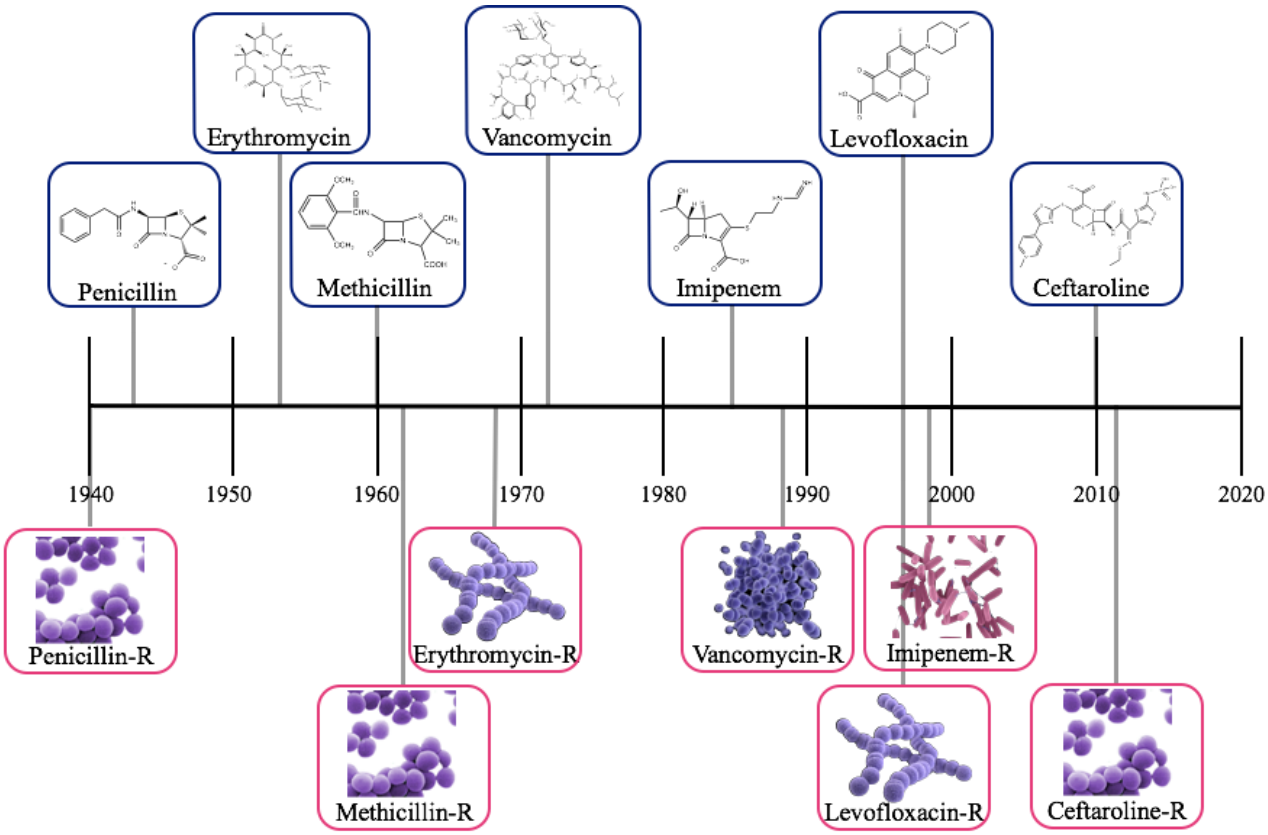
"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. There is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

Alexander Fleming, 1945

Coupled with this rapid development of resistance by bacterial species is a general decline in the discovery of new antibiotics. Part of this decline is caused by the fact that it is becoming harder to find not just new antibiotics but new classes of antibiotics. A new class of antibiotics would work in a different manner from current antibiotics available and thus would last longer before the development of resistance. A new antibiotic compound of an already

existing class stands the chance that the resistance mechanisms already available for that class can confer resistance to the new antibiotic.

Another important factor is the price of drug development. Initial development of a drug followed by extensive testing is thought to cost around $2.6 billion. The income from the development of a new antibiotic is unlikely to cover the cost of its production as it is likely that resistance will quickly spread. As such the focus on antibiotic development by drug companies has been significantly cut down.



Mechanisms of Resistance transfer-

One of the things that aids this rapid spread of resistance is the ability of bacteria to pass resistance genes to each other. This transfer of resistance usually occurs between neighbouring bacteria but isn't limited to bacteria of the same species. As such, a patient may be taking an antibiotic for a specific bacterial infection but all bacteria within their body will be exposed to the drug and all stand the chance of developing resistance and passing that on to others. There are several mechanisms through which this transfer can occur.

Vertical gene transfer-

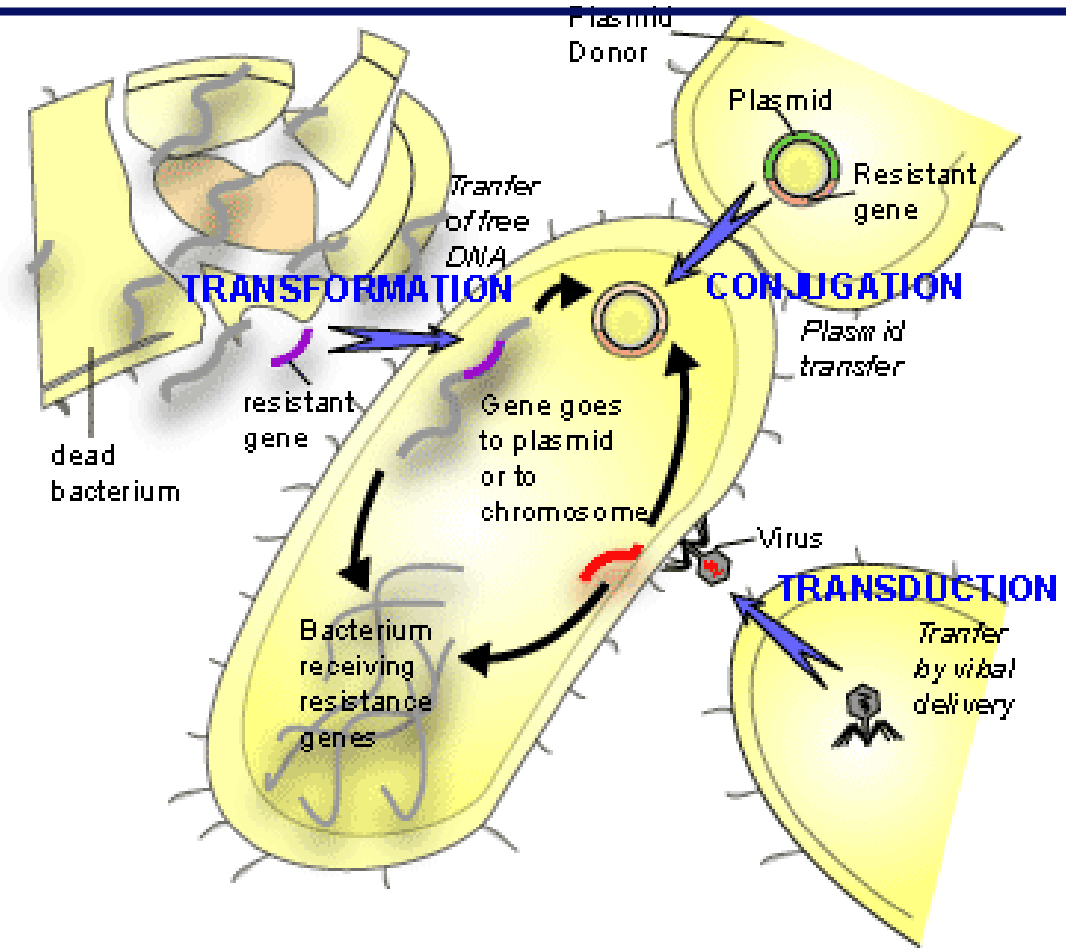
Horizontal gene transfer-

There are three mechanisms of horizontal gene transfer.

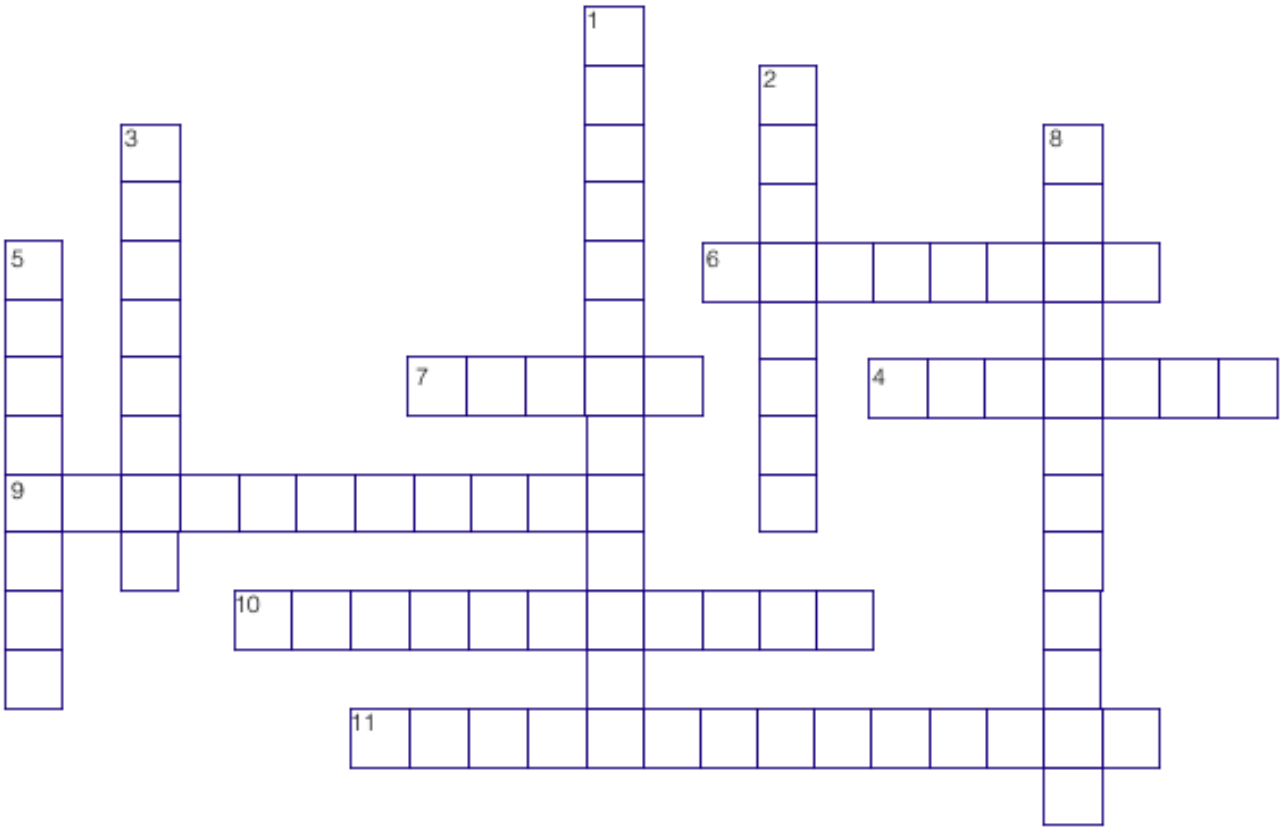
Transformation-

Transduction-

Conjugation-



Antibiotic Resistance



Down:

