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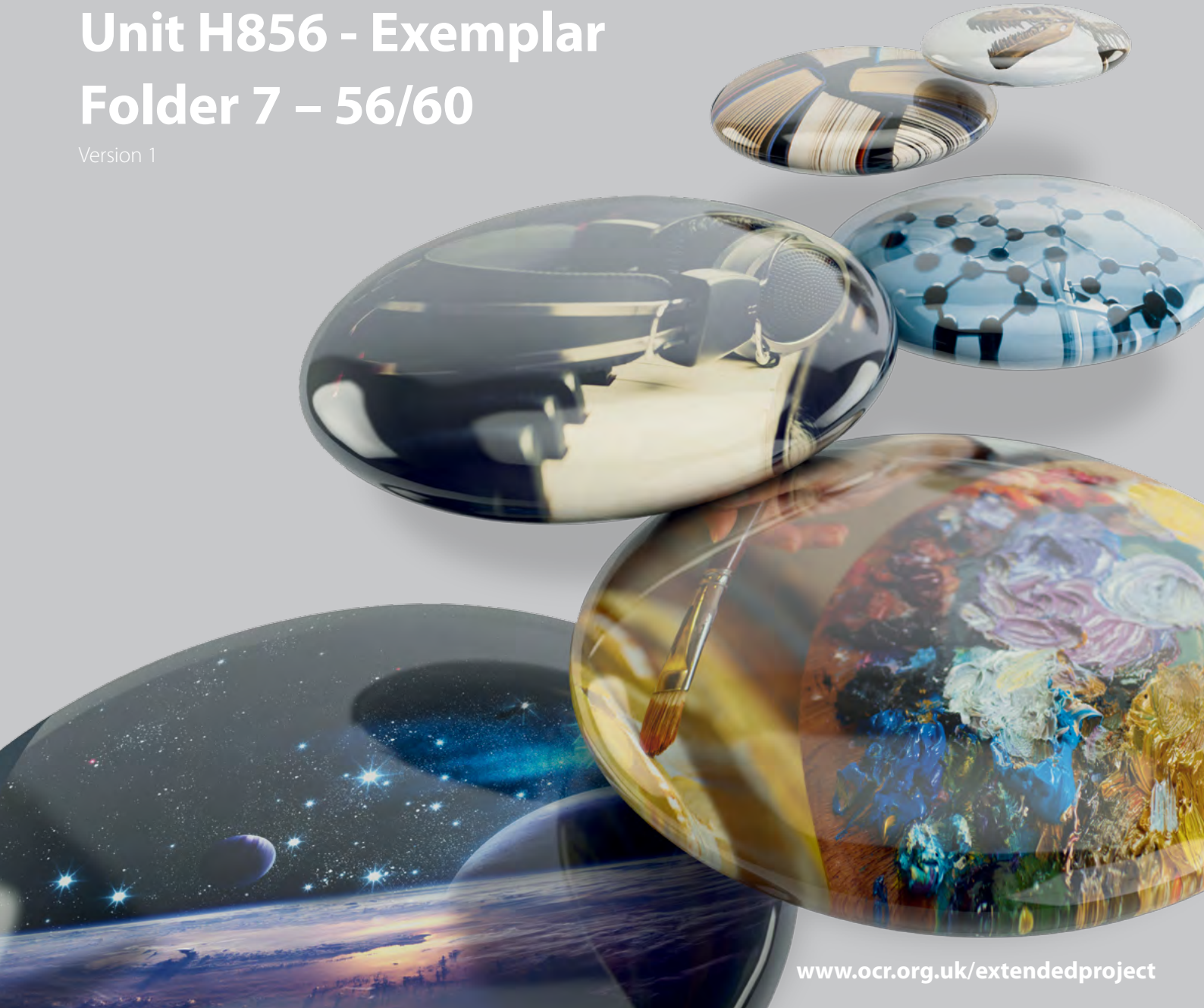
PROJECT
Candidate Exemplar Work

EXTENDED PROJECT

H856

Unit H856 - Exemplar Folder 7 – 56/60

Version 1



www.ocr.org.uk/extendedproject

Introduction

This is one of several live projects that have been marked within OCR centres. Each one, in its own way, provides insights into what makes for an excellent project. However, none of the projects is perfect and each of them provides useful pointers to common errors that moderators encounter. Therefore, both the strengths and weaknesses of each project will be discussed as an aid to teachers and students alike.

The Unit Recording Sheets [URS] used to record both marks and comments on each project have also been included and again some comments on best practice have been made. Teachers put enormous efforts into assessing their students' work fairly, but that effort is better evidenced in some of these projects than in others. Clear, focussed comments on the URS and signposting, within the portfolio can be particularly supportive of a student's efforts. Comments should support elements of the student's work that may not be immediately obvious to the moderator from reading it. This includes reference to the student's individual triumphs, particular difficulties they have encountered, their effectiveness in overcoming obstacles and the level of individual skills development the student has achieved. The watchwords here are know each student well and let the moderator know this is the case through what you write!

Commentary can be found after the portfolio on page 111.

HOW DOES ANTIBIOTIC RESISTANCE EMERGE AND HOW SIGNIFICANT IS THE THREAT OF ANTIBIOTIC RESISTANCE TO HUMANS?

By

Candidate Number:
Mentor:
Tutor: Word Count:

OCR
RECOGNISING ACHIEVEMENT

Extended Project (Level 3)

Unit Recording Sheet

Please read the instructions printed at the end of this form. One of these cover sheets, suitably completed, should be attached to the assessed work of each candidate.

Unit Code	H856	Year	2015
Centre Name		Centre Number	
Candidate Name		Candidate Number	

AO	Criteria			Teacher Comment	Mark
1	• Selected a suitable topic and produced a piece of work that reflects a design formulated with the assistance of their teacher/mentor • Taken an adequate degree of responsibility for their project, planning and managing the work through measures addressing its sequencing, its breakdown into intermediate tasks and monitoring its progress. In a group setting, responsibility will have been taken for closely defined tasks assigned by the group • Developed adequate organisational, IT, decision-making and problem-solving skills necessary to realise the project, responding to changing circumstances • Completed the project within the agreed time schedule [0 1 2 3 4]	• Proposed a suitable topic and produced a piece of work that reflects a design negotiated with their teacher/mentor • Taken substantial responsibility for their project, effectively planning and managing the work including sequencing, its breakdown into intermediate tasks and monitoring its progress. In a group setting, responsibility will have been taken for aspects of group work with active participation in group decision-making • Developed proficient organisational, IT, decision-making and problem-solving skills and used them effectively to realise the project, recognising and responding to changing circumstances • Completed the project within the agreed time schedule, meeting most intermediate goals [5 6 7 8]	• Proposed a suitable topic and produced a piece of work that reflects a design proposed to their teacher/mentor and with limited negotiation/support of their teacher/mentor • Taken full responsibility for their project, skillfully planning and managing every aspect of the work. In a group setting, responsibility will have been taken for directing and monitoring aspects of group work with some leadership of group decision-making • Developed proficient IT and sophisticated organisational, decision-making and problem-solving skills and used them creatively to realise the project, effectively managing changing circumstances • Completed the project within the agreed time schedule, meeting all, or virtually all, intermediate goals [9 10 11 12]	Helen took full responsibility for her project. She changed her topic to suit her future career plans which was a good decision. The diary is extensive and tracks progress efficiently. A Gantt chart was created online to aid planning. The PPR is extensive giving excellent information about the progress of the project, skill development and sources used. The project was completed and handed in on time.	12

URS908 Revised February 2009 H856/URS

Oxford Cambridge and RSA Examinations

2	• A limited range of sources has been used to obtain, select, collate and analyse information and data relevant to the project. Guidance on the choice and interpretation of sources has been given by the teacher/mentor • Some understanding of connections and linkages between different types of resource and the complexities inherent in their project has been developed • A limited range of appropriate technology and related technical skills have been used to aid the collection of information and data. E-learning has been used, where appropriate • Where relevant, some information and/or data has been obtained through working with others in the context of engagement in a business, social-community venture/enterprise or through involvement in a local, regional or international team Extended Project. The learner has participated in a limited way within the context [0 1 2 3 4]	• An appropriate range of sources has been used to obtain, select, collate and analyse information and data relevant to the project. Some guidance on the choice and interpretation of sources has been given by the teacher/mentor • An effective understanding of connections and linkages between different types of resource and the complexities inherent in their project has been developed • A range of appropriate technology and related technical skills have been used to aid the collection of information and data. E-learning has been used effectively to further the aims of the project, where appropriate • Where relevant, a range of appropriate information and/or data has been obtained through working with others in the context of engagement in a business, social-community venture/ enterprise or through involvement in a local, regional or international team Extended Project. The learner has been an active participant within the context [5 6 7 8]	• A wide range of sources has been used to obtain, select, collate and analyse information and data relevant to the project. Little or no guidance on the choice and interpretation of sources has been given by the teacher/mentor • A sophisticated and perceptive understanding of connections and linkages between different types of resource and the complexities inherent in their project has been developed • A wide range of appropriate technology and related technical skills have been used to aid the collection of information and data. E-learning has been used skilfully and critically to further the aims of the project, where appropriate • Where relevant, a wide range of appropriate information and/or data has been obtained working with others in the context of engagement in a business, social-community venture/enterprise or through involvement in a local, regional or international team Extended Project. The learner has offered leadership or direction within the context [9 10 11 12]	An extremely wide range of sources were used from both secondary and primary areas. There are a number of online articles, academic journals, and government websites used. In addition to this Helen managed to interview a nurse from Addenbrooke's Hospital and asked some key questions about her topic. There is extensive evidence of note taking and sophisticated cross-referencing.	12

3	• Some appropriate skills have been selected and used in relation to the context of the project in order to solve problems, take decisions and achieve the planned outcome. These skills may include problem-solving techniques, analytical techniques, PLTS, functional skills, presentational skills and technical skills of various kinds. There is some evidence of the critical, creative and flexible use of skills in the furtherance of the project's development and realisation • Some appropriate technologies, including relevant new technologies, have been used to assist the process of problem-solving, decision-making and achieving the planned outcome. There is some evidence of the critical, creative and flexible use of technology in the furtherance of the project's development and realisation [0 1 2 3 4 5 6 7 8]	• A range of appropriate skills have been selected and used effectively in relation to the context of the project in order to solve problems, take decisions and achieve the planned outcome. These skills may include problem-solving techniques, analytical techniques, PLTS, functional skills, presentational skills and technical skills of various kinds. There is evidence of the critical, creative and flexible use of skills in the furtherance of the project's development and realisation • A range of appropriate technologies, including relevant new technologies, have been used effectively to assist the process of problem-solving, decision-making and achieving the planned outcome. There is evidence of the critical, creative and flexible use of technology in the furtherance of the project's development and realisation [9 10 11 12 13 14 15 16]	• A wide range of appropriate skills have been selected and used in a sophisticated manner in relation to the context of the project in order to solve problems, take decisions and achieve the planned outcome. These skills may include problem-solving techniques, analytical techniques, PLTS, functional skills, presentational skills and technical skills of various kinds. There is clear evidence throughout of the critical, creative and flexible use of skills in the furtherance of the project's development and realisation • A range of appropriate technologies, including relevant new technologies, have been used in a sophisticated manner to assist the process of problem-solving, decision-making and achieving the planned outcome. There is clear evidence throughout of the critical, creative and flexible use of technology in the furtherance of the project's development and realisation [17 18 19 20 21 22 23 24]	A wide range of appropriate skills have been developed in this project. Helen does currently study biology but microbiology isn't in the syllabus. There is an element of cross over from a foundational level but with plenty of challenge and development. There is significant challenge in the types of sources used and gathered. Helen notes that she developed skills in IT for organisation and formatting. Also dissertation writing skills and project management skills.	22

4	• Although limited in scope, a critical, reflective and independent approach to learning has been developed. A limited attempt has been made to present an accurate review of their work covering both development aspects and the eventual outcome of the project. This may relate to the learner's participation and contribution to a group project in a social-community venture/enterprise and/or local, regional or international team project • A limited usage of communication skills and media to present a broadly effective review of the development and outcome of the project [0 1 2 3 4]	• A critical, reflective and independent approach to learning has been developed. They present a thorough and accurate review of their work covering both development aspects and the eventual outcome of the project. This may relate to the learner's participation and contribution to a group project in a social-community venture/enterprise and/or local, regional or international team project • A broad usage of communication skills and media to present an effective and comprehensive review of the development and outcome of the project • The presentation has broadly met the needs of its intended specialist and/or non-specialist audience* • They have appropriately addressed the issue of personal, academic and career development beyond the confines, but informed by, their participation in the project, including their development of transferable skills [5 6 7 8]	• An incisive critical, reflective and independent approach to learning has been developed. They present a perceptive, thorough and accurate review of their work covering both development aspects and the eventual outcome of the project. This may relate to the learner's participation and contribution to a group project in a social-community venture/enterprise and/or local, regional or international team project • A sophisticated usage of communication skills and media to present a perceptive, effective and comprehensive review of the development and outcome of the project • The presentation has met all the needs of its intended specialist and/or non-specialist audience. The audience was engaged and entertained* • They have addressed clearly and realistically the issue of personal, academic and career development beyond the confines, but informed by, their participation in the project, including their development of transferable skills. They clearly understand what has been achieved and where it can lead them [9 10 11 12]	The final evaluation is critically reflective and Helen discussed each of the areas of the project from planning through to research then completion. She comments on what would be done differently if again to improve on the dissertation. The diary has some elements of critical reflection that help the project develop successfully. The final presentation was delivered clearly and confidently. There was lots of text on the slides which was distracting for the audience at times. One of the final pieces of paperwork for the presentation is ripped, which is odd given the attention to detail applied elsewhere inthe project.	10
				Total /60	56

Guidance on Completion of this Form

1 One sheet should be used for each candidate.

2 Please ensure that the appropriate boxes at the top of the form are completed.

3 Circle the mark awarded for each strand of the marking criteria in the appropriate box.

4 Add the marks for the strands together to give a total out of 60. Enter this total in the relevant box.

CONTENTS

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DISSERTATION

HOW DOES ANTIBIOTICS RESISTANCE EMERGE AND HOW SIGNIFICANT IS THE THREAT OF ANTIBIOTIC RESISTANCE TO HUMANS?

INTRODUCTION

In 1928 a Scottish scientist called Alexander Flemming discovered a petri dish filled with a colony of mould and within it was a halo within which the Staphylococcus bacteria present on the rest of the dish were absent – he had discovered the 'magic bullet' of modern medicine: penicillin, an antibiotic. [1] The revolution of antibiotics has saved millions of lives, trivialising once fatal diseases and making chemotherapy and organ transplants possible. However, penicillin resistant strains of staphylococcus aureus closely followed in the footsteps of the new wonder drug as the growing popularity of penicillin put selective pressures on S.aureus to evolve resistance. In one English hospital the percentage of penicillin resistant S.aureus rose from 14% in 1946 to 59% two years later.[1] The extraordinary genetic capacities of bacteria have benefitted from the misuse of antibiotics by humans and have managed to exploit every avenue of resistance genes and every method of horizontal gene transmission to evolve complex mechanisms of resistance to every antibiotic introduced clinically, agriculturally or otherwise, with severe consequence for modern medicine. [2] Antibiotic resistant bacteria are now responsible for 23,000 deaths, 2 million illnesses and $2 billion in extra medicals costs each year in the US alone. [12] Leading academics, governments and the media are labelling the threat of antibiotic resistance as a public health emergency, as new forms of resistance emerge with only a perilously thin pipeline of new drugs to combat it – a mere two new classes of antibiotics have been brought to market in the last two decades. [14] Antibiotic resistance was voted the problem to solve for the £10 million Longitudinal Prize of 2014, showing a greater public awareness of this threat. [9] Meanwhile the New Scientist magazine names antibiotic resistance as an 'apocalyptic threat' of unknown proportions. With all the hype and growing public awareness surrounding this topic, this literature review aims to evaluate how significant the threat of antibiotic resistance is to society by investigating what causes and effects the evolution or resistant bacteria and what can be done to overcome it.