1. Type of population in which there is a wide variety in the levels of a single trait (e.g. levels of resistance in a population).
2. Common name for antibiotic resistant bacteria (particularly those resistant to multiple antibiotics).
3. Type of resistance (HINT: antibiotic degrading enzymes are an example).
4. Viral transfer of resistant genes.
5. Enzymes involved in unzipping the double helix during DNA replication.

Across:

6. Resistance transfer from parent to offspring.
7. Virus that affects bacteria.
8. Location of resistant genes in bacteria.
9. Process by which two bacteria come close together and transfer genes to each other.
10. The selection pressure which causes resistance.
11. Process by which DNA is taken up from the environment.

Homework 3- Future Treatments

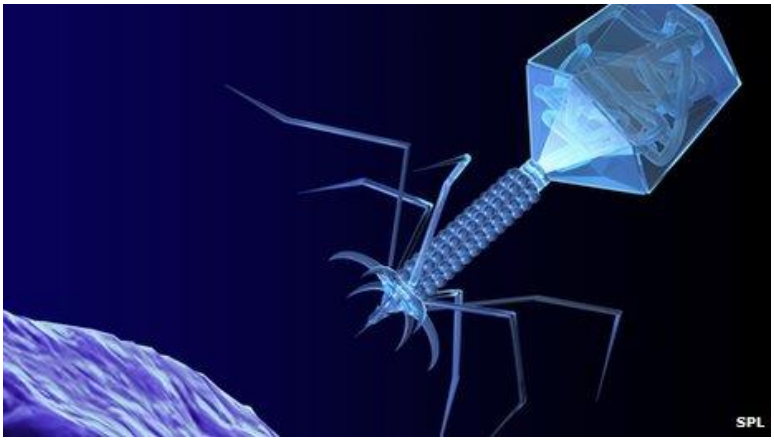
In groups you will be assigned one form of future treatment for TB (either phage therapy or the use of quantum dots). You will have to prepare a presentation (maximum of 10 minutes) that covers the following for your treatment:

- How does it work?
- Advantages over current drug therapy
- Disadvantages to this form of treatment

You will be required to present this at the next tutorial. You can either split the topics and research those individually and present your section at the next tutorial or arrange to meet up and research and present everything together- it is up to you! One article has been provided for each of the treatment forms- this is a starting point for your research only and you should aim to go beyond this in your presentation.

Phages may be key in bacteria battle

By Damien McGuinness and Deborah Cohen
Health Check, BBC World Service



The therapy can be injected, sprayed on to the site of infection or swallowed

They might look like sinister aliens, but these bacteria-munching viruses could be the next weapon in the fight against infectious diseases.

At the Eliava Institute in Tbilisi, Georgia, patients are treated for all kinds of bacterial infections with viruses called phages. In most places in the world antibiotics are given for these infections.

One patient says he regularly uses phages to treat a recurring eye infection.

"I've tried everything. I've even had operations on my eye but nothing helped. But this does help," he says.

Phages are naturally occurring viruses that kill bacteria. Once they get into bacterial cells the phages' DNA replicates until it kills the host.

Doctors in Georgia, and in other countries that were in the former USSR, have been using this therapy for 90 years. But medics and drug regulatory bodies in most places in the developed world have been reluctant to accept that it works.

Now that more and more bacteria have become resistant to antibiotics, the pharmaceutical industry is showing an interest in phage therapy.

The director of the Eliava Institute, Dr Revaz Adamia, explains: "In 2008 I had six letters from people in the West asking for help, but now in the last two months I've probably had about 150.

"People want to be cured because they are desperate that they cannot be cured with antibiotics. Now they are looking at what they can do and they are coming to us."

The phage hijacks the bacterium, turning it into a phage factory

Viral broth

Dr Martha Clokie, a microbiologist at the University of Leicester, carries out research into phages that could treat Clostridium difficile infections. She has tried therapy at the Eliava Institute.

"When I was in Tbilisi one winter I had tonsillitis, and every six hours I was given broth containing phages, which I gargled. Back in the UK my husband and child had the infection too and they were prescribed antibiotics. We all got better at the same time."

The institute also has some prepared phage solutions that it has worked out will kill the bacteria that cause common diseases, such as E.coli, which causes stomach upsets.

The therapy can be injected, sprayed on to the site of infection or swallowed. Each solution contains many types of phages, although usually just one attacks the bacteria.

Refrigerators

Dr Naomi Hoyle is an American who has trained to be a doctor in Georgia and now works at the institute.

She is married to the grandson of Dr Liane Gachechiladze, one of the scientists who kept the place going during the civil wars and economic chaos of the 1990s, following the collapse of the Soviet Union.

Dr Gachechiladze remembers: "We used to get a lot of power cuts in this neighbourhood which was a problem because phages have to be stored cold in refrigerators.

"But in the part of town where I lived, we would

Analysis

James Gallagher
Health and science reporter, BBC News

The need for new treatments for bacterial infections is desperate.

From tuberculosis to E. coli, Klebsiella to gonorrhea, resistance to antibiotics is rising fast.

Health officials around the world have warned that we may be entering a post-antibiotic era.

It could mean deadly diseases become untreatable while surgery and cancer therapies would carry enormous risks of patients catching untreatable infections.

Phages are one of the options that are often suggested as a possible new weapon against bacterial infection.

It is an appealing idea - the enemy of my enemy is my friend. However as far as mainstream medicine is concerned it is just an idea.

The field has not had the same level of funding as drug development. It means the big questions of effectiveness and safety still remain largely unanswered.

still often have electricity. So I bought an old fridge, and I used to take all the phages home and keep them safe in my kitchen."

Analysis: Antibiotic apocalypse

The drugs don't work - so what will?

Dr Hoyle says that one of the advantages of the viruses over antibiotics is that they target only the harmful bacteria.

"It doesn't have the side-effects or the negative aspects of antibiotics, like diarrhoea, because of its high specificity. It's not the silver bullet that antibiotics are, but it has its advantages as it works well on chronic infections. It enters the site and continues to do its work even after application."

Dr Martha Clokie says we may see the use of phage therapy outside the former Soviet Union in the next decade. "Large companies have done phase one and two clinical trials and are now finding ways to do phase three clinical trials, in which they will be seeing if the treatment works in patients.

"In the future we may see phages used to treat minor bacterial infections, and antibiotics kept for the serious life-threatening conditions."

"Superbugs" Destroyed Using Quantum Dot Nanoparticles

January 20, 2016 | by Robin Andrews

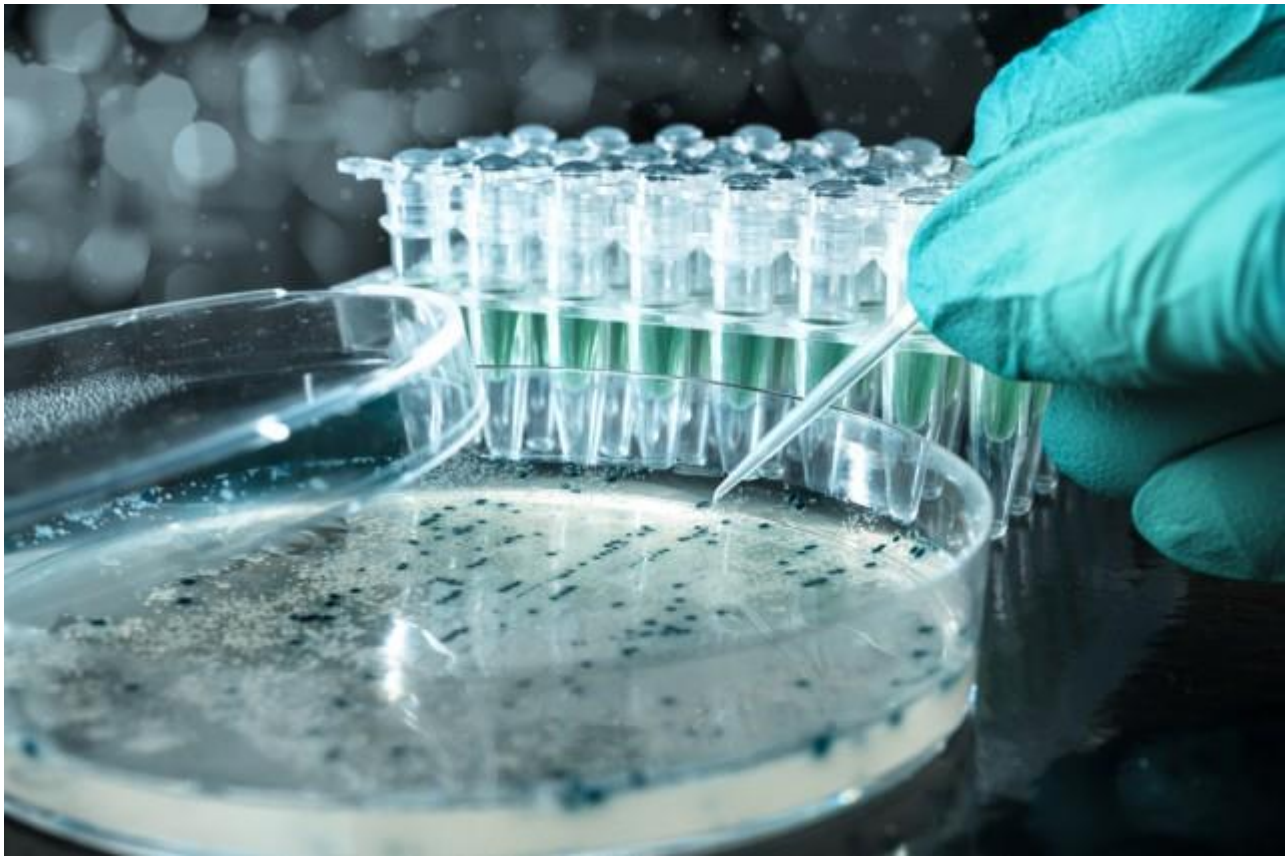


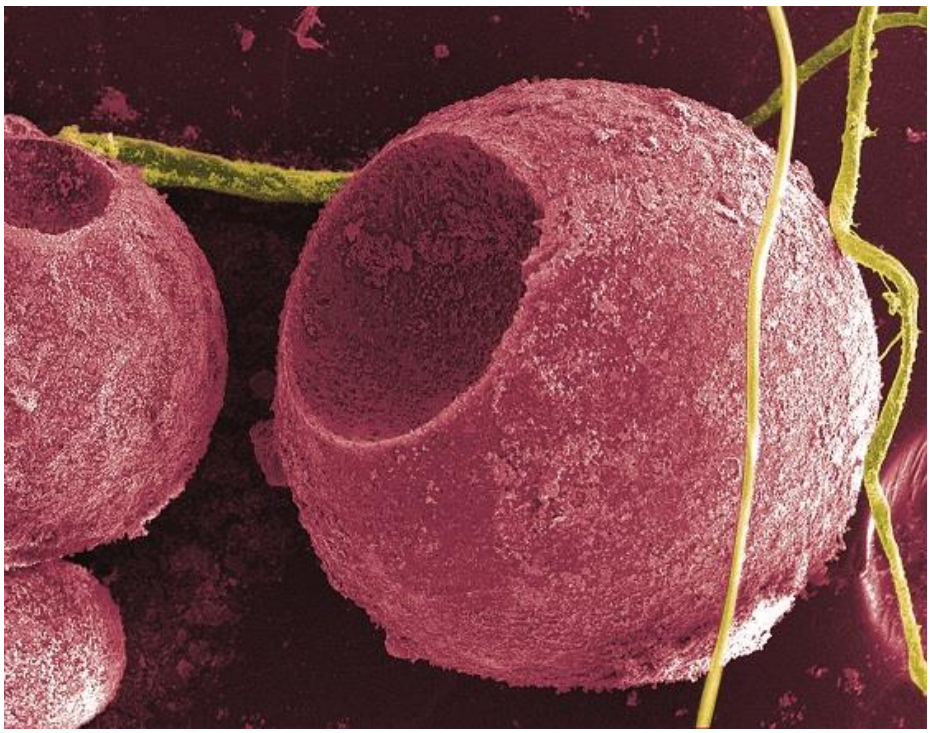
photo credit: Superbugs versus Quantum dots. Who'll triumph now that antibiotics are becoming increasingly ineffective? anyaivanova/Shutterstock

Back in 2014, the World Health Organization issued a report declaring that antimicrobial resistance (AMR) had become a global health security threat. Various "superbugs" are evolving too rapidly to be counteracted by traditional drugs. A new study published in Nature Materials could offer some hope, showing that tiny structures called nanoparticles can be turned into targeted, destructive weapons that can destroy resistant bacteria by using nothing more than light.

AMR occurs when microbes evolve defensive mechanisms designed to evade therapeutic agents, thus rendering these drugs partly or completely ineffective as forms of treatment. Largely due to the oversubscription of antibiotics to people and their overuse within intensive livestock farming, the situation has led many to suspect that we are entering a post-antibiotic era. Not only does this make once-treatable infections far more difficult to treat, it also means that they could

potentially become life threatening. Fortunately, a team at the University of Colorado Boulder has engineered a weapon for us to use against our bacterial foes.

Quantum dots (QDs) are essentially small crystals of nanometer-size dimensions – they're about 20,000 times smaller than the width of a human hair. They have distinctive electrical conduction properties that are determined by the incredibly small size and structure.



Nano-sized cadmium sulfide quantum dots – one of many types. U.S. Department of Energy.

When these QDs are hit with a specific frequency of radiation, their changeable structure, tailored by scientists, means that they can be finely tuned to emit a specific frequency of radiation; changing the wavelength of the light source can achieve the same effect. In this study, the researchers decided to try and use customized QDs against antibiotic-resistant bacteria, including *E. coli* and *Staphylococcus aureus*, in a laboratory setting. In the dark, the QDs remain inactive. When bombarded by visible light, they become energetically "excited."

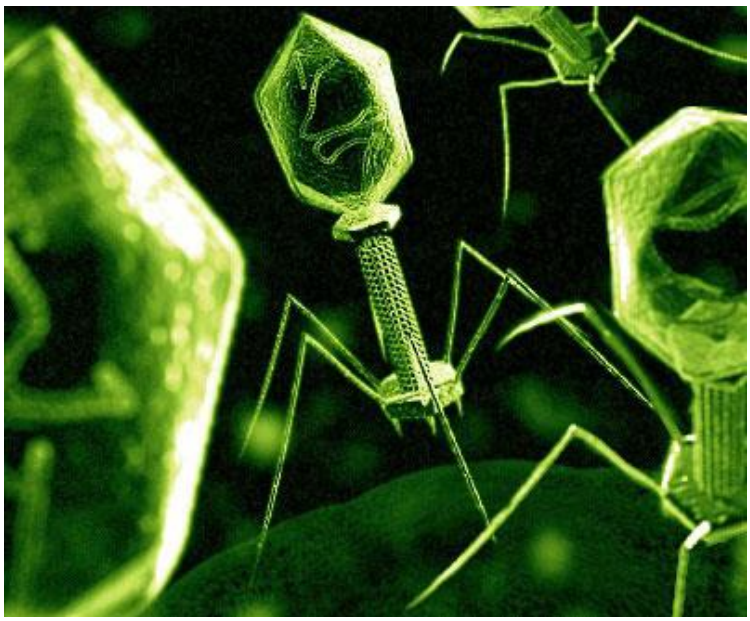
When placed among bacteria in a solution, something interesting happens. Bacteria rely on "redox" reactions, those involving the addition or removal of oxygen (reduction and oxidation, respectively). And when several QDs are "excited" nearby, they produce chemicals that are able to be reduced or oxidized by reactive compounds within the bacteria. This effectively interferes with their intercellular processes, disrupts their cell growth, and kills them. In a lab-grown culture, this method has been shown to kill 92 percent of a variety of drug-resistant bacterial

cells, while leaving other cells alone.

Previously, tiny graphene nanoparticles have been shown to effectively transport anti-cancer drugs inside them during novel chemotherapy treatment, and some can even be triggered to heat up to annihilate cancerous tissue. In a similar way, QDs – roughly the same size – could be injected into the human bloodstream, and designed to target specific infections by being stimulated with various wavelengths of light.

"While we can always count on these superbugs to adapt and fight the therapy, we can quickly tailor these quantum dots to come up with a new therapy and, therefore, fight back faster in this evolutionary race," said Prashant Nagpal, an assistant professor in the Department of Chemical and Biological Engineering at CU-Boulder and a senior author of the study, in a statement.

Tutorial 4- It's not all doom and gloom: future treatments



Today's Key Questions:

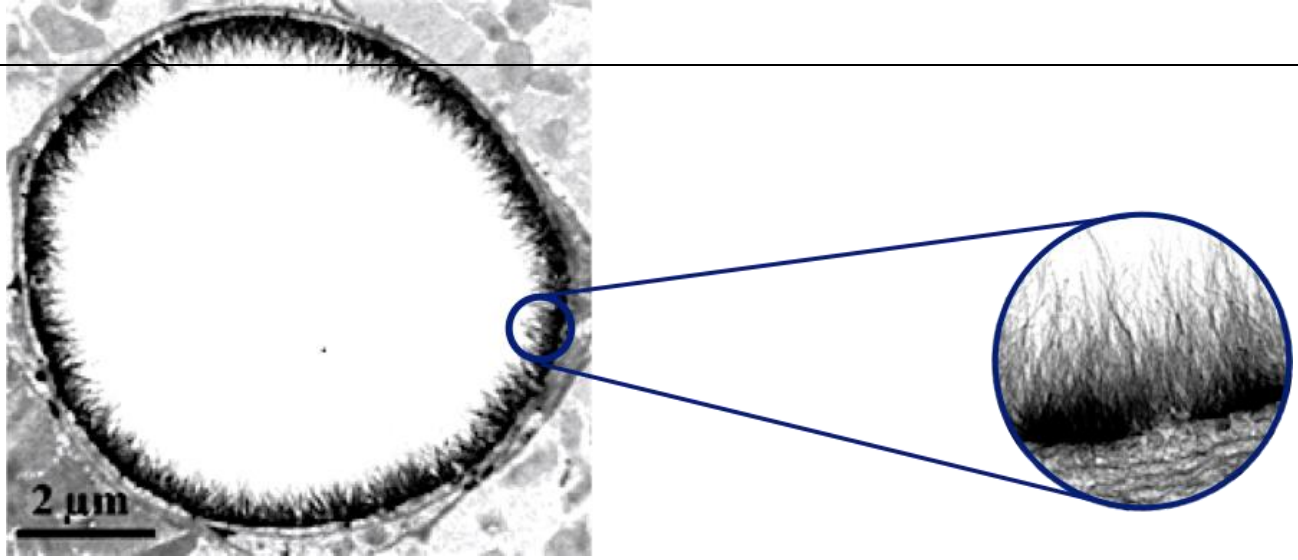
- What future treatments are available?
- How do they differ from current treatments?
- What are the key advantages and disadvantages of each option?