SECTION ONE – EMERGENCE AND SPREAD OF ANTIBIOTIC RESISTANCE

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Antibiotics are substances produced by micro-organisms which in low concentrations kill or inhibit the growth of other micro-organisms; antimicrobials are wholly synthetic molecules which also kill or inhibit the growth of other micro-organisms. Antibiotics exploit the difference between prokaryotic and eukaryotic cells as the drug effects targets not in eukaryotic (animal/human) cells such as the cell wall or protein synthesis, meaning the toxic effects are not felt by the patient.[6] Antibiotics like polymixins can affect the permeability of the bacterial cell membrane whilst other antibiotics like penicillin and cephalosporin prevent the synthesis of nucleopeptide in the cell wall – this effects gram-positive bacteria more than gram-negative bacteria as they have a thinner, simpler cell wall. Antibiotic resistance is the ability of a micro-organism to withstand the effects of an antibiotic, it evolves naturally via natural selection through random mutations but is increasingly engineered as humans apply selective pressure on strains of bacteria.[3] The consequences of this hereditary resistance are huge for human society: it can be fatal, reduce effectiveness of drugs against infectious diseases, increase health care costs, and even impacting upon trade and economics in developing countries. [16]

Antibiotic resistance originally arises from spontaneous random mutations in the sequence of bases in the DNA of a microbe; if these mutations are major they will be fatal for the organism, but if they are minor they can be beneficial.[4] The rate of reproduction of bacteria in optimum conditions is rapid – one single S. aureus cell can multiply into a colony of 1 million after 20 generations, or about 10 hours.[17] This means that with a genome size of 2.8×10^6 and a mutation rate of one mutation per 10^{10} base pairs, it would only take 30 hours for a single S.aureus cell to grow into a population in which every single base pair in the genome will have mutated 30 times. Therefore any individual mutation that could theoretically occur in the bacterial genome will have occurred somewhere in that population in just 30 hours. [17] This means bacteria can evolve resistance very rapidly, especially when put under strong selection pressure. The types of mutation that bacteria can acquire to overcome antibiotics is varied. Some may lose the target for the antibiotic, such as a peptidoglycan cell wall, so that they are resistant to the action of cell wall inhibitors like penicillin and cephalosporin. They may make the a target inaccessible, for example by making the outer membrane of gram negative bacteria acting as a permeability barrier so drugs cannot reach target; other mechanisms include chemically destroying the drug or having an efflux pump to pump drugs out of the cell wall before damage can be done – this mechanism can give a microbe multidrug resistance as it can pump out any substance – this means a microbe can evolve to be resistant to multiple drugs in very few mutations.[5] The fact that bacteria are capable of gaining complex mutations which effectively prevent antibiotics from working so

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incredibly quickly means that in any population of bacteria some, albeit very few, will always be resistant to the antibiotic, as one review stated: 'if resistance is biochemically possible, it will occur,'[2] therefore meaning that the threat of antibiotic resistance is always lurking in the shadows.

The natural environment acts as a vast reservoir for resistance genes (R genes) as many source materials agree. The resistance genes are found in the environment because the mechanisms, genes and pathways of antibiotic production and resistance have helped microorganisms compete for niches in their environment for millennia – ancient bacteria retrieved from permafrost were found to be resistant to modern day antibiotics, showing the genes for resistance are not new. This reservoir of naturally occurring genes is referred to as the environmental antibiotic resistome.[8] Although evidence is limited, an increasing amount of studies show that R genes found in the environment can be mobilized into pathogenic bacteria and expressed as resistance phenotypes seen in patients. For instance, the most international in distribution of resistance genes – an enzyme called B–lactamase which acts as a catalyst – are ancient and have been found in remote and isolated environments. The new extended-spectrum B–lactamase (CTX-M) was acquired from environmental Kluyvera strains and appeared in clinics in the 1990s.[2][11] Another study screening morphologically distinct spore-forming actinomycetes for resistance to 21 different antibiotics found that a significant number of strains were resistant to on average 7 or 8 antibiotics and novel resistance mechanisms were also found, showing that organisms in the environment can be naturally drug resistant.[2] This is also strong evidence that the pool of genes in the environment have the potential to be captured and expressed as resistance phenotypes. However, more studies are needed to establish how strong the environmental-clinic connection is. Bacteria can therefore acquire R genes by mutation or have them naturally so the tools for an antibiotic resistant strain to emerge are already in place by no influence from humans. How do the genes for resistance then spread from the bacteria with 'acquired' or 'natural' resistance to an entire population?

A bacteria can pass on its 'acquired' resistance or 'natural' resistance by clonal replication (the cell divides into two genetically identical cells) or by horizontal gene transfer, in which genetic information is passed between microbes, allowing resistance genes to spread within environmental or commensal microorganisms and pathogens, creating a reservoir of resistance genes. Horizontal gene transfer is the primary mechanism by which bacteria acquire antibiotic resistance.[1][2] Many R genes are carried on plasmids, transposons and integrons (all sections of DNA) these can act as vectors to transfer the gene between members of the same species of bacteria, as well as to bacteria of other genera or species.[7][4]There are

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three main mechanisms of horizontal gene transfer: conjugation, transformation and transduction. Conjugation involves the transfer of DNA via sexual pilus, this process needs cell-to-cell contact. Transformation involves uptake of short fragments of DNA from its surroundings and builds some of it into its own DNA when in the right state. In transduction bacterial viruses called bacteriophages transfer DNA between hosts, if the bacteria survives it uses the imported DNA. [4][7] In all cases the newly acquired DNA becomes hereditary and can be passed on to other organisms. Several sources comment on the fact that the highly mobile nature of plasmids and the ease of transfer of genes by horizontal gene transfer are 'next to impossible to control' [2] emphasising that it is this unique ability of bacteria that has allowed resistance genes to spread to become a global phenomenon.

The fact that genes can easily transfer between bacteria does not lead to an R gene dominating a population unless a selection pressure is applied. If no antibiotics or selection pressure were applied, the drug-resistant phenotype would have no selective advantage over other bacterial phenotype so would not spread to the whole colony or population.[16] Indeed, it is a slow random evolutionary process catalysed and expanded by human influence. When a bacterial population is exposed to antibiotics, only the very few or even single organism that carries a gene for a mechanism of resistance survives, the rest are killed off by the antibiotic. The surviving bacteria with resistance genes then pass on these genes to other organisms by horizontal gene transfer or clonal replication.[12] Selection pressure for antibiotic resistance most often occurs in non-pathogenic microorganisms as they comprise the majority of microorganisms. [11] When the selective pressure of antibiotics is removed, it would be expected that the frequency of the resistance genes decreases, however studies show that resistance genes do not disappear from a population after the antibiotic is no longer used. This could be because many of the genes retain their original essential cell functions to survive in the environment so losing them would be fatal. This means that the threat of antibiotic resistance cannot be removed even without use of antibiotics. In addition, the fact that whenever a selection pressure (antibiotic) is applied means the population will automatically evolve to overcome this selection pressure, this mean that if antibiotics are used, there will inevitably be an increase in frequency of R genes amongst the population.

The overuse and misuse of antibiotics is responsible for the escalating the spread of resistance genes. Even with the correct use of antibiotics, resistance within the population would occur because a selection pressure is being applied no matter how weak. Inaccurate and unnecessary prescriptions are a major factor in

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selecting resistance genes. Sources claim that in the region of 50% to 70% of antibiotics are unnecessary and are used to treat virus' which are unaffected by antibiotics. Furthermore there are examples of inaccurate prescriptions, for instance antibiotics are prescribed 70% of the time for bronchitis even though medical guidelines state not to. [1] There are also inaccuracies because consultants are forced to prescribe treatment based on an initial clinical diagnosis, rather than accurate lab results. The over use of drugs, particularly last line drugs like vancomycin, used for staphylococcus, (one third of vancomycin prescriptions are estimated to be inaccurate) decrease their long term efficiency as exposure to these drugs increases selection pressure and hence increases levels of resistance to that particular drug and others. It also means it is harder to treat patients and more toxic drugs must be used posing significant threat to their health. Genes can also be transferred globally by international trade and travel; In Finland, for example, a widespread outbreak of Campylobacter was recently linked to imported chicken. Aside from travel and trade, antibiotic resistance can move across borders via animal vectors (wild animals, rodents, birds, insects) and by the movement of water in rivers and oceans. There is also the potential for resistant bacteria to move long distances in dust clouds

However even more significant in spreading R genes than clinical use is the agricultural use of antibiotics in meat production to increase growth rates and hence profit margins for farmers; globally 50% of antibiotic production is used in farming animals, whilst in the US it is a staggering 80%. [1] As mentioned earlier, resistance genes are naturally present in nature, as are antibiotics, however the limited evidence available points out the fact that the concentrations of antibiotic compounds in natural environments are very low, so another selective pressure or source of R genes must be present to account for the large numbers of resistant bacteria found in waterways and the environment. The amounts of xenobiotic substances dumped into the biosphere are inestimable, one horrific example of dumping in Hyderbad, India, was 50 kg of toxic ciprofloxacin dumped into rivers every day. As most are not biodegradable, genomic studies of wastewater treatment plants and waterways have shown to be rich reservoirs of r genes. Dumping antibiotics into rivers leads to contamination with R genes of water systems and drinking water, leading to infections in humans; antibiotics used in farming end up in meat and can infect people, or on the soil as manure affecting wildlife. [2] The treatment of sewage also harbours 'hazardous' numbers of resistant bacteria, when comparing water samples from downstream to a water treatment plant, a study found a much higher level of resistance to new and old antibiotics and of genes found in clinical settings compared to purer water upstream. These genes are coming from faeces contaminated with resistant bacteria in peoples gut, from animals in the food chain and these are forms of

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biological pollution. It is an extreme cause for concern to find resistant strains of E.coli and K. pneumonia (predicted to be the next superbug overtaking MRSA) in the waterways. [16] In the US recently released figures show half of all samples of food poisoning bacterium salmonella, taken from retail poultry meat, are resistant to at least three antibiotics. This is due to contamination when the meat is processed, and shows that the use of antibiotics in farming, 'incubates' a reservoir of R genes, which can infect in humans. Furthermore, in samples of farm compost in China from pigs given antibiotics, it was found that the levels of some antibiotic genes were 'enriched' 28,000-fold compared to those from soil samples not taken from farms. Even more concerning was that the samples also contained enzymes that help antibiotic resistance genes move between bacteria. They also contained the antibiotics themselves, revealing that selection pressure for the resistant bacteria continues outside of the farm and pig. The source continued to say that 'some genes would be expected to migrate to human pathogens' this is particularly concerning and poses massive risk to humans. This would imply that resistant populations in the environment, of which there are many, do have a relationship with those found in hospitals and can spread to hospitals, showing that there is potential for antibiotic resistance to be an enormous threat as the genes are circulating and increasing in frequency in the environment as well as clinical settings.

There are a complex combination of factors contributing to the frequency of gene transmission in an environment. Knowing and understanding these factors could help us reduce the threat of antibiotic resistance. Many bacteria form dense communities called biofilms which are more difficult to eradicate on catheters for example. As professor of microbiology and immunology Roberto Kolter explains, sticking together helps bacteria shield each other from the effects of antibiotics so even when susceptible when isolated in the lab, the bacteria are in the right physiological state, despite no genetic change.[1] There are several other means that facilitate DNA exchange by horizontal gene transfer, for example host and clone specificity, virulence, duration of selection pressure and interactions with other commensal flora (other non-harmful microbes present). These factors will play an important role in enhancing gene frequency of gene exchange in environments such as farms, hospitals, and sewage systems, which all provide ideal incubation conditions for r gene acquisition. [2] There may also be economical factors in spreading resistance genes, as poorer countries often do not require prescriptions for drugs, so people can self-medicate what are often fake drugs. [3] The most crucial factor in increasing the frequency of resistance genes is the strength of selection pressure, in this case how strong the drug is. From experiments evolving 88 isogenic E.coli populations against 22 antibiotics from 7 drug classes for 3 weeks, the populations evolved against stronger

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antibiotics acquired higher levels of cross-resistance against several antibiotics, where as those evolved against milder antibiotics acquired relatively weak resistance. It was also concluded that strongly selected populations has a greater and more diverse range of pathway specific mutations and that selection strength contributes to evolution of resistance, cross-resistance and susceptibility. This means we are trapped in a cycle, as antibiotic resistance is increasing, we are using stronger doses of last line drugs, meaning we are encouraging the transfer of a wider range of mutations further accelerating the increase of antibiotic resistance.

SECTION TWO IS THE RATE OF ANTIBIOTIC RESISTANCE INCREASING?

Across the globe, the rate of antibiotic resistance is increasing at an alarmingly rate. In a World Health Organisation report published in 2014, it was reported that there were 'very high' rates of resistance in bacteria that cause common health-care associated and community-acquired infections such as urinary tract infections and pneumonia in all regions of the globe. There were significantly high proportions of resistance to 3rd generation cephalosporin antibiotics reported for E. coli and K. pneumonia, meaning the treatment of severe infections caused by these bacteria requires the treatment of carbapenems – a last resort drug to treat severe community and hospital acquired infections. These drugs are more expensive, less widely available and, in agreement with scientific journals, higher doses of these antibiotics accelerate the development of resistance. [15][10] Of great concern is the fact that K. pneumonia are also resistant to carbapenems, with proportions of resistance up to 54% reported. [15] The problem of MRSA is also increasing, with most staph infections in humans caused by methicillin-resistant *Staphylococcus aureus*, according to the U.S. Centers for Disease Control (CDC), in 2004, 63% of all reported staph infections in the United States were caused by MRSA (CDC, 2007). That figure represents a remarkable 300% increase in just 10 years' time. (In 1995, about 22% of all reported staph infections were MRSA, compared with only 2% in 1974.) The irony is that methicillin, a chemically modified version of penicillin, was developed in the 1950s as an alternative treatment for the growing proportion of staph infections already resistant to penicillin. At that time, about 60% of all staph infections were resistant to penicillin.[17] The high rates of MRSA illustrated in the World Health Organisations Report (over 50% in some regions) mean second-line drugs must be used in many countries, further accelerating the rate of antibiotic resistance emerging. [15] MRSA was also responsible for one of the highest death rates from antibiotic infection - 11, 000 people and 80,000 illnesses per year. [12] The occurrence of the infection C. difficile, which causes 14,000 deaths per year [13] and is the most common cause of antibiotic resistance diarrhoea, deaths

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related to it increased by 400% between 2000 and 2007, in part because of a stronger resistant strain emerging. Situations are increasingly arising where bacteria that are resistant to most, or even all, available antibacterial drugs are causing serious infections that were readily treatable until recently. This has consequences for modern medicine which relies on the availability of effective antibiotics. Examples of these consequences include common community-acquired infections such as pneumonia, which used to be readily treatable after the introduction of penicillin, not responding to available or recommended drugs in many settings, putting the lives of patients at risk especially in intensive care facilities, or may need more expensive treatment, imposing additional costs for health systems. Patients receiving cancer treatment, organ transplants and other advanced therapies are particularly vulnerable to infection. When treatment of an infection fails in such patients, the infection is likely to become life-threatening and may be fatal. Antibacterial drugs used to prevent postoperative surgical site infections have become less effective or ineffective. The reliable information that is available, although limited, shows that antibiotic resistance is increasing in occurrence and strength, and putting an increasing amount of lives at risk, as well as having a greater financial burden on health systems. [15] This demonstrates that antibiotic resistance is a huge threat to society and is becoming increasingly larger.