What is the Purpose of Tutorial 4?

- Describe other treatment options for bacterial infections
- Understand how new treatments differ from existing ones
- Identify the advantages and disadvantages of each.

Process of infection-

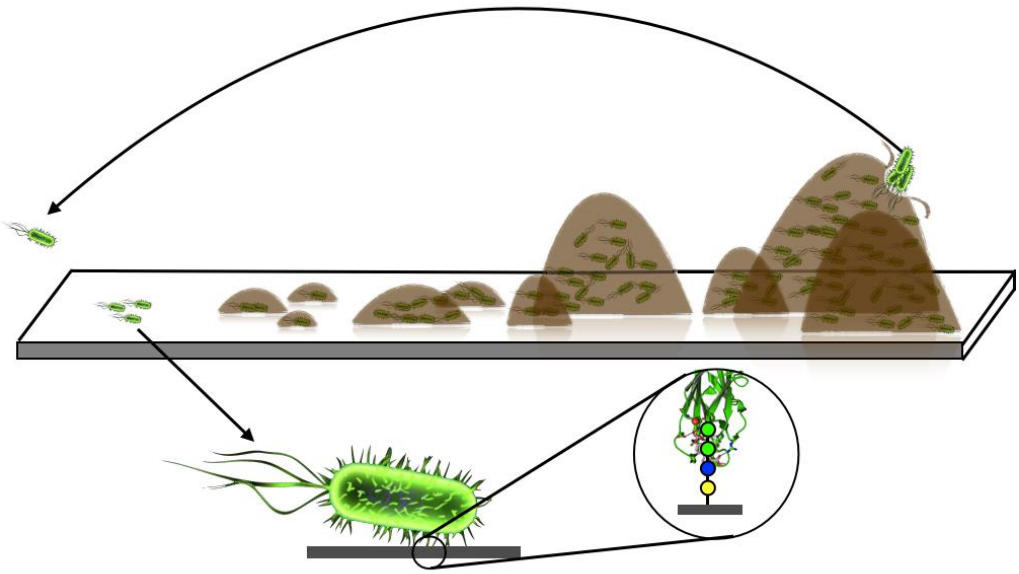
In order to develop drugs, we must first understand the process of infection. This starts initially with the attachment of one bacterium to the underlying surface of host cells. All of the mammalian host cells are surrounded by a glycocalyx, this is a layer of long chains of sugar molecules. This is crucial for the interaction of these cells with their environment and form important roles in cell-cell communication, fertilisation and both passive and innate immunity.



Interactions with the glycocalyx, usually involve an interaction between the carbohydrate on the surface and a protein. In the process of infection, bacteria have carbohydrate-binding proteins on their surface, which bind to the carbohydrates on the cell surface. Once a bacteria has bound it can begin to replicate, after several are present the next stage of infection requires the formation of a biofilm.

Bacterial biofilm production-

Initially when bacteria infect a region a single bacterium will bind to nearby cells. This will then reproduce making increasingly more bacteria. Eventually when there are enough bacteria they form a biofilm. This film allows bacteria to exist away from the surface and offers protection against antibiotics and the host immune system. The bacteria are coated in a slime that is made up of fatty acids and carbohydrates. Once the population of bacteria in the biofilm reaches a critical level some of the bacteria are released from the film in order to colonise other areas.

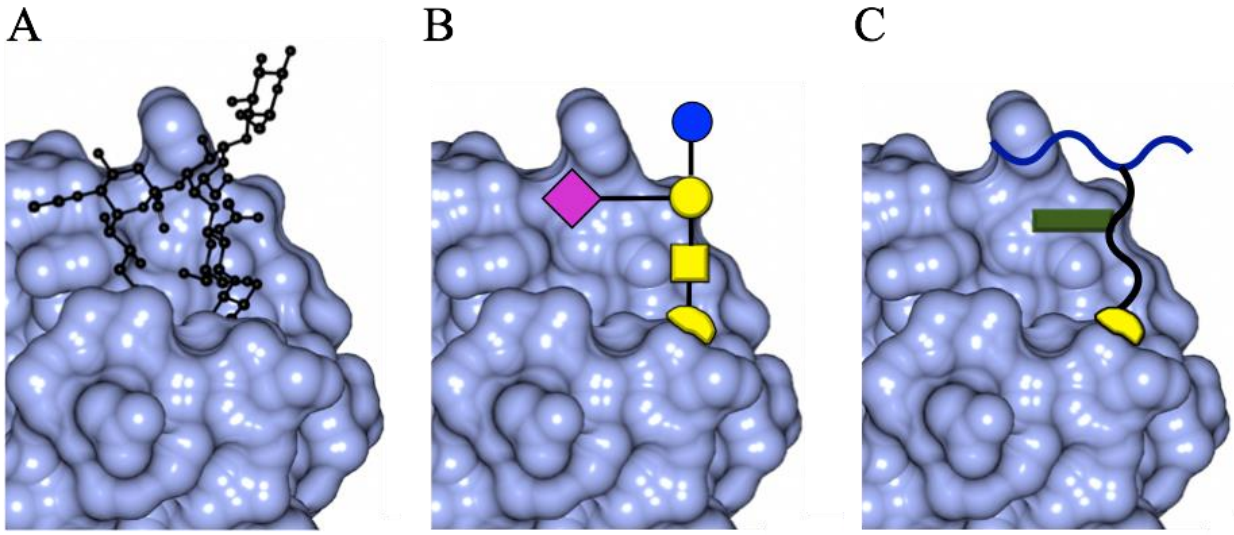


The initial binding of the bacteria to the surface is controlled by some highly important interactions known as protein-carbohydrate interactions. Proteins on the surface of the

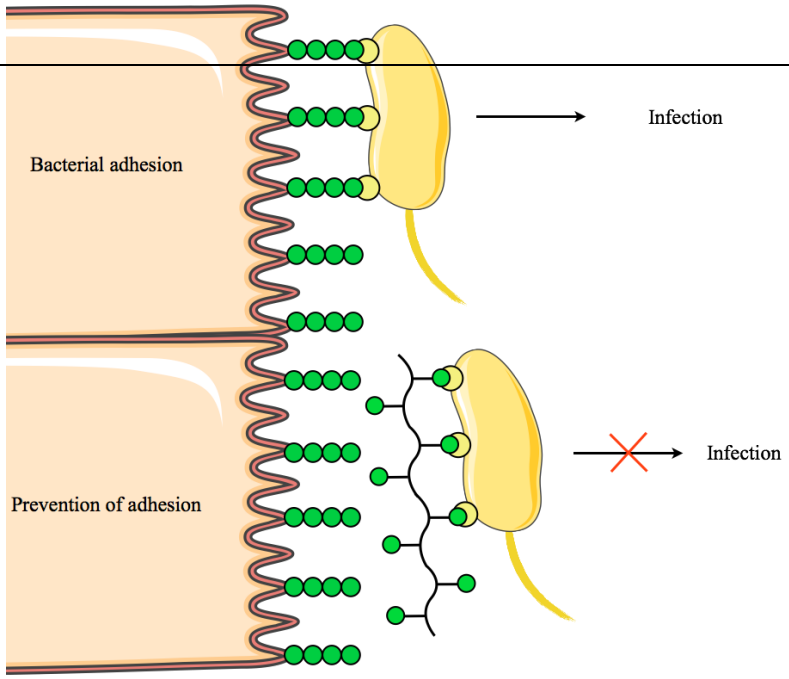
bacteria bind carbohydrates on the surface (host cells) and vice versa. Without this initial binding the bacteria pass through the system without causing damage and they will be more vulnerable to antibiotics and the immune system if they aren't coated by the biofilm.

Anti-adhesion therapy-

The principle of anti-adhesion therapy is based upon the development of drugs containing carbohydrates. Once you have identified the carbohydrates that a bacteria binds to on a cell surface you can develop drugs that either contain these sugars or drugs that mimic them.
If we consider cholera toxin, this binds to a large saccharide found on mammalian endothelial cells known as GM1 (A). A simplified version of the carbohydrate is shown in B. We can design a drug molecule that contains the final binding sugar and a group that mimics the pink binding sugar (C).

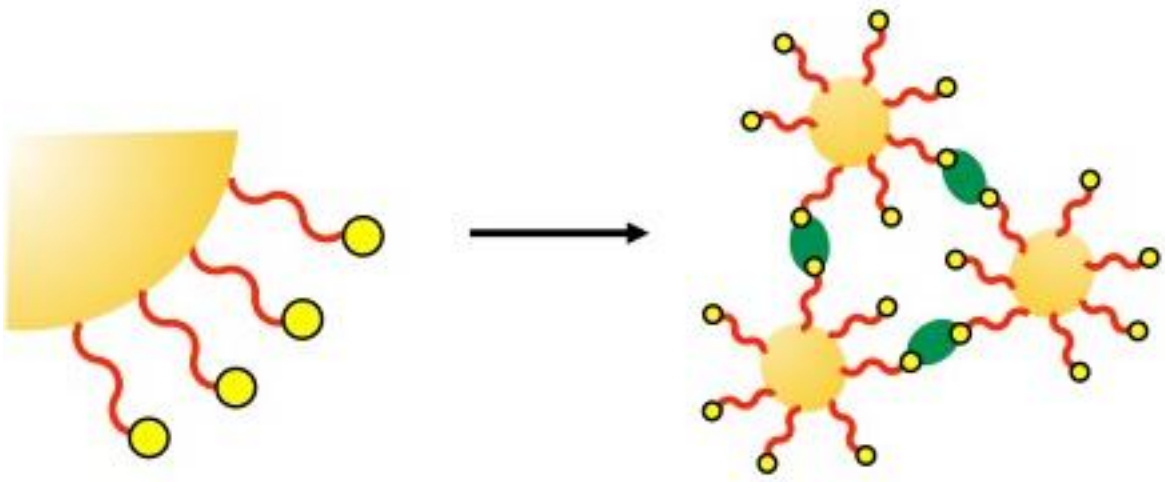


In the absence of a drug the bacteria will bind to the surface as normal and infection will occur. However, in the presence of a drug that mimics the cell surface, the bacteria will bind the drug and not the surface and as such the infection will not progress and no biofilm will form.

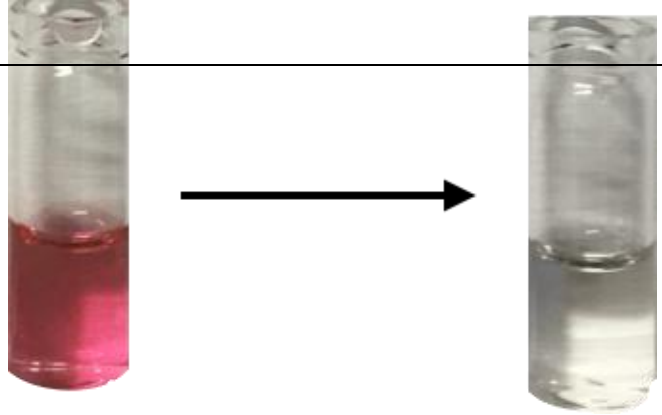


Bacterial identification-

As has been discussed, bacteria have proteins on their surface, which will bind to sugars on the surface of our cells. These proteins bind different sugars and this is one of the ways in which bacteria can target different organs. These proteins can be exploited in order to identify bacterial species. To do this we create some gold nanoparticles and then functionalise their surface with different sugars.



The reaction of particles that bind to a specific protein brings the particles closer together. The gold nanoparticles have a special property in that when the particles are far apart they appear pink and when they are closer together they change to blue/colourless.



This colour change will be different depending on the sugars on the particle surface and the bacterial species. Each bacterial species will have a specific 'bar code' of interactions.

Sample	glucose	galactose	mannose
P. aeruginosa			
M. tuberculosis			
E. coli			

Homework 4- Final Assignment Plan

Prepare an essay plan for the final assignment, further details about the assignment can be found on page 67. You should also aim to complete a draft of at least one section of your final assignment.

Section	Summary of what will be included
Abstract	
Case study	
Current treatment	
Resistance	
Future treatment	
Conclusions	

Tutorial 5- What is scientific writing?

Today's Key Questions:

- What does scientific writing mean?
- What makes a piece of scientific writing persuasive?
- What is an abstract?

What is the Purpose of Tutorial 5?

- Introduce the concept of scientific writing
- Understand the differences between scientific writing and persuasive writing
- Identify the key components of an abstract.

Scientific writing-

For the final assignment, you will be completing an essay answering the question of 'why haven't we won the war on tuberculosis yet?' It would be tempting to answer this question using persuasive writing. However, scientific articles are written in a very specific way that is very different from any other style of writing. The similarities and differences between these two styles will be explored in this tutorial in order to understand the style of writing that will be used in order to complete your final assignment.

Read the articles and fill in the following table highlighting the similarities and differences in the two styles of writing. Whilst the two articles you will read both tackle the question you will be answering in your final assignment it is important to know that they are not necessarily the best answers or layouts for your work. Any copying from this work will be noted and recorded as plagiarism.

	Scientific writing	Persuasive writing
Content		
Language		
Style		
Presentation		

How can scientific writing be persuasive?

Article 1- scientific article

Abstract

The emergence of antibiotic resistant strains of the bacterium adds a completely different dimension to the ever growing battle with TB and has panicked governments and scientists alike. On a global scale, there are currently around 10 million new cases of active TB (2). An estimation made by WHO suggests that one third of the world's global population is infected with the deadly bacteria, which is now becoming one of the most important causes of mortality worldwide, second only to HIV. As with all drugs, side effects are bound to be present. Anti-tuberculosis treatment is associated with significant side effects, which is one of the major factors to why there is little adherence to the tuberculosis treatment regime. Multidrug-resistant Tuberculosis (MDR TB) is the strain of TB that is resistant to 2 of the best anti-TB drugs currently out there; isoniazid (INH) and rifampin (RIF). These antibiotics are considered first line drugs to treat people with TB the first time they develop the disease. The alarming increase in drug resistant bacteria has led to the search of new means of battling TB. A promising approach is the use of agents that interfere with the bacteria's adhesion ability. Compared to the more traditional medicines currently used to treat TB, treatments such as anti-adhesive agents and phages tackle the cause of the problem instead of alleviating symptoms. For this reason, once more these treatments have been fully developed they may serve as a new way to fight infectious diseases.

Why we haven't won the war on tuberculosis yet?

Tuberculosis (TB) is a worldwide pandemic according to WHO. With molecular evidence that dates back to 17,000 years, TB is amongst the oldest diseases known to mankind (1). Advances in technology and our understanding of TB have led to useful discoveries and applications regarding prevention and treatment. Despite this, the disease continues to spread vigorously around the world and people are still suffering. On a global scale, there are currently around 10 million new cases of active TB (2). An estimation made by WHO suggests that one third of the world's global population is infected with the deadly bacteria, which is now becoming one of the most important causes of mortality worldwide, second only to HIV. There were an estimated 1.5 million deaths caused by *Mycobacterium tuberculosis* of which 1.14 million were among HIV negative people and an estimated 550, 000 cases of TB among children (3).

The emergence of antibiotic resistant strains of the bacterium adds a completely different dimension to the ever growing battle with TB and has panicked governments and scientists alike. It is of no surprise that an antibiotic resistant strain has surfaced when considering our weak immune systems caused by decades of over prescription and carelessness with antibiotic courses. Antibiotics play a big role in defense against bacteria and having antibiotic resistant bacteria, especially with TB; will cause nothing short of a catastrophe. Nevertheless, the outcomes some possible treatments promise are hopeful and with the dire need for a solution, more work and funding is being put into research to overcome this adaptable disease.

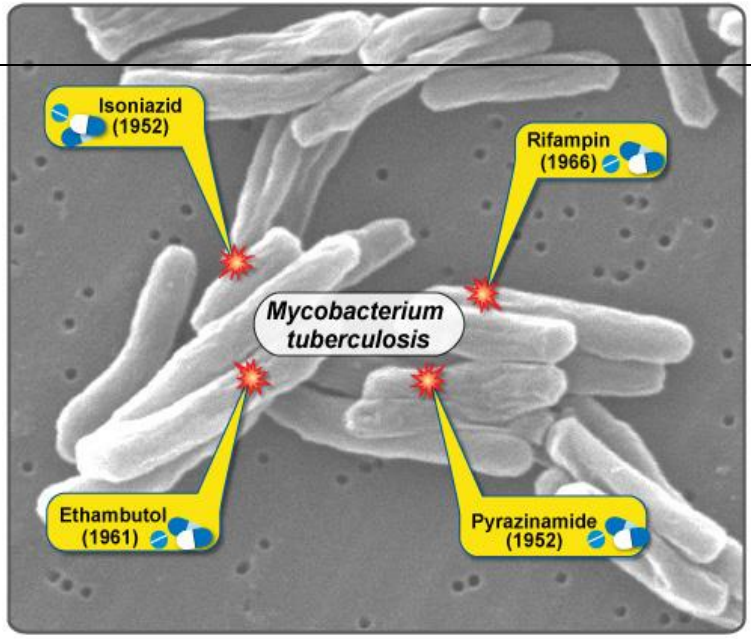
Tuberculosis is caused by bacteria that can spread from person to person through microscopic droplets expelled into the air. This can happen when someone with the active form of tuberculosis coughs, sneezes, laughs or spits (5).This bacterium is most famously known as *Mycobacterium tuberculosis* (6).Tuberculosis is airborne. Being able to spread from

person to person through coughing, sneezing and talking means it can circulate around a small population fairly quickly (7). Although TB has been found to be evident in various sites in the body including the central nervous system and other organ systems (4), it is predominantly a pulmonary disease. The disease is commenced by the accumulation of the deadly bacteria over time.

It is not easy to acquire TB, however after repeated contact with someone with the disease, such as friends and family, the chance of getting the disease increases drastically. TB is spread most easily in closed spaces over a long period of time however even if someone becomes infected it does not necessarily mean they will contract TB. Most people do not develop TB disease either because they develop a latent form of the disease or their body is strong enough to fight the malady itself. The latter, as expected, is less common in less developed areas around the world especially when basic healthcare and education is not sufficiently available. Having the latent form of the disease means the more explicit symptoms of TB such as coughing, fever and weight loss are not present. It also means that the disease itself cannot be spread from one person to another as it lays dormant in the host's body. This presents a problem in identification of an individual.

Generally, the procedure carried out to determine the presence of Tuberculosis involves x-rays. If a latent TB infection is present there will be nothing of significance in the x-ray image, compared to an active TB infection where an x-ray will easily detect any problems and show signs of tissue damage (8). Other tests such as the Sputum Test (SSM) also test whether or not a person has TB bacteria (9). A person with latent TB will produce a negative result for the Sputum Test compared to a person with active TB who will produce a positive result (10). Not being able to detect if the disease is present means an individual can go a long time without actually knowing whether they have TB or not. This is a disadvantage, as the earlier a disease is discovered the earlier the treatment can be started and the quicker a possible recovery can be made.

Although people with latent TB are not directly ill or do not suffer the symptoms it does not mean they cannot develop active TB. If TB bacteria becomes active it can spread throughout the body and a person can go from having latent TB to having active TB. For this reason people with latent TB are usually prescribed treatment to prevent and control the development to the more dangerous active TB. Because there are more bacteria in a person with active TB, treatment is usually more difficult and goes on for much longer. Currently there are several drugs that have been verified by the U.S FDA for successfully treating TB. These include isoniazid (INH), rifampin (RIF) and pyrazinamide (PZA) which are all first line anti-TB agents that form the main core of treatment (11)



The length of the treatment courses is standard with an initiation phase of 2-months followed by an additional optional continuation phase of either 4 or 7 months. This gives a combining average total of 6-9 months for each regimen. Usually a combination of the 4 different first line drugs (See Figure 1) is used to combat the deadly disease. After improvement or alleviation of some of the symptoms other second line drugs may be used.