There are major gaps in data on the extent of antibiotic resistance and on the types and number of infections caused by bacteria that have become resistant to antibacterial drugs, making it impossible to estimate precisely the global prevalence and impact of the problem. Nevertheless, it is clear that together, the burden of morbidity and mortality resulting from antibiotic resistance in many infections and settings has serious consequences for individuals and society in terms of clinical outcomes and added costs.[15][12] Levels of surveillance in less economically developed countries is far poorer, even though these areas have higher concerns for antibiotic resistance, overall the percentage of member countries of the World Health Organisation returning data regarding antibiotic resistance was only 66%. The data given for antibiotic resistance is gathered from a number of sources including scientific journals, and various tracking networks, usually as collaborations between governments, healthy systems and local health departments, by determining the antibacterial susceptibility test. [12] The data available should be interpreted with caution; there are no agreed global standards for antibiotic resistance surveillance, meaning there are discrepancies in performance and interpretation depending on which laboratory the samples were investigated at – the sample sizes and other control variables will differ. Furthermore, samples tend to be skewed towards hospitalized critically ill patients whose condition did not respond to first-line treatment so resistance will be overestimated although some samples come from healthy carriers without

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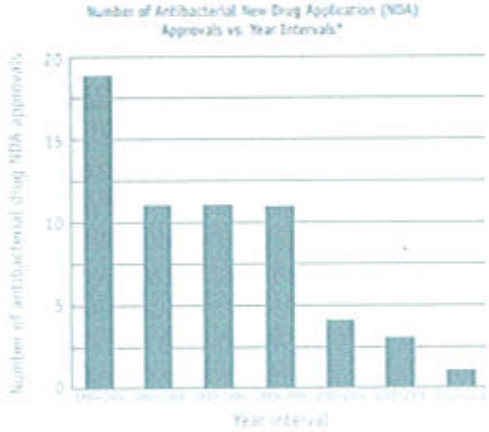
symptoms, further complicating the interpretation of results in terms of public health and comparisons of resistance populations. The data can however be used as a fairly accurate indicator of levels of resistance. With little accurate data, it is impossible to monitor how large the threat of antibiotic resistance is. [15]

Section 3 – SOLUTIONS TO OVERCOME ANTIBIOTIC RESISTANCE

The strength of trillions of microorganisms, combined with the power of evolution driven by the selecting pressure of antibiotics means that the struggle against antibiotic resistance will never be fully overcome by drugs, because bacteria will always evolve to survive every modification of antibiotics. Erythromycin illustrates this; it was introduced in the 1950s as an alternative to penicillin for the treatment of *S. aureus* in Boston City Hospital; after less than a year it was completely withdrawn because 70% of all the *S. aureus* isolates were found to have become erythromycin resistant. The same was observed with chlortetracycline and chloramphenicol and, subsequently, with other antibiotics. It is clear that antibiotic resistance seems inevitable [2]

Many sources agree that there is a perilously thin pipeline of new drugs being developed and approved. This is because it is intensely difficult, time consuming and expensive to screen compounds, have trials and tests – about $1-2 billion to bring one new drug to market – and so there is very little profit for pharmaceutical companies to research new drugs. [9] As this graph [12] shows, the number of antibiotics developed and approved has steadily decreased in the last three decades, leaving fewer options to treat resistant bacteria.

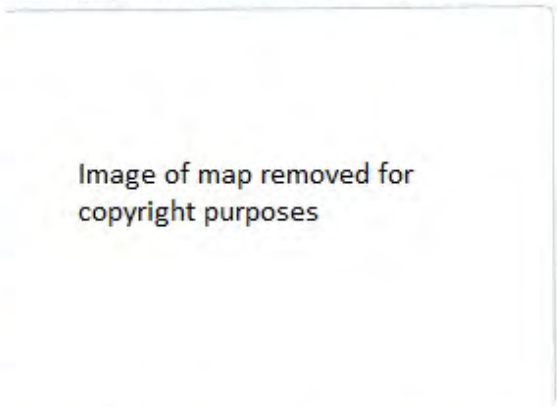
There is however a growing area of research into inhibitors of bacterial virulence which could be used to stop disease process by 'disarming' bacteria of their 'molecular weapons' – toxins, enzymes - instead of trying to kill the bacteria with antibiotics. This has the advantage that selection for resistance (survival in the host) might not occur because the growth of the infecting organism would not be impaired. Most virulence factors are proteins (enzymes for example); disulphide bonds form cross links between the polypeptide chain allowing them to withstand temperatures and acidity. In E.Coli, two key proteins DsbA and DsbB are essential for the correct folding and function of protein virulence factors, including catalysing disulphide bond formation in gram-negative bacteria which are more resistant to antibiotics due to a thicker cell wall. If the genes for DsbA and DsbB are removed, they have reduced fitness and



weakened virulence in infection models, so a possible new drug could interfere with these proteins. This would mean the bacteria is weakened so the host's immune system could deal with it; it also means no selection pressure of antibiotics has to be used so the frequency of resistant genes in the population should not increase. [8] Furthermore, innovative approaches such as genome wide mutagenesis techniques and rapid bacterial genome sequencing indicate that in spite of suggestions to the contrary, many potential drug targets remain to be exploited in antibiotic discovery.[2] If new drug targets are found, then many new classes of drugs can be developed, and the threat of antibiotic resistance can be reduced greatly.

Another approach to the situation is to use the tools we already have more carefully to preserve the use of antibiotics. At the moment, the frequency with which doctors prescribe antibiotics varies greatly, as shown in this chart [12] between the states of the US. The reasons for this variation are being studied and might suggest areas where improvements in antibiotic prescribing would be most helpful. In addition, there is development of reliable rapid genomic based diagnostics – these identify the microbe causing the infection and its level of resistance to drugs such as penicillin, cephalosporin and carbapenems within hours, rather than the current standard of two days. This would mean doctors could give better treatment tailored to the individual patient in a shorter time frame. [2] Polymicrobial diseases may not be dealt with as easily with rapid diagnostics however, because they have more complex combination of microbes effecting them. Quantitative detection of expressed virulence factors or strain-specific genes could present a solution, so long as the results are easy to translate into treatment strategies. [11] Despite speed of diagnosis being of great importance in detecting resistance, accuracy is of greater importance as the health of patients is at risk.

Antibiotic Prescriptions per 1000 Persons of All Ages According to State, 2010



More thorough and integrated resistance surveillance would also lower levels of antibiotic resistance. Ideally, surveillance is taken at local level and then collected and compared at the national level. In Northern Europe, proactive infection control and vigilant surveillance kept MRSA rates low at less than five percent of all samples in Denmark and Netherlands, whilst the percentage of methicillin

resistance was 50% in the US. Even in the US, increased hospital vigilance between 2005 and 2011, saw national MRSA rates fall by nearly a third and rates of hospital-acquired infections dropping by more than half; congress is now considering an act to strengthen disease surveillance at national level.[1] Furthermore, new measures of susceptibility and standards for conducting these tests need to be improved, so that surveillance data gathered from across the world can be compared accurately to create an overall view of patterns in antibiotic resistance.

A more radical antibiotic future is being researched, in which normal bacteria are used to counter relatively minor infections by exploiting microbial interactions to promote human health. This includes probiotic treatments such as fecal transplants, occasionally proven effective against recurrent *C. difficile* infections, that use live microbes in their infant stages evidence is beginning to suggest that humans' future with bacteria will depend, at least in part, on careful coexistence. [2] Antibiotic resistance is a major public threat, but governments and health organisations are still not fully aware of the scale of the problem due to lack of surveillance, whilst the general public are oblivious to the consequences it could have unless involved in education or employment in the scientific field 9as my primary research concluded) . Greater public awareness would mean people less willing to have antibiotic prescriptions, and more willing to follow hygiene regimes in hospitals which would lower the rate of resistance genes spreading.

There are also eco-sociological factors playing critical roles in the development and spread of antibiotic resistance. The non-regulated use of antibiotics is very concerning, and although it mainly occurs in developing countries, some shops in New York neighbourhoods carry antibiotic drugs without prescription. As for economics, there is a positive correlation between wealth and willingness and ability to seek health care. Changing behaviour can have a dramatic impact on the spread of antibiotic resistant pathogens; hand hygiene in particular has been shown to decrease the spread of diarrhoea and respiratory illnesses and limit spread of pathogens in multiple settings. [11]

The spread of antibiotic resistance in farming and veterinary practises should also not be neglected. One study found that farmers are host to more resistant bacteria than other members of the population, and another showed that multidrug resistant E.coli can spread from dogs to human hospital patients with no known direct connection between them. Despite the lack of evidence confirming that resistant strains can pass from humans to animals, it is clear that regulating and monitoring the amounts of antibiotics administered and prescribed would reduce the amount of resistance genes in the environment. As

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would treating all effluent from hospitals and farms before it is released to wastewater facilities.[11]

CONCLUSION

Fundamentally, antibiotic resistance is an inevitable outcome of the evolutionary principle that organisms will mutate to escape fatal selective pressure. As long as we use antibiotic agents designed to kill bacteria, antibiotic resistance will continue to emerge. This means that the threat of antibiotic resistance will always be present. Presently, the threat of antibiotic resistance is increasing, with a growing number of species of bacteria acquiring greater levels of resistance. This has massive implications for human society as the foundation on which modern medicine stand on are at risk of no longer being effective, putting the health of millions of people at risk, this in turn has economic and social consequences as people would no longer be able to work and healthcare would become more expensive as last-resort drugs are required more often. The factors that influence the development and spread of resistance are complex and interlinked: horizontal gene transfer and clonal replication allow R genes to spread through a population, the mis-use of antibiotics in agriculture and the incorrect disposal of them, combined with inaccurate prescriptions create a strong selective pressure for R genes to evolve in multiple strains of bacteria. The extent of this spread of R genes is not fully understood due to a lack of accurate and reliable data, especially from developing countries which are resistance hotspots. Data must be interpreted with caution because methodologies to measure susceptibility to antibiotics differ across the world; a significant amount of research needs to be carried out to collect data from all countries in order to discover patterns in resistance and predict future ones.

Overall it is clear that the threat of antibiotic resistant will never leave, however with new diagnostic techniques, more integrated surveillance and ongoing research into new alternatives to antibiotics, such as removal of virulence factors and co-existing with bacteria, the threat of antibiotic resistance is probably not described as an 'apocalyptic threat'. All my research suggests that antibiotic resistance has the potential to be an enormous threat, if the use of antibiotics was out of control. However, as the awareness of decision makers and the public grows, there is increasing optimism that we are not at all likely to have a 'post antibiotic era' and hence the threat of antibiotic resistance remains a threat to society, not a reality. It is a very important and highly significant threat though, but as long as the use of antibiotics is monitored and regulated, and investment is put into new research it is a threat we can keep at bay.

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PPR

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OCR

Project and Extended Project – Verification of topic and Title

Level 3 **Line of learning** (when taken as part of a Diploma) **Not Applicable**

Centre Name **Centre Number**

Learner name **Learner Number**

The Project title chosen must allow the learner:

- to be fairly assessed at the standard applicable to the Project level (level 1, 2 or 3).
- the opportunity to meet comparable demands to those made on other learners working at the same level
- to meet all of the Learning Outcomes and Assessment Objectives of the Project.

Project title:	How significant is the threat of Antibiotic Resistance to humans?
Project Aim:	To investigate and evaluate how serious the threat of antibiotic resistance is to society. To learn how antibiotic resistance arises and whether this is due to natural mutations or because of human actions. Also to include whether the rate of resistance is increasing across populations of bacteria, and the consequences of this on the health of humans. Also to include research in solutions to overcoming antibiotic resistance, especially how biological research is helping, as I will be studying biology at university, in order to evaluate whether this threat will grow in the future or whether the media hype is exaggerated.
Project Outcome:	A 5000 word dissertation including source material from science journals, reports and articles. I will also carry out primary research. My dissertation will evaluate how serious and how widespread antibiotic resistance is and what solutions are being researched to solve it. In particular for me, after undertaking this project I would like a better understanding of how biological research can reduce the threat of antibiotic resistance.

Project - Verification of Topic and Title 08.01

Project related to the Diploma

The Project title, including its aim and outcome, must be reviewed until Yes can be ticked for each question in the checklist below.

Stand-alone Project

The Project title, including its aim and outcome, must be reviewed until Yes can be ticked for questions 3 to 6 in the checklist below.

Verification of Title Checklist	Yes	No	Comments
1. Is the learner completing the OCR Project/Extended Project as part of the Diploma?		No	If the answer is NO, you are not completing the project as part of the diploma, please move to question 3
2. If the Project is taken as part of the Diploma, is the Project relevant to Principal Learning in either one or both of the following stated ways: - the Project complements and develops the themes and topics for learners' Principal Learning set out in the relevant line of learning criteria? OR - the Project supports learner progression			If the answer is NO you must review the title to ensure that it is related to the relevant Principal Learning in one of these two ways.
3. Is the title a question, a task or a brief?	Yes		If the answer is No you must review the title to ensure that the title is one of these three options.
4. Is there an aim and outcome of the project?	Yes		If the answer is No you must ensure that the title is accompanied by a clear aim and outcome.
5. If this a completely new area of study/activity for the learner, does it allow development appropriate to the level?	Yes		If the answer is No you must amend the title to ensure that it does.
6. If this is an extension of an area of experience/ study or part of an existing course, does it allow the learner to extend their skills beyond those already developed?	Yes		If the answer is No you must amend the title to ensure that it does.

Project - Verification of Topic and Title 08.01

RATIONALE

My project is to compile a literature review investigating how large the threat of antibiotic resistance is to humans. It will include how antibiotic resistance appeared, and assess whether it is as widespread and serious as the media and government reports claim. I have chosen it because I am interested in biology and during my as level course in biology I became interested in how organisms evolve, so it will be interesting to learn how resistance evolved in bacteria. Furthermore, biological research will be vital in creating solutions to overcome antibiotic resistance and this will be of great interest to me as to how I could apply a degree in biology when I am older. I have very few specialist skills in this area of knowledge, but look forward to developing my knowledge on this topic area.

To write my literature review I will use a range of sources, including websites, science journals, research papers and government reports, as well as books and online lectures for secondary sources of information. For primary research I will interview the head of department of biology and conduct a survey into how people feel about antibiotic resistance, this will reflect how media has effected people's perception of this threat. I have not yet decided on format, but it will be either a report or literature review. The ultimate purpose of this document is to investigate how widespread and how severe the threat of antibiotic resistance is to society. Skills I will develop include writing surveys, interviews, interpreting sources and analysing them critically.

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OCR

Project Progression Record

Level 3 **Line of learning** (when taken as part of a Diploma) **N/A**

Centre Name **Centre Number**

Learner name **Learner Number**

The topic chosen must allow the learner

- to be fairly assessed at the standard applicable to the Project level (level 1, 2 or 3).
- the opportunity to meet comparable demands to those made on other learners working at the same level
- to meet all of the Learning Outcomes and Assessment Objectives of the Project.

Activity	Date	Detail	Supervisor's initials	Comments
1. The date you started your project	15th January 2014	Attended introductory session on the Extended Project and what types of project can be done. Also had introductory sessions which were very helpful in learning new skills like note taking, referencing and carrying out primary research which I will use in my project.		Had a discussion with mentor about what sort of project I would like to do.

OCR Project Progression Record 06.01

Activity	Date	Detail	Supervisor's initials	Comments
2. First thoughts about topic and working title	25th January 2014 AO ✓	Initially my idea was to research, design and make a small collection of garments of clothing, inspired by the 1960s decade. However later in March I changed my mind because I realised it was too complicated for the time available, especially considering exams; also after deciding my university course choice was biology I wanted to do something related to it to gain knowledge in the field and aid my UCAS application. I changed the title to 'How significant is the threat of Antibiotic Resistance to humans?' as this was in a subject I had greater interest in as it involved how biology affected society. I study biology for a level but this topic is not covered in the syllabus and I do not know anything about it yet. My project format will now be a 5000 word dissertation. Initially I was worried about having enough source and material to use but after research I found lots online; also from doing this research I wanted to develop skills of handling sources – referencing, evaluating them and analysing them critically.		

OCR Project Progression Record 08.01

Activity	Date	Detail	Supervisor's initials	Comments
3. If completing the Diploma, • is topic relevant to Principal Learning? If yes • Does the project complement and develop the themes and topics for learners' principal learning set out in the relevant line of learning criteria? **and/or** • does it support learner progression (skills, knowledge, understanding?)		N/A		
4. What is the title of the project? This could be phrased as a question, hypothesis or statement.	March 2014	I phrased my title as a question so that my research would be focused and had an question to answer throughout my dissertation. I decided on 'How significant is the threat of antibiotic resistance to humans?' as a title. I'm not entirely satisfied with it, it isn't very inspiring but it gives a wide scope to research and can be split into sections to answer it so formatting a dissertation will be easier.		