Even with this supposedly effective treatment problems still arise. As with all drugs, side effects are bound to be present. Anti-tuberculosis treatment is associated with significant side effects, which is one of the major factors to why there is little adherence to the tuberculosis treatment regime. Some of the side effects include hepatitis (inflammation of the liver), dyspepsia (indigestion) and exanthema (severe rash), which have all been found responsible for termination of the antibiotic course in 23% of patients during the intensive phase (12). It is very important that people who have TB finish their antibiotic course completely and exactly as prescribed. Terminating the course or finishing too early may allow bacteria to evolve and adapt to resist the antibiotic treatment. Soon those treatments will no longer work on the bacterium strain and the person will have drug resistant TB. Drug resistant TB is much harder to treat as well as being much more expensive. More importantly, the presence of antibiotic resistant strains of the bacterium will ultimately become unstoppable and the lives lost to TB disease will increase drastically.

Antibiotic resistance occurs when an antibiotic has lost its ability to kill bacteria and control bacterial growth. In this case the TB bacterium becomes resistant and continues to multiply even in the presence of the antibiotic. How resistance is formed is a natural phenomenon, which can also be seen in many aspects of biology and nature. The presence of the antibiotic creates a selection pressure for survival, meaning those bacterium's that are susceptible to the antibiotics are destroyed leaving behind bacterium's which have a higher chance of survival. Over time, the remaining "successful" population survives, reproduces and passes on their resistant genes.

There are generally 2 ways in which a bacterium can become resistant. Random mutations that occur very rarely can give advantageous qualities to bacteria allowing it to survive in the presence of an antibiotic i.e. allowing it to produce enzymes that counteract antibiotics or similar characteristics. Another way bacteria can become resistant is by acquiring resistance from a different bacterium. Conjugation is a bacterial mating process, which involves the transfer of genetic material from one bacterium to another. This genetic information can also include genes encoding for antibiotic resistance meaning bacteria that may not be resistant can obtain the genes necessary for resistance so when that cell divides and multiplies any

cells originating from that cell will also be resistant.

Multidrug-resistant Tuberculosis (MDR TB) is the strain of TB that is resistant to 2 of the best anti-TB drugs currently out there; isoniazid (INH) and rifampin (RIF). These antibiotics are considered first line drugs to treat people with TB the first time they develop the disease. This presents a problem as it means that one person can spread MDR TB to a large population fairly quickly. This has the biggest impact on countries with poor healthcare systems and weak TB control programs. New figures for MDR-TB have revealed the highest ever recorded levels of the antibiotic strain, with 65% of patients who have been previously treated for TB ending up back in hospital with TB resistant strain. Cases of MDR-TB have now been reported in 80 countries and XDR-TB (Extensively Drug Resistant TB), which is even harder to treat in 77 of those countries. In the present time the treatment is not efficient enough the first time around due to improper antibiotic use. The fact that TB treatment is a 6 month long course doesn't help either. This emphasizes the need for shorter, faster reacting drugs to remove any chances of resistance emerging.

The alarming increase in drug resistant bacteria has led to the search of new means of battling TB. A promising approach is the use of agents that interfere with the bacteria's adhesion ability. The TB bacterium usually adheres to tissues and organs in its initial stages and preventing this means preventing the development of the disease. Within anti-adhesion therapy fall the different approaches including receptor analogs, dietary constituents and adhesion-based vaccines (19). The significance of these adhesion-based therapies is that they are non-bactericidal implying that the development and spread of antibiotic resistant is less likely to occur when exposed to agents such as antibiotics. Compared to the more traditional medicines currently used to treat TB, treatments such as anti-adhesive agents and phages tackle the cause of the problem instead of alleviating symptoms. For this reason, once these treatments have been fully developed they may serve as a new way to fight infectious diseases.

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Article 2- persuasive article

Why we haven't won the war on tuberculosis yet?

In this essay I will be talking about the main reasons why we have not won the war on Tuberculosis yet. My key points will be about, the current treatments for this bacterial infection, totally drug-resistant TB, also known as TDR-TB and the future treatments if there is any. What is Tuberculosis? Are the current drugs still useful for treating TB? Do we have the money to research and create new treatments to cure totally drug-resistant TB? How long will it take to finally eliminate TB if we can? All questions I will be answering and looking more into detail in this essay. There are different forms of TB, like Latent and active TB, meaning there is going to be different types of treatments for them. Some cures and treatments would not work for some types of TB and some are harder to cure like totally drug resistant TB.

How many people actually know what Tuberculosis is? Tuberculosis, or TB, is a very serious bacterial infection that is more commonly found in the lungs however it can spread through your bloodstream to any organ in your body and can kill you if not treated. On average around 2 billion people are infected with TB, about 9 million people each year become sick with TB and almost 1.5 million deaths are caused by TB. Some current problems with TB is that people who do not know they have it can spread it to uninfected people causing them to develop this bacterial infection. Linking on from this, another problem is that it is hard to diagnose people as if you have Latent TB you will not have any symptoms as it is dormant. However, you can have tests done to see if you have got Latent TB so you can be treated to prevent you from the TB disease. You can have a skin test or blood test and your results will indicate the TB infection or you can have a negative sputum test. Lastly the treatment form TB takes a minimum of 6 months, showing it's not a quick cure.

If you have TB, you will be isolated to stop it from spreading to other people and you will undergo Drug Therapy. You will have to take four common drugs and antibiotics called:

- Isoniazid
- Rifamipn
- Ethambutol or streptomycin
- Pyrazinamide

After two months' pyrazinamide can be stopped but Isoniazid and Rifamipn are continued daily or you can undergo intermittent therapy for 4 more months. Also patients diagnosed with active TB should undergo sputum analysis for Mycobacterium tuberculosis weekly until sputum conversion is documented.

This shows just how long it takes to try and cure TB. However, if you have Latent TB the treatment will be slightly different. Although there is a cure for TB the main problem is how long it takes to be completed as the infection is becoming more resistant to the drugs used. One advantages of this current strategy is that there are more than twenty drugs available for TB treatment and around 90% of people with TB that is not drug resistant can be cured in six months using a combination of "first line" TB drugs.

A bacterium can become resistant if it changes in some way that reduces the effectiveness of drugs, chemicals, or other agents designed to help prevent infections and as the bacteria multiplies more become resistant and this can cause more harm to your health. Bacteria becoming resistant to drugs is an example of natural selection. In a large population of bacteria, there may be some that aren't affected by the antibiotic and then they reproduce and create more bacteria that it resistant to drugs. MRSA is methicillin-resistant Staphylococcus aureus. It is very dangerous because it is resistant to most antibiotics. To slow down or stop the development of other strains of resistant bacteria, we should:

- always avoid the unnecessary use of antibiotics
- always complete the full course

There are three ways that rapidly spread the resistance to other bacteria cells and they are call:

- Transformation
- Conjugation
- Transduction

Transformation is the transfer of free DNA and it happens quickly. When a bacterium dies the cell breaks open and the resistant gene can be passed on to a living bacterium as the gene is free in the body. The resistant gene goes to the plasmid or to the chromosome. Conjugation is a plasmid transfer. This is when two bacteria, one a plasmid Donor, bump into each other and the Donor gives the resistance to the other bacterium, which has no resistance. Thus creating another plasmid donor. Two bacteria come together and the pill will form a hollow bridge allowing plasmids to pass between them. Lastly Transduction is a transfer by viral delivery and is specific to bacteria. This can pass on the resistance quickly to another bacterium to ensure they become resistant too. Transduction is the process by which DNA is transferred from one bacterium to another by a virus and it does not need physical contact for the transfer, like conjugation. This is a major problem because totally drug-resistant TB is already occurring in at least 58 countries, which estimates around 25 thousand cases occurring each year. Some factors of the increase of drug-resistant TB are:

- HIV
- Poverty
- Bad management of the disease
- Lack of development in new TB treatments

The main reason why this bacterium is becoming more and more resistant is because we keep using antibiotics to try and treat TB. As we are trying to find a new treatment for totally drug-resistant TB and a better cure for Active TB that doesn't take six months to work, if it does work, the bacterium is becoming even more resistant. The longer we take to find a better and new cure the quicker the bacteria will become fully resistant and then we will not be able to treat and cure it. Also it costs a lot of money to research and try to find a new cure and we might not have the money to do so. Another problem is that more people are living in poverty and contracting HIV which is leading to people getting TB. However, the only problem is that we cannot stop people from getting HIV's as it's their own choice what they do in their life so we can only suggest what we believe is best and we cannot help everybody who is in a tough position with money problems. Also some people have got Latent TB in their system already and that could quickly become active if somebody

who is infected coughs as TB is contagious and they could get some resistant bacterium in their body so they wouldn't just have TB they would have totally drug-resistant TB which is harder to treat and cure.

With all of this being said about the bacterium becoming resistant to antibiotics and the are there any new treatments to cure drug-resistant TB? Some of the newest treatments for TB is:

- Fluoroquinolones
- Moxifloxacin
- Pharmacokinetics

Fluoroquinolones is known as a promising class of drugs for the treatment of TB. These drugs circulate around the body, including in the cells too, and this is a main reason why it's so effective against the infection. Moxifloxacin is a broad-spectrum and has action against gram-negative and gram-positive bacteria. Lastly, Pharmacokinetics works together with Moxifloxacin. Numerous new drugs for TB are being assessed in clinic trials. This suggests that progress is being made in finding a new and better drug for TB. One advantage of using new drugs is that it should take less time to effectively work and help treat this bacterial infection. It should take less time to start to work as the bacterium would not be as resistant to the newer drugs unlike the current ones which are becoming less efficient and useful. However, one disadvantage is that all of this costs money. It cost a lot of money just to do the research and make the new drugs so if the scientists ever run out of money they cannot carry on and this then postpones the whole development of a new drug. Then they have to get them tested, to ensure they are safe and working right, which takes time. So the process of creating a new drug is a long term process. Another disadvantage is that the new drugs might work on one person but not on another so you have to make sure there is an alternative solution where needed. In my opinion we need to improve the research of TB so that we can find a quick cure and learn more about this disease so we can hopefully wipe it out for good. Similarly, we also need to put more money into development so all of this is possible and so that more lives are saved rather than lost to TB. Lastly, we could have a better screening program for when holiday makers and those looking to move here, from countries that are most likely to have the highest rating of TB (For example Africa and Russia) enter a different country they will be tested to see if they have Latent or Active TB. They should start by having a blood test to identify the TB infection. Then those who have been identified should have a chest x-ray and a sputum test carried out. If you have Latent TB, your chest x-ray will be normal and you will have a negative sputum test whereas if you have active TB you will have an abnormal chest x-ray and a positive sputum smear. Then after this we can quarantine those effected and treat them so they won't be bringing the infection into the country. This is why we would need to find a quicker cure so that people will not be isolated for 6 months to cure them from TB if they only came for a two-week holiday. If we could do this, it would reduce the number of people contracting TB and will help to abolish TB. Also linking onto my first point about finding a quicker cure if less people have TB then we could take our time into perfecting the new cure so that hopefully we can eradiate TB one day. All of these are ways in which we can improve the future for treating TB. These changes might take time but they will be effective.

In conclusion, current treatment, the bacteria becoming resistant and the future for TB treatment are all main factors of why we have not won the war on Tuberculosis yet. Current treatment for TB is good and efficient as it does cure 90% of patients and it is helping towards eliminating this disease for good. However due to the increase of totally drug-resistant TB these drugs are becoming less and less useful to use and soon we will have no cure or treatment to use. As the bacterium is becoming more resistant to the antibiotics and current drugs, the percentage of people who are being cured by using these drugs will slowly fall and decrease. This is why it is so important for us to find a new treatment that the bacterial infection is not immune to and that will be quicker in curing the patients with TB. Hence why we need to put more money and time into researching and testing experimental drugs. However, this cannot be done unless we have volunteers who are willing to try these drugs. There are many ways in which we can improve the future treatment but it all comes down to if we can afford it and how long it will be before these changes will be enforced. Over all, the main reasons why we haven't won the war on TB yet is purely because we need to take our time to perfect a new cure and also because we simply cannot afford it.

Abstracts-

An abstract is a short piece of text that is usually found before the main body of a scientific article. This should be a summary of the entire article, which covers everything from the introduction, the current solution, the main challenges and the final conclusions of the text. It is similar to the blurb of a book but it gives away the ending. Essentially the purpose of an abstract is to allow someone to quickly work out what the article is about and thus decide whether it is something they want to read. Whilst this means that it can be persuasive it is important to note that it should still be written using the scientific style of writing and as such questions should only be included if there is no other way to make your point.

Here is a useful checklist for writing an abstract:

- The introduction is summarised ☐
- The main content is summarised ☐
- The conclusions are summarised ☐
- The style of writing is scientific ☐
- Facts are used to draw the reader in ☐
- The abstract is less than 150 words ☐

Using the checklist read article 3 and write a scientific abstract for it in the box provided. Once you have finished, swap abstracts and complete the following peer assessment.

What went well?

Even better if…

A solution to antibiotic resistance may have been under our noses all along

Abstract

Alexander Fleming discovered penicillin in 1928 and revolutionised the treatment of bacterial infections. Ever since then we have been searching for new antibiotics to address the myriad of infections humans encounter and the growing risk of resistance to them.

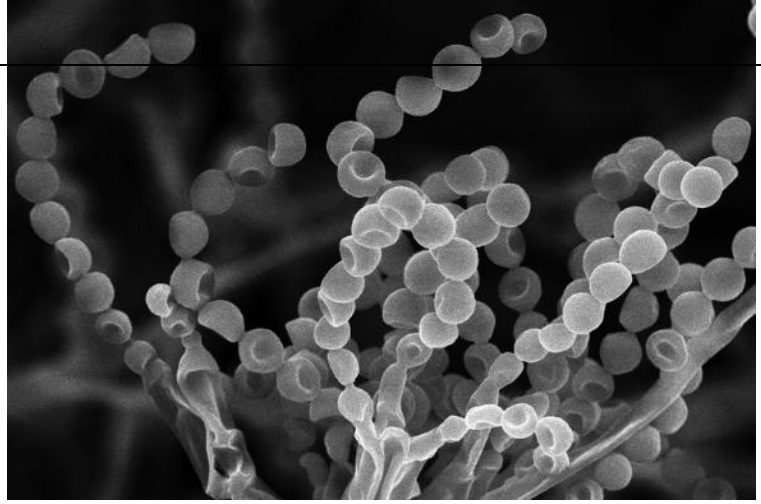
Researchers have now found a bacterium in the human nose that produces an antibacterial product called lugdunin, which is able to suppress the common human pathogen *Staphyloccocus aureus* (commonly known as "Golden Staph"). This discovery marks a new frontier in the discovery of potentially useful antibiotics as the researchers found it in our own bodies.

Where antibiotics come from

Traditionally, antibiotics were sought in nature. This was based on the premise that all things on earth — plants, soil, people, animals — are teeming with microbes that compete fiercely to survive. Trying to keep one another in check, the microbes secrete biological weapons: antibiotics.

Serendipitously, and based on this principle, Alexander Fleming recognised the mould *Penicillium chrysogenum* produced penicillin when he noticed it inhibited the growth of common bacteria.

In the second world war, many wound infections were treated with a newly discovered antibiotic called tyrothricin, which was isolated from another organism, *Bacillus brevis*. This was the first time researchers had turned to soil organisms to seek sources of new antibiotics.



A group of bacteria called actinomycetes was the source of almost half of the early antibacterial compounds found in nature. It is responsible for many of the commonly used antibiotics such as streptomycin (still occasionally used to treat tuberculosis), tetracyclines (still a first-line antibiotic used in treating pneumonia in Australia), chloromycetin (used as ear drops to treat ear infections) and the macrolide family, which includes common antibiotics such as azithromycin and clarithromycin (used to treat many common ailments such as stomach ulcers and chest and sinus infections).

In nature, antibiotics have been sourced from other bacteria, fungi, algae, lichens, plants and even some animals, which use antibiotics to prevent bacteria from colonising the surrounding environment or creating disease.

Vancomycin, an antibiotic we use today to treat life-threatening infections, was discovered by a chemist at a pharmaceutical company from a bacterium in a soil sample sent from Borneo by missionaries. This single discovery has saved millions of lives around the world.

Over the last decade, few new antibiotic classes have been discovered. This means bacteria that are becoming resistant to the antibiotics we have may be untreatable in future.

In early 2015, researchers used modern techniques to culture a soil-derived bacteria, *Eleftheria terrae*. This produced a new antibiotic, teixobactin, which kills bacteria in a unique and previously undescribed way.

Researchers have been expanding the environments where they search for new antibiotics by focusing on areas around the world that are so hostile they might induce unique organisms to grow that produce previously undiscovered antibiotic substances.

A British group has been searching the depths of the sea. Canadian researchers are carrying out experiments on bacteria from deep within caves. Many other groups are isolating potential antibiotic-producing bacteria from volcanoes, glaciers and deserts.

Why is this new discovery important?

Humans have a microbiome that covers the body's entire surface area, inside and out, and numbers around 10-100 trillion symbiotic microbial cells. The bacteria that live inside each of us live in harmony and are able to suppress the growth of potentially harmful bacteria.

This is done through competition for nutrients and modification of the micro-environment, but also through the production of substances that suppress the growth of certain bacteria that normally are not found in humans.

Imagine if we could harbour the antimicrobial potential of our own microbiome. This new discovery opens the road to further studies harnessing the potential of our own bodies.

Homework 5- Final Assignment

The task is to compile a 2000 word case study where you diagnose what bacteria is affecting patient X and whether or not the bacteria has antibiotic resistance (linking to your genetic analysis), detail the current treatment for that disease, describe antibiotic resistance, suggest some future methods of treatment. See page 69 for details about patient X.

Section	Description	Key questions
Abstract (150 words)	Give a brief overview of your essay summarising	
Case study (200 words)	Identify which bacteria is affecting patient X and complete the genetic analysis.	What bacterial species is responsible for the infection? How do their symptoms compare with that of the disease? Does the bacteria contain the mutation responsible for antibiotic resistance?
Current treatment (200 words)	Describe the current treatment options for the disease affecting patient X.	What is the current treatment? Are there any problems with the treatment? What are the advantages/disadvantages of the current strategy?
Resistance (600 words)	Outline the way in which a bacterium can be resistant and the mechanisms through which resistance can be spread between bacteria.	How can a bacterium be resistant? How is resistance spread between bacteria? Why is it a problem?
Future treatment (600 words)	Outline potential future treatments that could replace antibiotics, including but not limited to anti-adhesion therapy.	What current future treatments are available? What are their advantages/disadvantages?
Conclusions (250 words)	Summarise the key conclusions of your essay.	What treatment would you recommend overall for patient X?

The Deadline is:

Mark Scheme

Key Skills	1st	2.2
Knowledge and Understanding	Pupils demonstrate accurate and detailed knowledge of key concepts and incorporate the relative content to provide evidence for their arguments throughout the essay. Pupils will (where appropriate) provide detailed explanations of key concepts where descriptions go beyond that discussed in tutorials and are backed up with accurate evidence from independently researched sources.	Pupils highlight some of the key concepts and show some understanding of the basic principles behind how they work but some inaccuracies feature. Pupils make a good attempt at answering the question but descriptions of key concepts do not go beyond that discussed in tutorials and there is little evidence of independent research and thought.
Communication	Pupils construct arguments that are coherent and the essay clearly flows between sections. The conclusions logically follow from the discussion throughout the essay and pupils show evidence of a range of appropriate vocabulary including the use of scientific words where appropriate.	Pupils construct clear arguments but the essay lacks a logical order with some sections disjointed. Pupils largely demonstrate appropriate language but with some misuse of scientific words or the use of informal language.
Critical thinking	Recognition of the strengths and weaknesses of treatments and concepts are made and these are used to make an informed conclusion that considers these points. The purpose, scope and importance of the work is clearly understood and highlighted.	Some attempts are made to discuss the limitations of certain treatments but these have not necessarily been used to inform conclusions. Few attempts are made to highlight the importance of the work they are communicating.