Activity	Date	Detail	Supervisor's initials	Comments
5. What do you hope to achieve by the time you complete the project?	March 2014	Overall I would like to gain knowledge in the area of microbiology as it will help me in my university course and also I find it interesting as the power of microbes can have such a profound effect on humanity. I also want to gain better time management and self-motivation skills so that I can plan ahead and manage a project and keep to a deadline effectively and not leave it to last minute. Furthermore, in writing a dissertation and dealing with sources I hope to develop my referencing, note taking and ability to interpret and analyse sources critically and how to compare and contrast them.		
6. What form will the assessment evidence for the project take? (ie design, performance, report with findings from an investigation, artefact, [*dissertation – level 3 only*])	June 2014	I will do a 5000 word literature review on Antibiotic resistance. This format was best suited to this topic because it allows me to develop my ability to compare different sources to come up with my own opinion on the subject and means instead of reciting facts as in a report I have to actively interpret them.		
7. Have you produced an outline plan to show your project timeline?		I have done a detailed Gantt chart stating each stage of the project and the estimated time it should take. This means I know at which stage of the project I should be at during which month and so allows me to ensure I make the deadline in plenty of time. It was helpful to see if I was working to target or falling behind and gave me a realistic view as to whether I would finish (such that I decided to change my project from an artefact). I did stick to it to begin with once restarting the project; I later did another one and better factored in outside of college commitments as at first I didn't and this meant I fell behind schedule.		

OCR Project Progression Record 08.01

Activity	Date	Detail	Supervisor's initials	Comments
8. What will you need to achieve your project? eg tools, equipment, techniques and technologies	March 2014	I will need a computer and access to the internet, as well as access to a library. I will need IT skills like making mind maps, Gantt charts, scanning and photocopying. I will also need essay writing techniques like note taking and drawing persuasive conclusions from source material. I will also need people to carry out primary research on and people like teachers to give me feedback on ideas about the subject.		
9. Will you or have you used a range of sources for your information?	June 2014	I have used numerous types of sources in my dissertation. Electronic ones like science journals, articles, digital magazines, podcasts and interviews. As well as non-electronic sources like magazines and books. The best sources I found were large scientific reports found online published by reliable sources such as academics and World Health Organisations and were all very up to date – published in the last year or two. There were multiple science journals I would have liked to have been able to use because they were very detailed in areas I needed but they are not all open access and so otherwise you have to pay to view them.		
10. Is the information selected suitable and sufficient to fit the question/task/brief?	June	Yes, the vast majority I found was relevant. Some sources were very lengthy but they had relevant sections within them which I used. Some of the science journals and articles were very complicated and too technical for me to understand, however I used simpler sources first to build up background knowledge so that I could access the more complex source material. Most of the sources agreed with each other, there were some discrepancies but on the whole not many contradiction in major areas.		
11. Have you identified any links with other areas of study or areas of interest which relate to your project?	June	There were very few links with my a-level study of biology as microbiology is not a topic we cover. However some broader topics did overlap such as the structure of DNA, this was helpful as it meant I could interpret more complex sources. My project has definitely increased my interest in the topic and has made me look more forward to studying biology at university. I found the adaptability of bacteria amazing and the process behind it very interesting too, the genetic mechanisms behind it are something I would like to learn more about in higher education.		

OCR Project Progression Record 08.01

Activity	Date	Detail	Supervisor's initials	Comments
12. What skills need to be applied to use the information you have collected?	July	To turn my notes into my final project I first condensed the sources by taking notes using methods such as the Cornell method and mind maps and annotating passages on word documents. I then referenced and evaluated the quality of my sources to see if they were reliable enough to include. I then compared and contrasted the sources against each other to analyse them in a critical manner. I used connect – extend – challenge templates to compare and analyse sources effectively. A lot of the time I have to turn narrative text into evaluative text to include in evaluating the threat of antibiotic resistance instead of repeating factual sources. I also had to organise my project into the format and sections to make answering the overall broad question easier and more logical, I used subheadings to do this and then used each subheading as a topic to compare and contrast sources against each other. This worked well as it made writing the dissertation much quicker as I had already analysed and interpreted sources and organised them into the paragraphs of my dissertation.		
13. Did you apply the tools, equipment, techniques and technologies to use the information that has been collected to complete your project?	August	I used all the skills I set out to as mentioned earlier; I think being able to condense the sources into simpler notes using methods like the Cornell method and mind maps were particularly useful because it meant interpreting them was much easier as the information was relevant. Also, my way of organising sources into sections and using the connect – extend-challenge template to compare the sources on one particular section at a time worked really well as it all slotted together for the whole dissertation. What didn't work as well was when sources were too complex – some science journals – and I ended up with too much information that wasn't relevant, I sorted this by reading easier sources first so it was easier to understand more difficult ones. Also with my primary data I collected, I applied statistical skills to find the mean and modal value of data and also put the values into graphs on excel to illustrate their results more effectively. I then compared these results to secondary data to see if they were similar.		

OCR Project Progression Record 08.01

Activity	Date	Detail	Supervisor's initials	Comments
14. What outcomes/objectives have you achieved so far (mid-term review)?	July	At halfway point I was slightly behind; I had not factored exams and revision and work outside of college into my first timeline. However, during the summer holidays I was able to catch up, and re did a timeline to factor in these aspects. From it I improved my time management skills and have learnt to be realistic with what is possible in a given time, especially if there are other commitments. As for the dissertation, I have yet to start writing it but have gathered all source material and started to analyse it.		
15. Evaluation of own learning and performance so far (mid-term review).	July	At this point in the project, I have developed my source skills significantly as I have managed to handle a number of long and complicated sources and simplify them, analyse, evaluate and use them in my dissertation. I think my organisation skills have also improved as when I first started looking at source material my notes were less relevant and too long, rather than interpreting sources I was just repeating them however now I can properly use them. Weaknesses of my project would be that the title is very broad so it cannot go into lots of detail on one sub-topic as there is not enough space to do so, however it offers a broader wider look at antibiotic resistance as a whole. Also, I am unsure where to include my primary research, it seems almost irrelevant compared to some sources, but I will try to use it to support secondary sources as I think it adds an interesting perspective to my source material.		

Activity	Date	Detail	Supervisor's initials	Comments
16. What have you changed after reviewing your work?		I reorganised my notes from sources into more relevant sections and decided to disregard some sources as they were irrelevant and unreliable. This made it much easier to manage source material and meant I had less to sift through when writing up the dissertation.		
17. Final phase - Do you feel that you have achieved all of the outcomes/objectives of your project?		I feel I have achieved most of the skills and outcomes I wanted to achieve. I think my time management skills still need improving as I tend to leave bits to the near the deadline but my time keeping has improved. I do however feel that the final dissertation could have been improved – the middle section lacked direction. I have definitely improved my source skills and IT skills which I can use and apply to other situations and future projects, especially at university.		
18. Presentation of Portfolio • written section (compulsory, even if the outcome is a performance or artefact) • other evidence can be DVD, photographs, slides, CD, artefact, digital technologies etc		5000 word dissertation and accompanying planning and source material.		
19. Describe how you have presented your project to an audience		Powerpoint or 'Prezi' (presentation software)		
20. Have you evaluated your project, taking into account any feedback from your audience?		SEE END OF PROJECT		

OCR Project Progression Record 08.01

Activity	Date	Detail	Supervisor's initials	Comments
21. Date of project submission to teacher		6th October 2014		

Extended PPR #07

Notes

This form should be used to record the progress of each learner and may also assist in forming a basis and justification for the mark awarded under each assessment criterion (for example, by indicating the level of support needed by the learner).

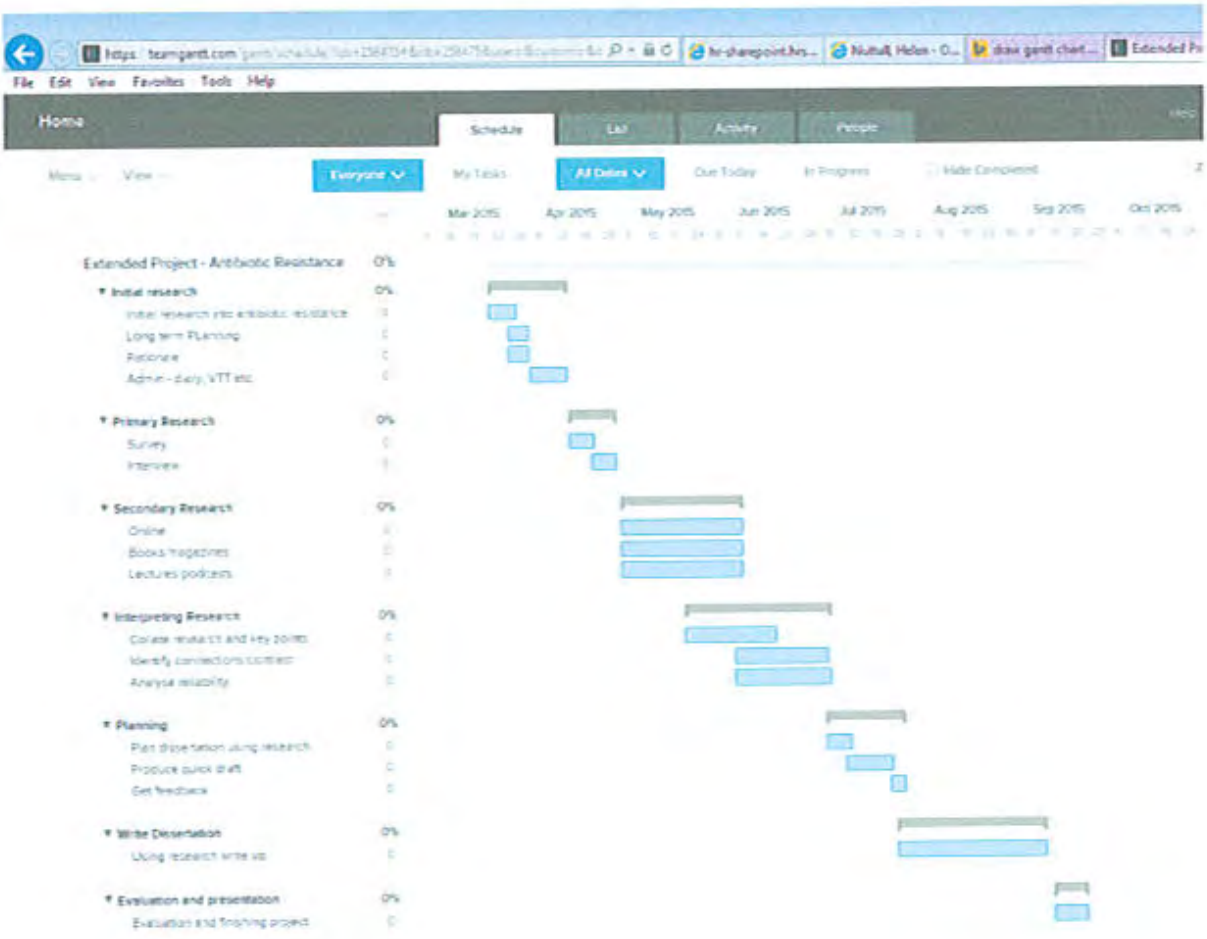
At Level 3 it is not intended that the supervisor gives any written feedback to the learner in the comments section. *Verbal feedback may be given by the supervisor; this should not be recorded on this form. Learners may use the comments section for taking notes.*

A copy of this form must accompany each learner's work when it is submitted for Moderation.

OCR Project Progression Record 08.01

LONG TERM PLANNING

This is my projected timeline of the stages of my project, created using free software on a website. It starts from when I decided to change my project to now, and gives me enough time to complete each stage in order to move onto the next stage. It also allows me to see ahead and make sure I keep up with it so that I meet the deadline.



https://teamgantt.com/gantt/schedule/?ids=258475#&ids=258475&user=&custom=&company=&hide_completed=false&date_filter=

DIARY

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Diary Progress

Date	Work Completed	Successes/Problems	What to do Next
15/01/14	Introduction to the EP and how to successfully manage one. Researching a broad range of topics, looking for ideas as to what would make a good potential project, paying particular interest to ideas to do with events and artefacts.	Became accustomed to EP projects and the various stages of them so I know now what sort of ideas could work as a project and which ones would not. However, my research at the moment is very vague and so not entirely useful and some of my ideas are too impractical/expensive.	Narrow down the areas of research to two or three ideas in order to come up with an EP title.
20/01/14	Talk with mentor to discuss ideas; decided that an artefact would be an ideal project for me and discussed what sort of things need to be included in an artefact project.	Starting to narrow down ideas for project, I have decided to do an artefact to do with fashion.	Now I have decided on fashion, I need to decide what exactly I will make and what the aim of my project will be. To do this I will further research fashion but specifically different time periods so my project can be inspired or based upon a different decade.
27/01/14	We learnt different methods of primary research, including how to write surveys and questionnaires in order to get the most relevant and accurate information from them. Decided I would like to make an item of clothing from the 1960s as this looks like an interesting decade for fashion.	Developed primary research skills, and will be able to use these to write a questionnaire on potential designs later in my project. Further narrowed down ideas for my project however still unsure the practicalities and cost implication of my project.	Decide exactly what I would like to do for my project by looking at various designs on the internet; evaluate if this is a viable project and within a realistic budget.
4/02/14	Looked various completed EP projects and evaluated what made them successful and what needed improving. Looked in detail at the mark schemes of EPs so I know what to include and how to get the best grade I can.	Was very useful to look at other people's projects, especially those of an artefact as gave me an idea of how they are put together and how long they should be. Looking at the mark schemes showed me how to fulfil the criteria for a good project.	Now I know what to include in my project, once I have finalised my idea I should start to write a rationale.

6/02/14	Learnt how to effectively use the Harvard bibliography system to reference sources properly. Decided that I will research, design and produce a small selection of garments of clothing inspired by the 1960s for my EP project. Then wrote my rationale explaining my project.	Learning how to make an accurate bibliography was important as I will need to reference all my sources used in my research. Finally deciding exactly what I want to do for a project and ensuring it is viable means I can now start to research and plan my project.	Next, I will make a projected timeline of the stages of reaching, designing and making my artefact. This will give me an idea of the amount of time I should spend on each section to get it completed before the deadline.
10/02/14	Practised various note taking skills by watching a video on it. Quick discussion with mentor about progress of my project and where to go next. Managed to complete a Gantt chart for my timeline using free software online. AO3/1	Developing my note taking skills for secondary sources is important because the majority of my research will be from secondary sources and I will need to summarise it in note form. Developed ICT skills by creating a Gantt chart on the computer - looks more professional and smart. Problems encountered were that for my timeline I had to realistically factor in other commitments that would prevent or limit the amount of work I could do on my EP at a certain time – like in May time progress on my EP will be slow due to exams.	Start researching the 1960s fashions and trends, collect images of clothes from this time period.
13/02/14	Carried out research into the 1960s fashion and trends and historical context of the decade. Learnt a lot about the key styles of the time and found some very useful websites to inspire me. Started a bibliography of key sources to use in my project using the Harvard system previously learnt.	Gained lots of knowledge and ideas that can be included in my project and incorporated into my designs. However, it can be hard to tell which websites are more accurate about the 1960s clothes, as lots of websites are based on the modern perspective of 1960s clothes which isn't necessarily accurate of the time period.	Continue further research, specifically on exactly what styles of clothes were worn in the time period.
20/02/14	Again further research on 1960s clothes. Now moving onto what sort of materials are used and types and styles of patterns. Started to fill out the VTT and PPR vital documents for my project.	Successfully found a couple of websites which are very useful – Vogue.com has pictures of 1960s inspired catwalk designs which are very useful. However, filling out the VTT and PPR was tricky as couldn't	Start to collate research in note form on documents and copy pictures into files.

		complete some questions, but did make me consider exactly what the aim/result of my project will be.	
22/02/14	Watched parts of a series called The Great British Sewing Bee from BBC 2 and made notes on relevant sections. Decided that I should rephrase my project aim/outcome in my VTT and rationale to researching and designing a small collection of garments of clothing inspired by the 1960s decade, and produce at least two of my favourite/most successful designs. Before I was aiming to make 3-4 garments and unclear on how many to design, with this new aim, I hope to use my research to design a small collection of garments, and display them in an artistic way, however I will only make my two favourite designs. This means I can spend more time on each garment, ensuring they are finished to a high standard. I have edited my rationale accordingly.	The notes I made were on how to sew and included lots of key terms which I became familiar with. It introduced me to several key techniques to making clothes, which I can now explore further. Changing my project aim has made it less vague and more focused and will hopefully allow me to finish garments to a higher standard. Problems encountered were that I may be slightly slipping behind my timeline, college commitments and out of college activities like work have been quite time consuming recently although hopefully this weekend I will be able to make further progress.	In order to keep up to date with my timeline, I need to neaten up all my notes from sources and put them into one document. AO1
05/02/14	Made notes from the Victoria and Albert Museum website.	It gave me good contextual background and knowledge to the 1960s decade, allowing me to understand the fashions of the time, so my project will be more historically accurate. Also, I used the Cornell method of taking notes, so developed my secondary research skills. AO2	I need to finish all my research and put it together in order to keep up to date with my timeline.
10/03/14	Today I decided that I will change my project to a dissertation, about a topic to do with biology. I realised that I was behind schedule according to my timeline due work	Starting a new project three months in is a bit difficult, but I know that I will be more focused on this one and hopefully make more progress on it. I was successful today	At the moment my searches are very broad and wide and so next session I would like to look at specific questions that I could focus on to form a title.

	and college commitments, and that it was unrealistic that I would complete the artefact to a high standard in the time remaining. Furthermore, I have now decided on my university course of biology, and feel that an extended project would aid my UCAS application and extend my knowledge on the subject. I discussed this with my mentor who agreed it would be a good idea.	in narrowing down which aspects of biology I could focus on by completing a mindmap of ideas and googling the topics to see how many sources there were for each one.	
15/04/14	I further narrowed down my ideas and looked up controversial or important topics in biology, ones that particularly stood out was antibiotic resistance because it involves microbiology which I find really interesting and would like to learn more about, and it involves how these microbes interact and affect the lives of humans.	It was successful because I did narrow down my topics and have decided that I will focus on antibiotic resistance as my subject for a dissertation. I then used smart art formatting on word to create a mind map with further questions relating to the topic.	I would like to start thinking of a working or draft title and start to collect sources for this.
26/04/14	I gathered a range of source material and have decided from these that my working title will be something like 'Antibiotic Resistance: An apocalyptic Threat?' this is catchy and refers to the fact that a lot of sources suggest antibiotic resistance is a huge alarming threat.	It was successful because I know have a draft title to work from so I can be more focused in my research.	I need to keep collecting sources and start to make a bibliography using Harvard referencing.
06/05/14	Today I researched sources for my project. I already had a range of good sources from initial research and today found different types of sources like podcasts.	Finding sources was successful in that I found podcasts and online videos to broaden the type of sources. However I had to be careful as some sources were not within date and so were not as reliable as others. Another problem is that at the moment my research is very vague and I do not have specific questions or topics I need to find out about so my research may not be	Next I will start to look at primary research and decide which methods of collecting primary data would be most appropriate. I will also come up with a list of objectives or questions to ensure my research is more relevant and specifically answering the overall question.

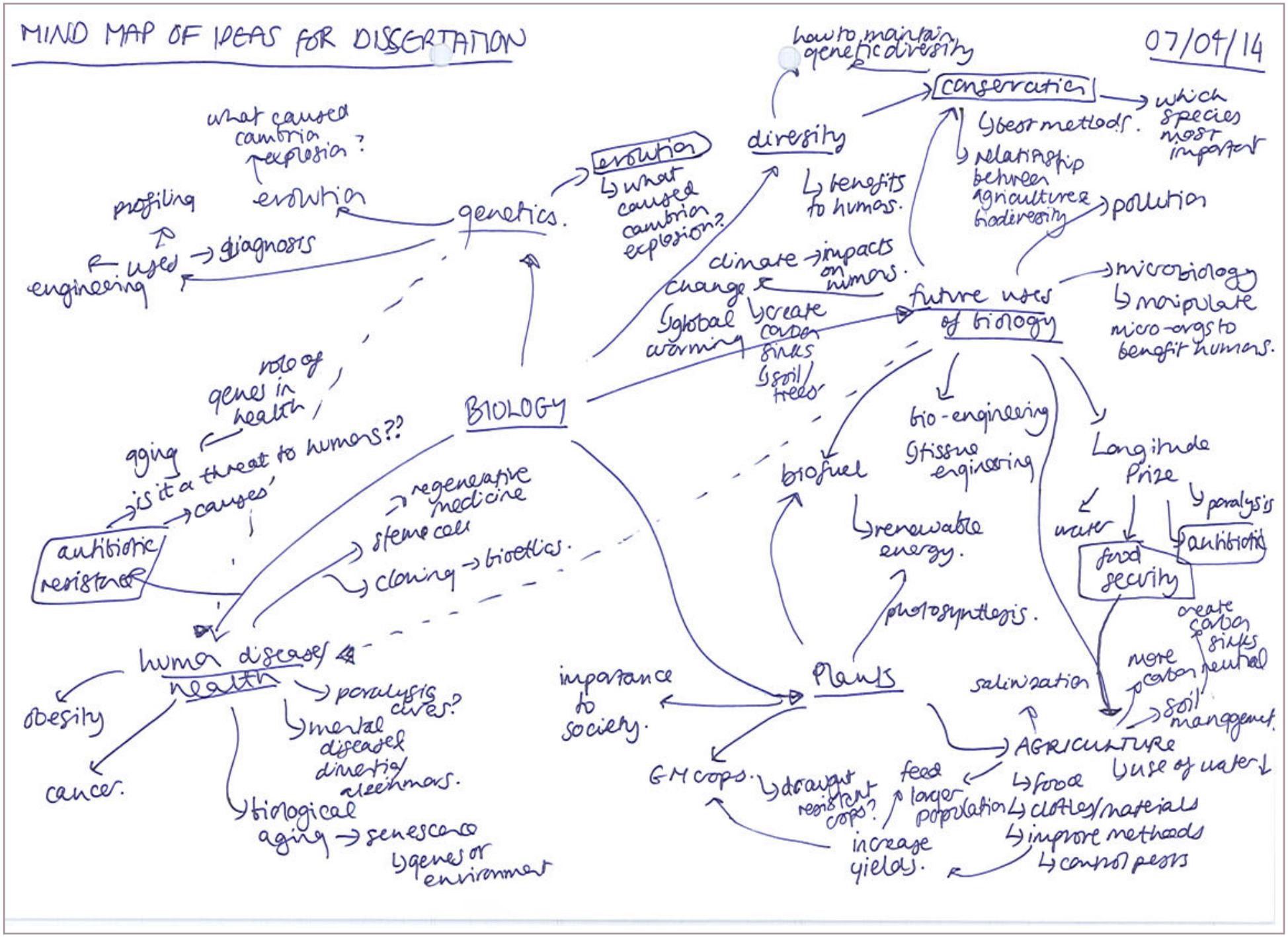
	necessary.		
11/05/14	Before completing further research, I decided to make a list of objectives and aims for my dissertation. I also split the dissertation up into sections to make it easier because I have gathered an awful lot of source material which was making it difficult to ensure it was relevant and focused. Splitting the main title up into section will also help structure my dissertation.	I successfully selected questions to do with antibiotic resistance that helped to answer the overall question of: how significant is the threat of antibiotic resistance? I used my initial research and new sources to do this.	Next I will start to collect my research together by taking detailed notes.
14/05/14	I learnt how to Harvard reference sources and condense them down into brief but useful note form, I used the Cornell method and mind maps to gather my source material.	The range of secondary sources I have collected is very varied and includes lots of reliable reports from governments and science journals. However, I have accumulated too many notes which is making it very difficult to sift through to find relevant parts, to overcome this I have further condensed them and highlighted sources as well as annotating them on paper to make key ideas stand out easily when glancing back on them.	Some of the source material has been very hard to decipher as it is very technical and very complicated concepts that I have not come across before. To overcome this problem I have decided to look at some simpler sources first to build knowledge of the topics so that I can fully interpret more complicated sources for my dissertation.
30/05/14	Over the next two weeks I have continued to collect, annotate, and highlight key points in my source material.	The sources I have selected provide me with all the information I need to answer the aims and objectives I outlined earlier.	Next I will write a rationale and start to piece the sources together to create an overall picture of the threat of antibiotic resistance.
10/06/14	I wrote out the rationale and also completed templates on connect extend challenge to compare and contrast sources to each other.	I was successful in that by outlining by goals earlier, I was able to select source material answering each specific section or goal which means when it came to comparing sources I could compare sources to each other over the same factors.	I feel that some of my sections in dissertation are lacking clear direction and focus so I will re-evaluate my rough plan.

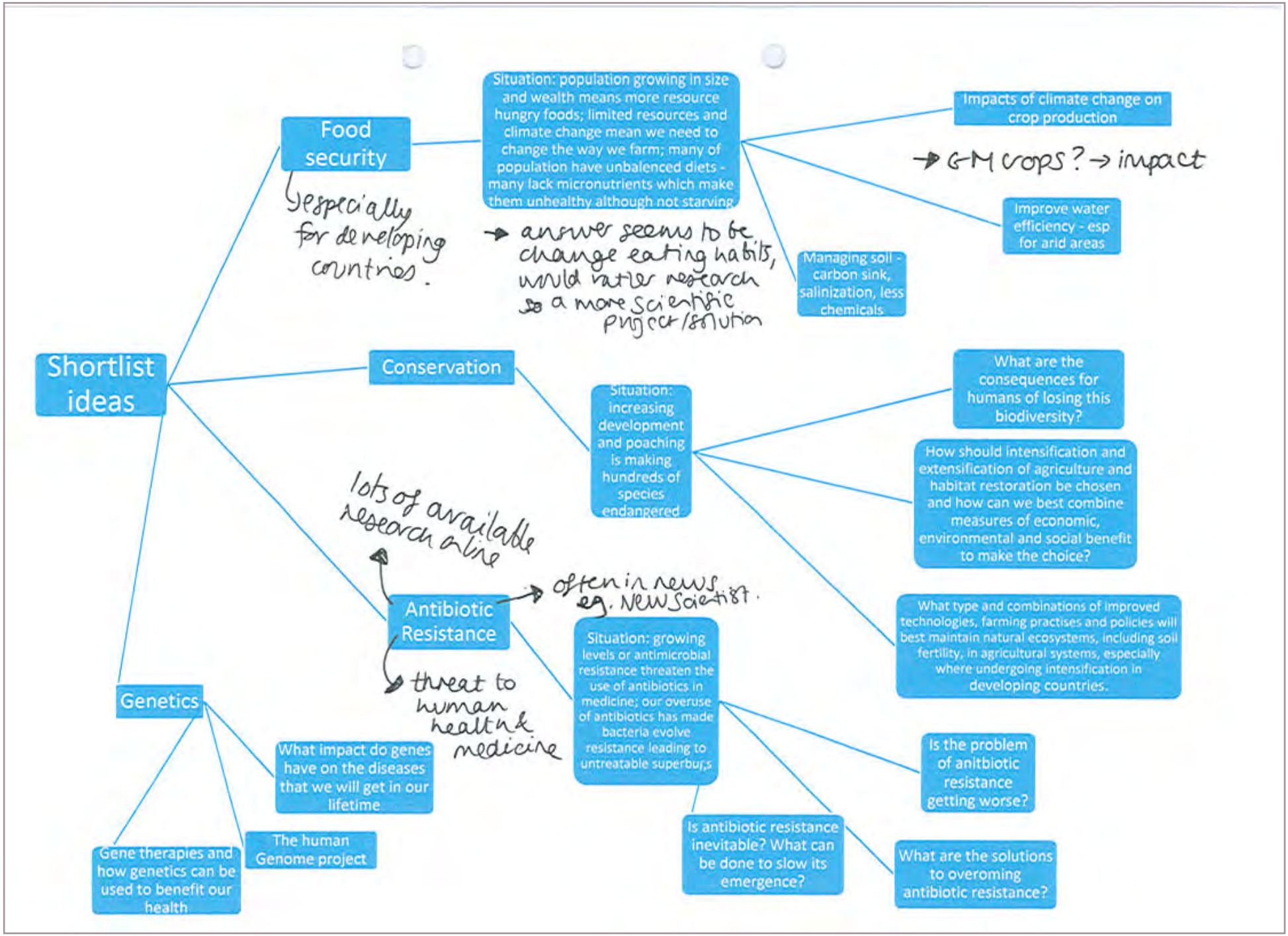
20/06/14	I completed extend-connect- challenge sheets, so my secondary data is now ready to use to write a final draft. I also decided to carry out primary research and drafted a questionnaire and interview for a senior nurse.	I later carried out the interview which was useful in understanding an opinion of someone on the frontline fighting antibiotic resistance. I also made a pilot survey which I handed out to several people for feedback.	I will alter the survey so it retrieves the information and data I need for my project, I will also review how much progress I have made.
1/07/14	I carried out a mid-project review to evaluate how much progress I have made.	I realised that I was behind my first timeline, which made it difficult to see if I was on target, however, I made another more realistic timetable which factors in holidays and commitments, unlike before as I am developing my time keeping skills.	I will start to evaluate my sources for reliability.
10/07/14	I evaluated my sources according to how useful and reliable they were.	Most of my sources are very useful and from reliable sources which is good. Also, I used my primary research to make graphs on excel to show the data collected in an easier to understand format.	Now I have collected all source material I will plan my essay.
25/07/14	I planned my essay in detail. I can now start to write it.	Planning my essay allows me to see the direction of the text and what source material to include.	I will start writing!
30/07/14 – 2/09/14	I have drafted and redrafted my dissertation and it is now finalised.	I used feedback from my parent and a teacher to redraft my work which was very useful.	
5/09/14 – 5/10/14	I finalised all my notes, final draft and assembled everything to together, ensuring I have included plenty of evidence of research and skill development.		

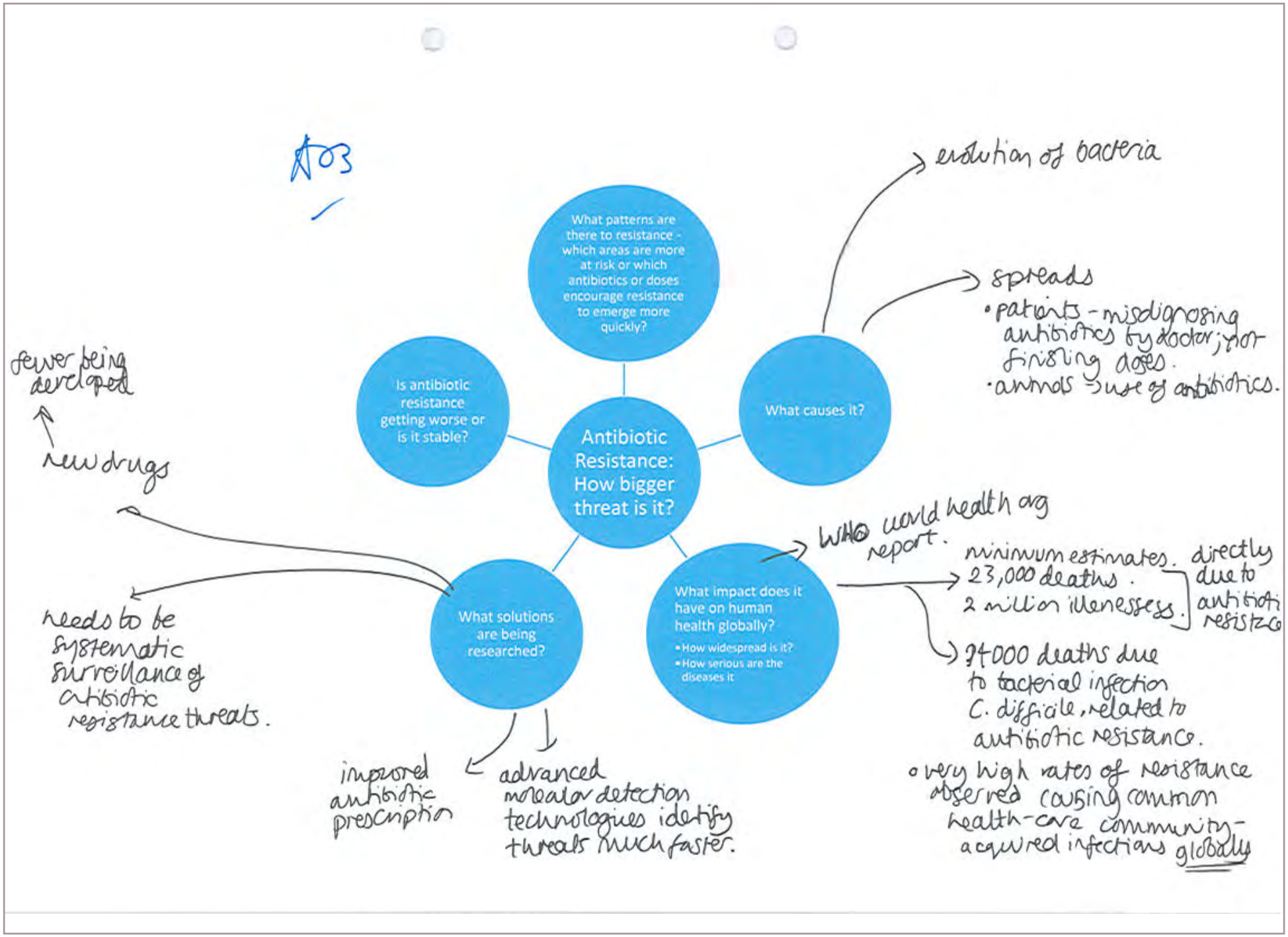
Excellent tracking of progress. AO1

INITIAL IDEAS

21


MIND MAP OF IDEAS FOR DISSERTATION
07/04/14
BIOLOGY
genetics.
profiling
engineering
used
diagnosis
growth
what caused cambria explosion?
evolution
what caused cambrian explosion?
diversity
how to maintain genetic diversity
conservation
best methods.
which species most important
relationship between agriculture & biodiversity
pollution
benefits to humans.
climate change
global warming
impacts on humans.
create carbon sinks
soil/trees
future uses of biology
microbiology
manipulate micro-orgs to benefit humans.
bio-engineering
tissue engineering
biofuel
renewable energy.
Longitude Prize
water
paralysis
antibiotics
food security
role of genes in health/aging
is it a threat to humans??
causes
antibiotic resistance
regenerative medicine
stem cell
cloning → bioethics.
human disease/health
obesity
cancer.
paralysis
mental diseases
dementia
alzheimers.
biological aging → senescence
genes or environment
importance to society.
Plants
photosynthesis.
GM crops.
drought resistant crops?
increase yields.
feed larger population
AGRICULTURE
food
clothes/materials
improve methods
control pests
use of water
salinization
more carbon
create carbon sinks
soil management
neutral