Assignment Submission – Lateness and Plagiarism

Lateness	
Submission after 4.00pm on **Wednesday 6th April 2016**	10 marks deducted
Plagiarism	
Some plagiarism	10 marks deducted
Moderate plagiarism	20 marks deducted
Extreme plagiarism	Automatic fail

Case study- patient description:

A 23-year-old man presented with a 4-week history of coughing, breathlessness and malaise. He had lost 4kg in weight, but had no history of night sweats or haemoptysis. He had returned from holiday in Pakistan 2 months earlier. On examination, he was mildly pyrexial (37.8°C) but had no evidence of anaemia. The chest X-ray showed bilateral upper- and middle-lobe shadowin. A Mantoux test was strongly positive.

Case study- gold nanoparticle test results:

Sample	glucose	galactose	mannose
P. aeruginosa			
M. tuberculosis			
E. coli			
Patient X			

Case study-genetic analysis of the bacteria found in patient X:

Patient X Sample:

DNA sequence:

(5`) GCCAAGTCACTTTGATTGACCATAAACATT (3`)

mRNA sequence:

Amino acid sequence:

Species	Amino acid sequence
Wild type	RFSETKWYL stop
Mutant	RFSETNWYL stop

Tutorial 6 – Feedback

What are the key questions?

- What strengths have I demonstrated in my work?
- What areas of development are there left for me to address?
- What steps do I need to take to improve my academic output?

What is the Purpose of Tutorial 6?

- Reflect on skills learned on the programme with a view to encouraging resilience
- Receive feedback on final assignment

What does my mark mean?

Grade	Marks	What this means
1st	70+	Performing to an excellent standard at A-Level
2:1	60-69	Performing to a good standard at A-Level
2:2	50-59	Performing to an excellent standard at current key stage
3rd	40-49	Performing to a good standard at current key stage
Working towards a pass	0-39	Performing below a good standard at current key stage
Did not submit	DNS	No assignment received by The Brilliant Club

Lateness	
Any lateness	10 marks deducted
Plagiarism	
Some plagiarism	10 marks deducted
Moderate plagiarism	20 marks deducted
Extreme plagiarism	Automatic fail

Activity 1 – Marking your own

Using the mark scheme, identify three things you did well and three things you could improve.

What went well?

What could be improved?

Activity 2 – Responding to feedback

Read through your feedback sheet and highlight on your assignment where you received positive feedback (one colour) and areas for improvement (different colour). You might find it helpful to annotate this with a brief comment or two.

Activity 3 – Looking Forwards: Think, Pair Share

1. Think about how you can use this feedback in your future school work.
2. Talk to your partner about how you both plan to make changes to your school work in the future as result of this feedback
3. Share your ideas as a group.

Word	Definition	In a sentence…
Pathogen	A bacterium, virus or other microorganism that can cause disease.	*Mycobacterium tuberculosis* is a pathogen.
Disease	A disorder of function that has specific symptoms.	Tuberculosis is a disease that affects millions of people.
Bacterium	A member of a large group of unicellular microorganisms, which have cell walls but lack organelles and an organised nucleus.	During infection a bacterium binds to the cell surface. NB Bacteria is the plural
Parasite	An organism, which lives within another organism and benefits by gaining nutrients at the hosts expense.	Malaria is a disease caused by the parasite *Plasmodium falciparum*.
Virus	An infective agent that comprises of a nucleic acid molecule (usually RNA) inside a protein coat.	A bacteriophage is a virus that infects bacteria.
Plasmid	A genetic structure within cells that replicates independently of the chromosomes or other nuclear DNA.	A plasmid usually contains resistance genes that can be transferred between bacteria.
Fimbria	An attachment structure found on many bacteria.	A fimbria can be used by bacteria to attach to cell surfaces. NB Fimbriae is the plural
Pilus	A bridge like structure that forms between bacteria and allows the transfer of genetic material.	During conjugation, a pilus forms between two bacteria.
Genotype	The genetic constitution of an individual organism.	Insertion of a resistance plasmid alters a bacterium's genotype.

Gene	A distinct sequence of basis, which determines the order of amino acids in a protein and is passed from parent to offspring.	The active part of the DNA that determines protein formation is known as a gene.
DNA	Deoxyribonucleic acid is a self-replicating material that contains the genetic information of an organism.	Resistance can be caused a mutation in the DNA.
Translation	The process by which mRNA is converted into protein.	During translation, mRNA is converted into protein.
Transcription	The process by which DNA is converted into mRNA.	During transcription, DNA is converted into mRNA.
Replication	The process by which one DNA molecule becomes two prior to cell division.	Prior to cell division, the genetic material of a cell is doubled through the process of replication.
Phenotype	The set of observable characteristics of an individual resulting from the interaction of their genotype with the environment.	Antibiotic resistance is a bacterial phenotype.
Genetic code redundancy	A codon (comprising of three nucleotides) encodes the same amino acid.	The affect of a mutation can be limited at the genetic level through genetic code redundancy.
Selection pressure	An agent of differential mortality or fertility that tends to make a population change genetically.	Antibiotics form a selection pressure which results in antibiotic resistance.
Heterogeneous population	A heterogeneous population is a population in which the members differ based on a genotype or phenotype.	Bacteria exist in a heterogeneous population with differing levels of antibiotic resistance occurring naturally.

Transformation	The transfer of a resistance gene from a neighbouring bacterium that has died and broken apart.	Transformation is a mechanism of horizontal gene transfer.

Transduction	The transfer of an antibiotic resistance gene through infection with a bacteriophage from a neighbouring bacterium.	Transduction is a mechanism of horizontal gene transfer.
Conjugation	The formation of a pilus between two bacteria in close proximity allows the transfer of plasmids.	Conjugation is a mechanism of horizontal gene transfer.
Horizontal Gene transfer	The process by which a bacterium can acquire a gene from another bacterium.	Bacteria can pass resistance genes between each other through a process known as horizontal gene transfer.
Vertical gene transfer	The process of passing a gene from a parent cell to an offspring.	Bacteria with a resistance gene will pass that gene to their daughter cells through a process of vertical gene transfer.
Efflux pump	A protein within a cell membrane, which actively pumps out antibiotic compounds as they enter the cell.	One example by which a bacteria can be resistant is by having an efflux pump.
Altering enzyme	A protein that is expressed by the bacteria which binds to an antibiotic and changes the chemical structure in some way rendering it useless.	A bacterium that expresses a specific antibiotic altering enzyme may be resistant to that antibiotic.
Degrading enzyme	A protein that binds to an antibiotic and breaks down the chemical thus stopping it from working.	Expression of an antibiotic degrading enzyme can result in antibiotic resistance.
Antibiotic resistance	The ability of a bacterium to withstand the effects of a compound designed to kill it.	Antibiotic resistance represents a global threat to health.

Superbug		

	A colloquial term for a strain of bacteria that has become resistant to antibiotics.	Superbugs represent a threat to global control of bacterial infections.
Bacteriophage (phage)	A virus that infects bacteria.	Bacteriophages represent an alternative to antibiotic treatment.
Anti-adhesion therapy	The prevention of an infection through interfering with the crucial process by which a pathogen binds to a host cell.	Anti-adhesion therapy represents an alternative to antibiotics.
Protein-Carbohydrate interaction	The binding of a protein on one cell to a carbohydrate present on another's cell membrane.	Infection occurs through a crucial protein-carbohydrate interaction.
Glycocalyx	A glycoprotein-polysaccharide covering that surrounds the cell membranes of cells.	The glycocalyx of a cell is essential for a number of biological processes including cell-cell communication.

Appendix 1 – Referencing correctly

When you get to university, you will need to include references in the assignments that you write, so we would like you to start getting into the habit of referencing in your Brilliant Club assignment. This is really important, because it will help you to avoid plagiarism. Plagiarism is when you take someone else's work or ideas and pass them off as your own. Whether plagiarism is deliberate or accidental, the consequences can be severe. In order to avoid losing marks in your final assignment, or even failing, you must be careful to reference your sources correctly.

What is a reference?

A reference is just a note in your assignment which says if you have referred to or been influenced by another source such as book, website or article. For example, if you use the internet to research a particular subject, and you want to include a specific piece of information from this website, you will need to reference it.

Why should I reference?

Referencing is important in your work for the following reasons:

- It gives credit to the authors of any sources you have referred to or been influenced by.
- It supports the arguments you make in your assignments.
- It demonstrates the variety of sources you have used.
- It helps to prevent you losing marks, or failing, due to plagiarism.

When should I use a reference?

You should use a reference when you:

- Quote directly from another source.
- Summarise or rephrase another piece of work.
- Include a specific statistic or fact from a source.

How do I reference?

There are a number of different ways of referencing, and these often vary depending on what subject you are studying. The most important to thing is to be consistent. This means that you need to stick to the same system throughout your whole assignment. Here is a basic system of referencing that you can use, which consists of the following two parts:

A marker in your assignment: After you have used a reference in your assignment (you have read something and included it in your work as a quote, or re-written it your own words) you should mark this is in your text with a number, e.g. [1]. The next time you use a reference you should use the next number, e.g. [2].

Bibliography: This is just a list of the references you have used in your assignment. In the bibliography, you list your references by the numbers you have used, and include as much information as you have about the reference. The list below gives what should be included for different sources.

Websites – Author (if possible), title of the web page, website address, [date you accessed it, in square brackets].

E.g. Dan Snow, 'How did so many soldiers survive the trenches?', http://www.bbc.co.uk/guides/z3kgjxs#zg2dtfr [11 July 2014].

Books – Author, date published, title of book (in italics), pages where the information came from.

E.g. S. Dubner and S. Levitt, (2006) *Freakonomics*, 7-9.

Articles – Author, 'title of the article' (with quotation marks), *where the article comes from* (newspaper, journal etc.), date of the article.

E.g. Maev Kennedy, 'The lights to go out across the UK to mark First World War's centenary', *Guardian*, 10 July 2014.