Shortlist ideas
Food security
especially for developing countries.
Situation: population growing in size and wealth means more resource hungry foods; limited resources and climate change mean we need to change the way we farm; many of population have unbalenced diets - many lack micronutrients which make them unhealthy although not starving
→ answer seems to be change eating habits, would rather research so a more scientific project/solution
Impacts of climate change on crop production
→ GM crops? → impact
Improve water efficiency - esp for arid areas
Managing soil - carbon sink, salinization, less chemicals
Conservation
Situation: increasing development and poaching is making hundreds of species endangered
What are the consequences for humans of losing this biodiversity?
How should intensification and extensification of agriculture and habitat restoration be chosen and how can we best combine measures of economic, environmental and social benefit to make the choice?
What type and combinations of improved technologies, farming practises and policies will best maintain natural ecosystems, including soil fertility, in agricultural systems, especially where undergoing intensification in developing countries.
lots of available research online
Antibiotic Resistance
often in news eg. NEWScientist.
threat to human health & medicine
Situation: growing levels or antimicrobial resistance threaten the use of antibiotics in medicine; our overuse of antibiotics has made bacteria evolve resistance leading to untreatable superbugs
Is the problem of anitbiotic resistance getting worse?
Is antibiotic resistance inevitable? What can be done to slow its emergence?
What are the solutions to overoming antibiotic resistance?
Genetics
What impact do genes have on the diseases that we will get in our lifetime
The human Genome project
Gene therapies and how genetics can be used to benefit our health


A03
Antibiotic Resistance: How bigger threat is it?
What patterns are there to resistance - which areas are more at risk or which antibiotics or doses encourage resistance to emerge more quickly?
Is antibiotic resistance getting worse or is it stable?
What causes it?
What solutions are being researched?
What impact does it have on human health globally?
• How widespread is it?
• How serious are the diseases it
evolution of bacteria
spreads
• patients - misdiagnosing antibiotics by doctor; not finishing doses.
• animals = use of antibiotics.
fewer being developed
new drugs
needs to be systematic surveillance of antibiotic resistance threats.
improved antibiotic prescription
advanced molecular detection technologies identify threats much faster.
WHO world health org report.
minimum estimates. directly due to antibiotic resistance
23,000 deaths.
2 million illenesses.
74000 deaths due to bacterial infection C. difficile, related to antibiotic resistance.
• very high rates of resistance observed causing common health-care community-acquired infections globally

SECONDARY RESEARCH NOTES

22

Key Aims and Objectives of Dissertation:

Now I know the key areas my dissertation will focus on, I am outlining the main goals and aims of this dissertation before planning it. This enables me to keep focused and only include relevant information to the question.

- Overall aim of this dissertation is to evaluate how significant the threat of Antibiotic Resistance is to society by comparing and interpreting up to date research in the field.
- In order to do this I will split the topic up into five sections:
  - Introduction to antibiotics and what antibiotic resistance is
  - How did antibiotic resistance emerge and how does it spread?
  - Is the rate of antibiotic resistance emergence stable or increasing, and what factors effect this? - To include methods of monitoring antibiotic resistance
  - Solutions in overcoming antibiotic resistance
  - Conclusions

This table allows me to clearly outline the objectives and questions that should be answered within each section, in order that each section directly relates and helps to answer the overall question which is how significant is the threat of antibiotic resistance is? This table will then allow me to use and interpret my research in such a way that I know which section it will relate to and therefore how it will help answer the overall question. My next step will be to then collect and note take from sources and sort them into these sections which will form the foundation of my plan and therefore dissertation.

How significant is the threat of antibiotic resistance

Section	Aims of each section	How this aim helps to answer the overall question
Introduction	1. Explain how antibiotics work 2. Explain what antibiotic resistance is 3. Explain the consequences of antibiotic resistance	1. Understanding how antibiotics work gives an appreciation of how important and fundamental they are to modern medicine, and how without working antibiotics many common diseases would be fatal 2. An understanding of what antibiotic resistance is, is essential to understand why it is such a threat 3. The consequences of antibiotic resistance could be severe and I will look at which diseases cannot be treated as a result of resistance, which means the threat of antibiotic resistance is very significant
Section 1 – Emergence and spread of antibiotic resistance	1. How does antibiotic resistance occur? 2. How does antibiotic resistance spread globally? 3. How widespread is antibiotic resistance globally?	1. To investigate whether the evolutionary process of a pathogen gaining resistance to an antibiotic means antibiotic resistance is inevitable and this therefore means the threat of antibiotic resistance is inevitable with the use of antibiotics 2. Once a pathogen has the genes to survive antibiotics, how do these genes spread to other populations of pathogen

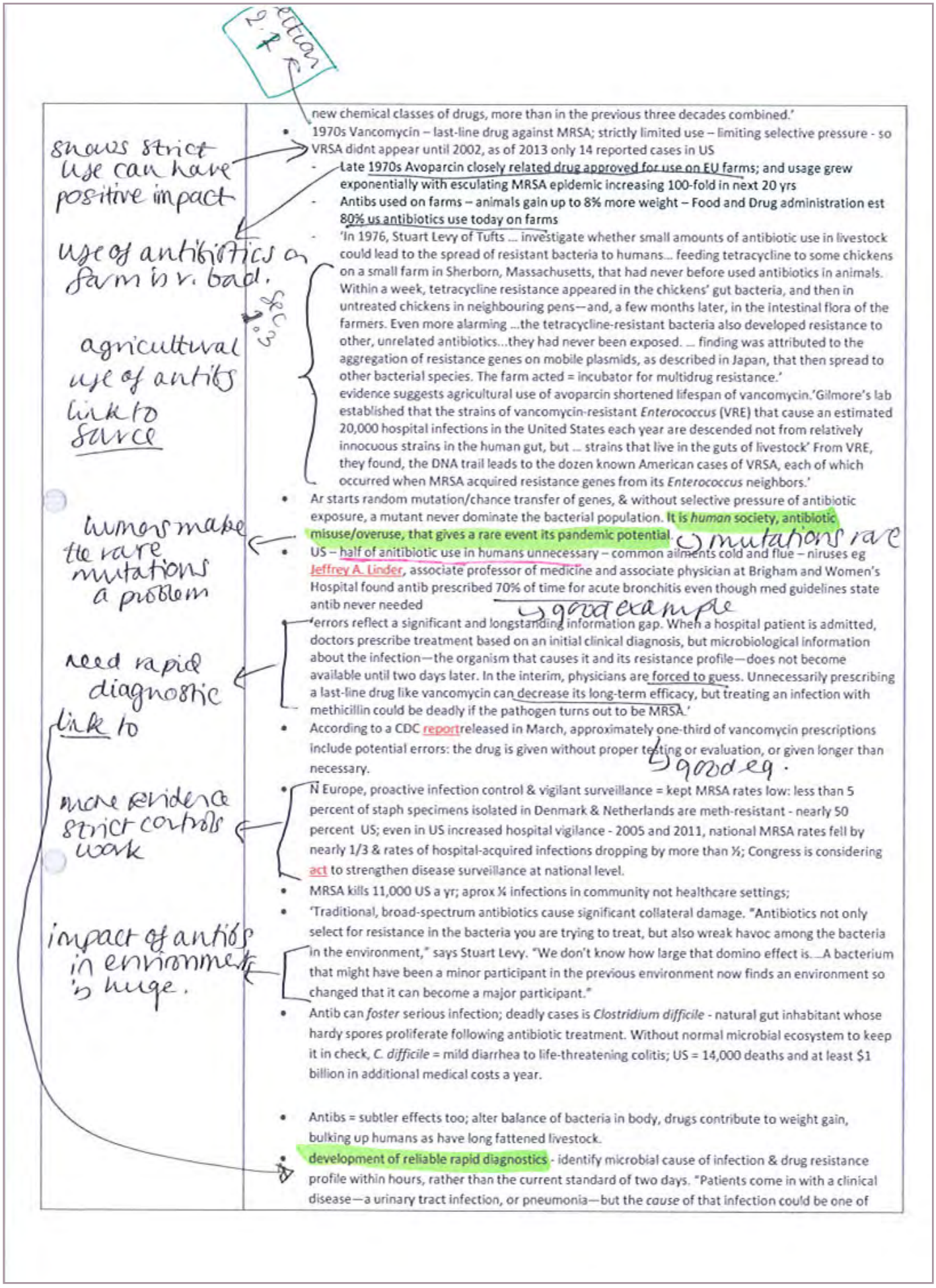
	4. Why are there more resistant micro-organisms?	3. The wider spread antibiotic resistance is, the greater threat it poses to society and harder it is to overcome. 4. When some bacteria become resistant to even last line of defence drugs, the consequences and therefore threat of resistance is greater
Section 2 – Is the rate of antibiotic resistance emergence stable or increasing, and what factors effect this?	1. Is the rate of antibiotic resistance emergence stable? 2. Which factors affect the rate of antibiotic resistance emergence? 3. How is antibiotic resistance levels monitored and are these effective enough?	1. If the rate at which antibiotic resistance is emerging is increasing, the threat from antibiotic resistance is much larger 2. If we know what factors affect the rate of antibiotic resistance emergence, we can control these factors to control the emergence of antibiotic resistance. 3. If we do not monitor the levels of resistance, we have no estimation of the potential threat of untreatable diseases to humans. I will find out if there are gaps in our surveying of resistance and the consequences of this.
Section 3 – Solutions to overcome antibiotic resistance	1. What can doctors and patients do to slow the emergence of antibiotic resistance? 2. What biological research is being carried out to overcome antibiotic resistance?	1. A collective effort between doctors and patients could significantly reduce the threat of antibiotic resistance 2. I want to know what are the best solutions being researched and by how much could they reduce the threat of antibiotic resistance
Conclusions	1. How significant is the threat of antibiotic resistance to society?	1. By drawing on all the research into how resistance emerges, spreads, what effects the rate of emergence, and what solutions to overcome resistance are in place now and in the future, I will evaluate how significant the threat of antibiotic resistance is. - Also, is the threat long term or short term, ...

Which format should I use?

Now that I know what questions and objectives need to be covered in my dissertation, I have decided that a literature review of the threat of antibiotic resistance would be most appropriate. I have decided this because this format allows me to evaluate source material in order to come to a conclusion, whereas a report is more an account of the subject, a literature review means I can form my own opinion by investigating sources which is more skilful and more involved.

Source:
Harvard Magazine article – Source 1

CUES headings, themes, questions that connect points, main ideas	NOTES and content, quotations, references
agrees with Surce on statistics.	• 'antibiotic revolution inaugurate the era of modern medicine, trivializing once-deadly infections and paving the way for medical breakthroughs: organ transplants and chemotherapy would be impossible without the ability to eliminate harmful bacteria' • US – a r = 2million deaths, 23,000 illnesses and $20 billion extra medical costs • Penicillin - 1928, Scottish scientist Alexander Flemming discovered petri dish with colony of mould and a halo within which the Staphylococcus bacteria were absent – penicillin - 'magic bullet' 'powerful, almost miraculous, new weapon' - Penicillin resistant strains of S.aureus in hospitals yrs later – 'it's newton meets Darwin' - kills bacteria by binding to and incapacitating an enzyme that maintains the cell wall - as popularity grew, plasmids carrying penicillinases entered Staph pop; in one English hospital the resitant staph infections quadrupled from 14% 1946 to 59% two years later • Bacteria resistance had added feature to other micro-organisms – their resistance can be transferred - Bacteria exchange small, circular pieces of DNA called plasmids – carry genes for resistance – plasmids spread naturally occurring resistance genes - Most genetic material is transmitted parent to offspring, but plasmids can be transferred horizontally – neighbour to neighbour - 'unique ability makes bacteria an even greater threat' - Many resistance genes can gather on a single plasmid and spread to different species as the host bacterium moves through environment - In clinical settings horizontal gene transfer most common mechanism through which bacteria become drug resistant
→ how do plasmids spread r-genes? what is horizatal gene transfer. ↳ look at Surce	
LINK TO – Surce 2 → as evidence of vast environmental pool of genes for resistance	• Most antibiotic derive from naturally occurring compounds evolved to destroy other bacteria to colonize limited spaces - Bacteria evolved to harbour natural resistance mechanism like enzymes pump hostile compounds out/chemically alter drug so ineffective; studies found soil bacteria naturally resistant to most known antibiotics some use antibiotics as food ↳ so is it inevitable? • New antibiotics – 1940s and 1950s golden aged of discovery – streptomycin, chloramphenicol, tetracycline new classes of chemical compounds employed in antibiotic arsenal - Scientists synthesizing molecules - make chemical modifications to improve drug activity – adding extra chemical group – methyl tail- methicillin so not destroyed by penicillinase - Strains of methicillin resistant S.aureus – MRSA- appear 2 years later in 1962 and acquired new mechanism – a mutant target protein borrowed from another staphylococcus species that unaffected by the drug - Drug development slow 70s and 80s – closely related to drugs before, chemical modification could only breathe few yrs of new life into drugs • S.aureus – 2002 nearly 60% cases in us hospitals were methicillin resistant; 2005 100,000 Americans suffered severe MRSA infections, 20,000 died – more than HIV and TB combined
MRSA ↳ 2002 = 60% cases in US resistant	
thin pipeline no new drugs being produced. LINK TO –	• Large pharmaceutical companies – unfavourable economics – drug development and sifting through early leads = risky expensive time consuming, not revenue chronic infection drugs do – 'perilously thin pipeline' John Rex head of infection development at AtraZeneca; aprox 10 years and a billion $ to bring drug to market • 2009 professor of micro and immune biology Suxanna Walker from Harvards programme on antibiotic resistance discovered compound Targocil – prevents bacterial growth by interfering with cellular pathway that creates critical component of S.a cell wall; potential to treat drug resistant strains like MRSA – compound restores lethal effect antibiotics like p and m by disabling bacterial modes or resistance • Interactions with host/other bacteria make microbe take on distinct properties that can diminish antibiotic's success - Many bac inc s.a form dense communities – biofilms – dif to eradicate esp on catheters eg - Sticking together help bacteria shield each other from ab effects even if susceptible when isolated in lab – "There is no *genetic* change, but the physiology has changed," explains professor of microbiology and immunobiology Roberto Kolter, who, with Richard Losick, studies the genetic basis of biofilm formation as part of HWPAR. "A few bacteria might survive antibiotic treatment because they were in the right *physiological* state." - • 'approvals of linezolid in 2000, daptomycin in 2003, and tigecycline in 2005 have introduced three
significance of biofilms Surce Sec 2.2	



new chemical classes of drugs, more than in the previous three decades combined.'

- 1970s Vancomycin – last-line drug against MRSA; strictly limited use – limiting selective pressure - so VRSA didnt appear until 2002, as of 2013 only 14 reported cases in US
- Late 1970s Avoparcin closely related drug approved for use on EU farms; and usage grew exponentially with esculating MRSA epidemic increasing 100-fold in next 20 yrs
- Antibs used on farms – animals gain up to 8% more weight – Food and Drug administration est 80% us antibiotics use today on farms
- 'In 1976, Stuart Levy of Tufts ... investigate whether small amounts of antibiotic use in livestock could lead to the spread of resistant bacteria to humans... feeding tetracycline to some chickens on a small farm in Sherborn, Massachusetts, that had never before used antibiotics in animals. Within a week, tetracycline resistance appeared in the chickens' gut bacteria, and then in untreated chickens in neighbouring pens—and, a few months later, in the intestinal flora of the farmers. Even more alarming ...the tetracycline-resistant bacteria also developed resistance to other, unrelated antibiotics...they had never been exposed. ... finding was attributed to the aggregation of resistance genes on mobile plasmids, as described in Japan, that then spread to other bacterial species. The farm acted = incubator for multidrug resistance.'
evidence suggests agricultural use of avoparcin shortened lifespan of vancomycin.'Gilmore's lab established that the strains of vancomycin-resistant *Enterococcus* (VRE) that cause an estimated 20,000 hospital infections in the United States each year are descended not from relatively innocuous strains in the human gut, but ... strains that live in the guts of livestock' From VRE, they found, the DNA trail leads to the dozen known American cases of VRSA, each of which occurred when MRSA acquired resistance genes from its *Enterococcus* neighbors.'
- Ar starts random mutation/chance transfer of genes, & without selective pressure of antibiotic exposure, a mutant never dominate the bacterial population. It is *human* society, antibiotic misuse/overuse, that gives a rare event its pandemic potential.
- US – half of anitibiotic use in humans unnecessary – common ailments cold and flue – niruses eg Jeffrey A. Linder, associate professor of medicine and associate physician at Brigham and Women's Hospital found antib prescribed 70% of time for acute bronchitis even though med guidelines state antib never needed
- 'errors reflect a significant and longstanding information gap. When a hospital patient is admitted, doctors prescribe treatment based on an initial clinical diagnosis, but microbiological information about the infection—the organism that causes it and its resistance profile—does not become available until two days later. In the interim, physicians are forced to guess. Unnecessarily prescribing a last-line drug like vancomycin can decrease its long-term efficacy, but treating an infection with methicillin could be deadly if the pathogen turns out to be MRSA.'
- According to a CDC report released in March, approximately one-third of vancomycin prescriptions include potential errors: the drug is given without proper testing or evaluation, or given longer than necessary.
- N Europe, proactive infection control & vigilant surveillance = kept MRSA rates low: less than 5 percent of staph specimens isolated in Denmark & Netherlands are meth-resistant - nearly 50 percent US; even in US increased hospital vigilance - 2005 and 2011, national MRSA rates fell by nearly 1/3 & rates of hospital-acquired infections dropping by more than ½; Congress is considering act to strengthen disease surveillance at national level.
- MRSA kills 11,000 US a yr; aprox ¼ infections in community not healthcare settings;
- 'Traditional, broad-spectrum antibiotics cause significant collateral damage. "Antibiotics not only select for resistance in the bacteria you are trying to treat, but also wreak havoc among the bacteria in the environment," says Stuart Levy. "We don't know how large that domino effect is....A bacterium that might have been a minor participant in the previous environment now finds an environment so changed that it can become a major participant."
- Antib can *foster* serious infection; deadly cases is *Clostridium difficile* - natural gut inhabitant whose hardy spores proliferate following antibiotic treatment. Without normal microbial ecosystem to keep it in check, *C. difficile* = mild diarrhea to life-threatening colitis; US = 14,000 deaths and at least $1 billion in additional medical costs a year.

- Antibs = subtler effects too; alter balance of bacteria in body, drugs contribute to weight gain, bulking up humans as have long fattened livestock.
- development of reliable rapid diagnostics - identify microbial cause of infection & drug resistance profile within hours, rather than the current standard of two days. "Patients come in with a clinical disease—a urinary tract infection, or pneumonia—but the *cause* of that infection could be one of

future solution.

many different things," explains Scott Evans, senior research scientist in biostatistics at Harvard School of Public Health. "Currently, we often have to initiate treatment of clinical disease based on unknown causes and antibiotic susceptibility. If we could get rapid diagnostics, then we could better tailor patient treatment."

- 'genomics-based rapid diagnostics are able to accurately detect resistance to certain drugs like penicillins, cephalosporins, and carbapenems.'
- More radical antibiotic future - using normal bacteria to counter relatively minor infections. Growing area of research explores how to alter microbial interactions to promote human health. Fecal transplants, occasionally proven effective against recurrent *C. difficile* infections. Such probiotic treatments that use live microbes are in their infant stages—no one knows exactly *how* normal gut bacteria keep *C. difficile* in check—but evidence is beginning to suggest that humans' future with bacteria will depend, at least in part, on careful coexistence.

idea of co-existence
Link to Source 11
idea of using them

SUMMARY including reactions, cross-references, ideas, confusions, questions

- antibiotics crucial to medicine
- rate of ABR has increased
- very few new drugs being produced
- new areas of research → research physiology, Torgocil, biofilms
  co-existance.
- spread of ABR on farms as well as humans.
  → investigate rapid diagnostics.

NB: ABR = antibiotic resistance

Notes from Source 2 - Origins and Evolution of Antibiotic Resistance. *Microbiology and Molecular Reviews*

This source was very long and had many complex explanations. I have picked out the most relevant and important paragraphs and sections and bullet pointed them so they are easier to understand. Some of this is direct quotations from the text but most is a condensed version. Highlighted and bold sections are areas I think are key and like with other sources. The comments on the right are how I can incorporate this source material into my dissertation etc.

Genetic Jugglery

- Genes for β-lactamase enzymes = most international in distribution; random mutations of the genes encoding the enzymes have given rise to modified catalysts with increasingly extended spectra of resistance. The β-lactamase genes are ancient (15) and have been found in remote and desolate environments (4), which implies that novel β-lactamases with altered substrate ranges occur in the environment. New extended-spectrum β-lactamase (CTX-M) was acquired from environmental *Kluyvera* strains and appeared in the clinic in the 1990s; this gene and subsequent variants are highly successful at transmission and are a global phenomenon and threat. Such epidemics of r genes with efficient HGT and rapid mutational radiation are next to impossible to control.
- If resistance is biochemically possible, it will occur.

Intrinsic Resistance

- Intrinsic resistance refers to the existence of genes in bacterial genomes that could generate a resistance phenotype, i.e., proto- or quasi-resistance. Different genera, species, strains, etc., exhibit ranges of antibiotic response phenotypes. Availability of genome wide mutagenesis techniques and rapid bacterial genome sequencing has revealed many potential/intrinsic gene functions in bacteria that may lead to resistance phenotypes in clinical situations. For example, a common genetic route to enhanced antibiotic resistance is gene amplification, notably for resistance to the sulphonamides (79) and trimethoprim (25). These studies provide good clues as to what may happen in the future.
- Yassin and Mankin used a mutant approach to identify putative target sites for inhibitors of ribosome function (151). Studies with rRNA characterized a number of RNA segments that may be novel targets for small-molecule inhibitors of translation. Such innovative analyses indicate that in spite of suggestions to the contrary, many potential drug targets remain to be exploited in antimicrobial discovery. Predicting resistance reliably—and acting appropriately—would be a valuable approach to extending antibiotic lifetimes (91).

The Resistome

- The population of r genes in nature is referred to as the environmental antibiotic resistome
- In study to see r genes/phenotype density in the environment, collections morphologically distinct spore-forming actinomycetes were screened for resistance to 21 different antibiotics; significant number of strains were resistant to an average of 7 or 8 antibiotics - naturally multidrug resistant.
- Novel resistance mechanisms, & many pathogen related ones identified also.
- This is the best evidence available for the presence of a vast environmental pool of genes with the potential to be captured and expressed as resistance determinants for any overused inhibitor. More studies are necessary to establish a strong environment-clinic connection

The Subsistome

- by screening soil bacteria for biochemical processes that degrade or inactivate antibiotics; 100s strains randomly isolated from 11 diverse urban and rural soils and tested for the ability to subsist or grow on one or more of 18 different antibiotics as sole carbon and nitrogen sources.
- Many strains grew efficiently on common antimicrobials, including aminoglycosides, fluoroquinolones, and other classes. – shows full extent and distribution of degradation/r genes in the environment and further verified the roles played by reservoirs of soil bacteria as origins of antibiotic r genes.
- catabolic pathways responsible for antibiotic digestion in nature provide a rich source of potential resistance determinants;

Commented [RN1]: Pose largest threat link to source 5

Commented [RN2]: Remote and desolate environment suggests that antibiotic resistance is inevitable and occurs naturally

Commented [RN3R2]: Horizontal gene transfer allows successful gene transmission causing global phenomenon

Commented [RN4R2]: 'Beta-lactamases are enzymes produced by some bacteria that provide resistance to β-Lactam antibiotics like penicillin, cephamycins, and carbapenems (ertapenem), although carbapenems are relatively resistant to beta-lactamase.'

Commented [RN5]: Link with source 1 of studies in soil bacteria, showing bacteria have genes for resistance naturally

Commented [RN6]: Horizontal gene transfer – see source

Commented [RN7]: Section 3.3 – there is hope to overcome ABR as still potential drug targets

Commented [RN8]: Solutions for the future – using genomewide mutagenesis techniques to predict resistance

Commented [RN9R8]: Many potential drug targets – shows signs of hope and so in future may not be as bigger threat as new drugs developed

Commented [RN10]: This links with sources 1 and 11 that the environment is a huge reservoir for resistance genes

Commented [RN11]: Evidence backing up source 2

- The roles of these environmental reservoirs in clinical resistance development are still hypothetical, and the primary metabolic functions of proto-/quasi-r genes in microbial populations are as yet unknown. Little evidence any of the putative r genes identified in these environmental studies have been mobilized into pathogenic bacteria and expressed as resistance phenotypes. If concentrations of antibiotic compounds are essentially undetectable in natural environments, what are the selective pressures for the variety of r genes?

Resistance Due to Anthropogenic Activities

- The amounts of unnatural substances (xenobiotic) released into the biosphere are inestimable.
- Most aren't biodegradable. As other examples, genetic and genomic studies of wastewater treatment plants have shown that they are rich reservoirs of r genes and resistant organisms; the genes are frequently carried as genomic islands on transmissible plasmids and provide ready sources of resistance determinants. Do these populations have any relationship with resistance in hospitals?

Commented [RN12]: Disagreeing with sources about whether genes from environment enter pathogenic strains of bacteria and can cause harm to humans, Section 1.1

Commented [RN13R12]: The selective pressures for the variety of r genes are humans as agreed by most other sources

Commented [RN14]: Agreeing with sources - -

Graph removed for copyright purposes

FIG. 4.
Dissemination of antibiotics and antibiotic resistance within agriculture, community, hospital, wastewater treatment, and associated environments

Recent studies have uncovered the presence of antibiotic r genes and even resistance-encoding integrons in the gut flora of peoples who live in isolated areas apparently untouched by modern civilization and not exposed to antibiotic therapies. Where did the r genes come from?

GENETICS OF RESISTANCE

- Resistant development - gene pickup, heterologous expression, HGT, and mutation
- acquisition of resistance not a serious energy cost to the microorganism – thought that multidrug-resistant strains would be unstable and short-lived in the absence of selection
- Two recent studies of the development of multimutant, multidrug-resistant *S. aureus* and *M. tuberculosis*. In the first study, isolates from a hospitalized patient treated with vancomycin were sampled at frequent intervals after hospital admission and analyzed by genome sequencing. In the steps to the development of the final (mortal) isolate, 35 mutations could be identified over the course of 3 months! Similarly, it has been reported that genome sequencing of antibiotic-resistant strains of *M. tuberculosis* revealed 29 independent mutations in an MDR strain and 35 mutations in

Commented [RN15]: major environmental reserves of resistance

Commented [RN16R15]: quite probably, of virulence genes and the organisms that harbour them

Commented [RN17R15]: link to Podcast on sewage

Commented [RN18R15]: 50 kg of ciprofloxacin dumped into rivers a day by pharmaceutical manufacturers in Hyderabad, in central India possibly the most extreme of the horror stories concerning irresponsible disposal; however, similar levels of pollution probably occur (unreported) elsewhere in the world.

Commented [RN19]: Huge number of adaptations and mutations highlights that it is a major threat as bacteria have unique ability to transfer these mutations agreeing with source - -

an XDR strain. The functions of these mutations are not understood; they could well be compensatory changes.

Resistance Gene Transmission

- plasmid-mediated transmission is far and away the most common mechanism of HGT
- Frequencies of gene transmission by conjugation in microorganisms varies significantly depending on environmental conditions
- DNA acquisition in the environment, *Acinetobacter* spp. are naturally competent, and HGT is frequent and pathogenic strains typically carry large genomic islands Might *Acinetobacter* and related environmental genera play roles in the capture and passage of r genes from environment to clinic? Such processes surely involve multiple steps and intermediate bacterial strains, but it has been suggested that heterogeneous gene exchange occurs readily in networks of multihost interactions
- Genome sequencing of bacterial pathogens isolated before the "antibiotic era" = plasmids common, r genes were rare (38) and showed environmental microbes were filled with plasmids—mostly large & carrying multigene pathways responsible for the biodegradation of xenobiotic molecules
- In summary, what is occurring in our lifetimes is an evolutionary process intensified by anthropogenic influences rather than the slower, random course of natural evolution. The existing processes of gene acquisition, transfer, modification, and expression that were in place are expanding and accelerating in the modern biosphere.
- Bacterial cell-cell fusion might be favoured in complex mixed microbial communities, such as those found in biofilms. The efficiency of the processes is not critical; selection and the efficiency of heterologous gene expression are likely the most important constraints. During therapeutic use, the exposure of bacterial pathogens to high concentrations of antibiotics for extended periods creates severe selection pressure and leads to higher levels of resistance. The pathway from an environmental gene to a clinical r gene is not known
- In lab, HGT can be enhanced by physical means that facilitate DNA exchange – egg physical proximity by immobilization on a filter or agar surface, and there are likely numerous other environmental factors that promote gene uptake. Such factors may play important roles in enhancing the frequency of gene exchange in environments such as farms, hospitals, and sewage systems, which provide ideal incubation conditions for r gene acquisition.

ECOLOGICAL ROLES OF ANTIBIOTICS AND ANTIBIOTIC RESISTANCE

- An antibiotic resistance phenotype does not necessarily occur solely in response to antibiotic selection. It can occur due to other selective pressures such as expression of efflux or influx systems. Different selective pressures such as mutations in ribosomal protein genes may lead to mutations that coincidentally confer a level of antibiotic resistance.

HOW TO CONTROL OR REDUCE ANTIBIOTIC RESISTANCE DEVELOPMENT

Erythromycin was an early example; introduced as an alternative to penicillin for the treatment of *S. aureus* in Boston City Hospital in the early 1950s, it was completely withdrawn after less than a year because 70% of all the *S. aureus* isolates were found to have become erythromycin resistant. The same was observed with chlortetracycline and chloramphenicol and, subsequently, with other antibiotics (55).
It is clear that antibiotic resistance seems inevitable.

- strict controls on antibiotic use by humans, requiring accurate prescriptions
- no delivery of antibiotics without a doctor's prescription (reducing needless use of antibiotics)
- and controlled therapeutic use in animal husbandry and agriculture
- Universal adherence to the suggested rules for restraint could have a positive effect, but would resistance be eliminated? Almost certainly not. However, if well-considered restrictions and rules for usage were supported by a pipeline of structurally novel antibiotics and semisynthetic designed to be refractory to resistance mechanisms, one could expect some significant and lasting improvements in the treatment of infectious diseases.
- developing nations, antibiotic use is relatively uncontrolled; comparatively inexpensive in these nations (often costing 10- to 30-fold less)

Commented [RN20]: Agreeing with source 1 that this is natural evolution, but that it is fuelled by humans applying the selective pressure; and agrees source 13 that the rate of emergence of antibiotic resistance is accelerating

Commented [RN21]: Agrees with source 11 oxford journal that strength of selection pressure increases the rate of emerging resistance

Commented [RN22]: Section 2.2 – factors affecting rate of DNA exchange – spread of ABR

Commented [RN23]: Conclusion – ABR will always be present

Commented [RN24]: Supports data from source one where strict regulation led to decrease in ABR

Commented [RN25]: Linking to source 3 that poverty and economic conditions of country can effect spread of ABR

Novel semisynthetic compounds generated by such chemical modifications of antibiotic core structures have extended the useful life of several classes, such as methicillin (oxacillin). The r genes evolve in response to new selection pressures, and since multiple mechanisms of resistance exist for every class of antibiotic, the avoidance of each and every modification is impossible. In addition, in some cases, chemical modification of antimicrobials has led to enhanced toxicity.

- New drug which interfere with efflux of active inhibitors from the cell is an attractive strategy for the design of modified or combination therapeutics; but for the time being, it remains little more than a pipe dream.
- "Cycling" antibiotics to try to reduce selection pressures for resistance and thus prolong the useful life of compounds; periodic replacement of front-line antibiotics with alternative structural classes in hospitals; not long-term solution, as resistant strains never disappear from the resident population; when related antibiotics are reintroduced, the problem strains (or r genes) are quickly reselected. In large hospital complexes, it may be difficult to decontaminate the "infected" intensive care centres appropriately while cycling between different antibiotics
- Combinationatorial approach - combinations of inhibitory compounds that have different modes of action – eg (fluoroquinolone plus a macrolide or a β-lactam plus an aminoglycoside or tetracycline) been successful with cancer and HIV infection.
- Inhibitors of bacterial virulence could be used to stop disease process instead of antibiotics. Advantage that selection for resistance (survival in the host) might not occur because the growth of the infecting organism would not be impaired. Some success has been obtained in small-animal models. Other nonantibiotic approaches for the treatment of bacterial diseases involve stimulation or recruitment of the innate immune system of the host (56). Recent advances in our understanding of the roles of the human gut microbiome in innate immunity may lead to other therapeutic options

Commented [RN26]: Philip allan magazines

CONCLUSIONS

- Resistance mechanisms are pandemic; clinical/financial burden on health care systems worldwide
- Decisive actions that require significant commitment and enforcement, backed stopping dumping of antibiotics into the environment through sewer systems; complete destruction of antibiotics before disposal should be common practice.
- No let-up in the search for new antimicrobial agents. Many uninvestigated drug targets exist in bacterial pathogens. Need more knowledge of processes of inhibitor-target and inhibitor-resistance interactions at the structural level will surely provide new leads.
- Prescription of the antibiotic be restricted to those uses. Defined "niche" antibiotics should be developed as a class separate from broad-spectrum agents. Given the increasing knowledge of environmental reservoirs of resistance, it should now be possible to have early warning of potential resistance mechanisms to new or old antibiotics and thus prepare for problems in the clinic in a proactive manner. It is incumbent on us to renew a concerted offensive that takes full advantage of new understanding and technologies. If not, the preantibiotic era awaits our descendants.

Source:
Source 3 – book – Deadly Companions, How Microbes Shaped our History by Dorothy H. Crawford

CUES headings, themes, questions that connect points, main ideas

- process of acquiring genes for resistance.
- shows country measures do have positive feedback impact.
- factors affecting spread of ABR.
  - Poverty?
    - less good AB treatment.

NOTES and content, quotations, references

- Alex Flemming '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'
- Chance genetic mutation → individual microbe has competitive edge → rapid reproduction rate = offspring with resistance genes outcompete competitors → dominate population
  - Bacteria don't have to inherit gene – pick up from others by gene swapping
  - Can do this as many antibiotic resistant genes are extra-chromosomal – carried by plasmids or other transposable elements → highly mobile → dangerous.
- Case study:
  - Community microbe Streptococcus pneumonia
  - Resp for deaths worldwide – causes bronchitis, ear/sinus infections, pneumonia, meningitis
  - Developed penicillin resistance – incidence of resistance risen from 5% → 35% in 20 yrs in US – antibiotics freely available; remained at 5% UK
  - New vaccine used US first in 2000 reduced childhood infections – reduced antibiotic use reversed rising tide of resistant microbes by removing their selective advantage
- 50% antibiotics used in farms globally – agrees source 2 that farming contributes to ABR
  - Whole herd gets does to prevent microbes spreading
  - And to promote growth often lifetime treatment
  - Multi-drug resistance eg Salmonella typhimurium – diarrhoeal disease millions each yr emerged in animals and spread to humans
- Is poverty responsible for increased spread of antibiotic resistance?
  - M.tuberculosis evolved resistance to individual anti-TB drugs after treatment begin 1950s; successfully controlled by multidrug regimes
  - By 1990s resistance to multi-drug – 'global emergency'
  - Outbreak New York 1978 – started deprived inner city districts Central Haarlem and Lower East Side colonized all city accept wealthiest
  - Peaked 1992 – worst areas 100 new cases per square mile
  - Alarming resurgence of TB → increasing poverty and homelessness (cutbacks in public health expenditure US cities 1980s)
  - TB and HIV affect poorest developing countries – Figure 8.3 page 201
  - Unlike MRSA TB relies on spontaneous mutations, since these rare double mutation needed can only arise from drug misuse: poor supervision, inconsistent prescriptions, erratic drug supply, unregulated over the counter sales
  - Multidrug resistant TB is 10% of new cases world-wide
  - Solution is longer term treatment regimes but these are 200 times more expensive

SUMMARY including reactions, cross-references, ideas, confusions, questions

- farming is major ~~not~~ producer of ABR genes.
- in developing countries, ABR is worse as spreading.

Source:
Source 4 – Microbes and Man by John Postgate pages 209-221

CUES headings, themes, questions that connect points, main ideas

Methods of spreading resistance genes from bacteria to other bacteria

Role of plasmids

Definitions:

Conjugation is a type of prokaryotic reproduction in which DNA is transferred between prokaryotes by means of a pilus. Reproduction in prokaryotes is asexual and usually takes place by binary fission. The DNA of a prokaryote exists as a single, circular chromosome.
A **pilus** is a hair like appendage for conjugation found on the surface of many bacteria.
Virulence is the degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. The pathogenicity of an organism - its ability to cause disease - is determined by its **virulence** factors.

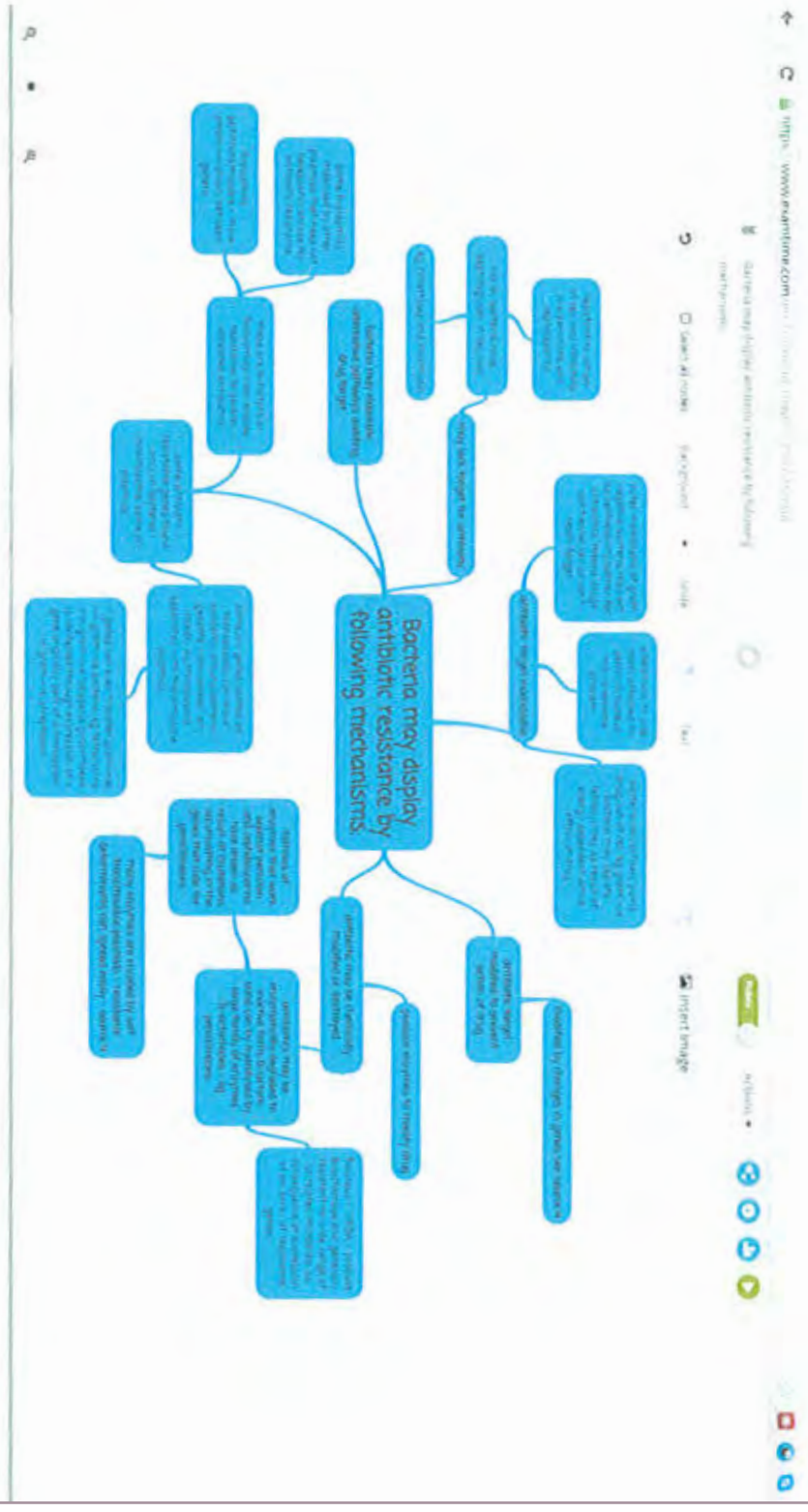
NOTES and content, quotations, references

- DNA – deoxyribonucleic acid - two complementary sugar-phosphate backbones joined together by hydrogen bonds between ATCG
  - Arranged in double helix
  - Most bacteria have additional mini-circles of DNA called plasmids
  - A gene is a sequence of bases that codes for a protein; a codon is three bases which codes for an amino acid
- Mutation
  - arises as spontaneous chemical change in DNA of an organism if major = fatal; if minor can be beneficial caused by X rays, UV, chemicals can damage DNA
  - means part of code of bases is incorrect so protein made by gene is different
  - Escherichia coli, about one organism in every 10 million is a mutant
- Conjugation – major means of genetic variation between microbes – 'male' bacterium donates some DNA (usually as a plasmid) to 'female' recipient giving her new genes which become hereditary; can include genes that change her into a 'male'
  - Pseudo-sexual conjugation between individuals in populations observed in electron micrographs
  - Means genes can recombine and transfer between organisms
  - In majority of conjugating bacteria, the genes transferred are not on the chromosome proper but a mini-chromosome → the plasmid
- Plasmids
  - Little coiled circles of DNA; exist alongside the chromosome but replicate themselves independently of it
  - Some plasmids encode resistance to two or three antibiotics at a time
  - Self-transmissible (sexual) plasmids can carry genetic info → recipient microbes →alter microbe significantly
  - Self – t plasmids can co-transfer (pull) other DNA –chromosomal or whole other plasmids – with themselves into recipient micro
  - Means plasmids can transfer between genera of bacteria so drug resistant E.coli can pass ability to resists a drug to eg Salmonella.
  - Mobile means plasmids can be exchanged among strains, species, even genera of bacteria
- Transformation – gives microbial variation; bacterium in suitable state (eg subject to abrupt cooling) take up raw DNA from its surroundings and builds some of it into its own DNA – become hereditary
  - absorb DNA from their surroundings without damaging it
  - If DNA from bacterium (P) added to culture of another (Q), some of Q culture takes up the DNA of P from chromosomes of P or whole plasmids→ acquires P-like characteristics
- Transduction – bacterial virus carries some DNA from previous host into a new host and later survives to use the imported DNA which becomes hereditary.
  - Many bacteriophages kill their hosts but some – temperate 'phages don't
  - Live peacefully within hosts, multiply and damage under influence of some external stimulus (UV eg) can re-infect new hosts and carry some of hereditary characteristics of their previous host into new one

SUMMARY including reactions, cross-references, ideas, confusions, questions
This source illustrates in writing the information from source 6 – the ways in which bacteria spread genetic resistance genes and how this means that it can spread very rapidly making it a large threat.

Source 5 notes – Book - Microbiology in Action by J. Heritage

Although this is hard to see clearly when printed, the mind map below illustrates the key points in this book relating to my dissertation. I did it as a mind map as it has several key subtopics with ideas that are linked to these. It is simple and easy to read layout of notes. I used a website called https://www.examtime.com/ which has software to produce mind maps. This is a screenshot of the one I produced:



Book: Micro-organisms Biotechnology & Disease
Student's Book
page 188-192.

Source b

substances produced by micro-orgs which in low concs kill/inhibit growth of other micro-orgs.

antibiotics

antimicrobials → wholly synthetic molecules eg sulphonamides.

cell wall → effect gram +ve bacteria) gram -ve
penicillin
cephalosporins
vancomycin
↳ prevent synthesis of murein peptide

cell membrane → effect permeability
-polymixins

protein synthesis
-chloramphenicol
-tetracyclines → broad spectrum
-erythromycin
↓ effective against wide range of micro-orgs.

metabolic reactions
- sulphur drugs.
↳ competitive inhibitors of enzymes in bacterial reactions.

bacteria cell no)

- bacteriostatic stops growth
- bactericidal kills bacteria.

exploit differences between pro + eukaryotic cells
↳ if drug affects/targets not in eukaryotic cells, eg cell wall, toxic effects not felt by patient

Sarce 7 Notes → 'Microbes & Disease' text book.

antibiotic. In other words, the resistant bacterium is selected: Bacteria become antibiotic-resistant when they obtain the genes for drug resistance. There are two ways this can happen:

- spontaneous mutation;
- transfer of genes for resistance from other bacteria.

Mutations in the bacterial chromosome do not occur very often but when they do, they can make the bacterium resistant to an antibiotic. The most common mutations change the binding site for an antibiotic (for example, the ribosomes) so that the antibiotic cannot bind.

Besides the bacterial chromosome, bacteria can also contain genetic information on small circular pieces of DNA called **plasmids**. If a gene for antibiotic resistance is among the genetic information on a plasmid, it is called an **R plasmid**. Once a bacterial cell contains an R plasmid, the resistance gene on the plasmid can be transferred to other cells by transformation and transduction (Fig. 10) and also through conjugation (Fig. 11). Plasmids can cross species boundaries.

↳ major threat!? if genes can cross species bandaries, then any form of microbe can gain them → dangerous.

with them. Sometimes these bacteria include resistant strains that are at a selective advantage in hospitals because the generally high concentration of antibiotics allows the resistant strains to multiply as the rest fall victim to the effects of the drugs. Today, a major reservoir of genetically altered resistant strains is found in hospitals. This reservoir of resistant bacteria carries a pool of resistance genes in bacterial plasmids. A single plasmid can contain genes for resistance to more than one antibiotic. This means that resistance to several antibiotics can spread rapidly through the bacterial population. Pathogens with multiple resistance have caused difficult-to-treat infections called **super-infections** → eg MRSA

How is genetic resistance such a threat then?
this links to Sarce 2 that although acquiring genes is random + natural, spreading them so they are dominant is due to man-made selection pressure.

Image removed for copyright purposes

Sarce 7

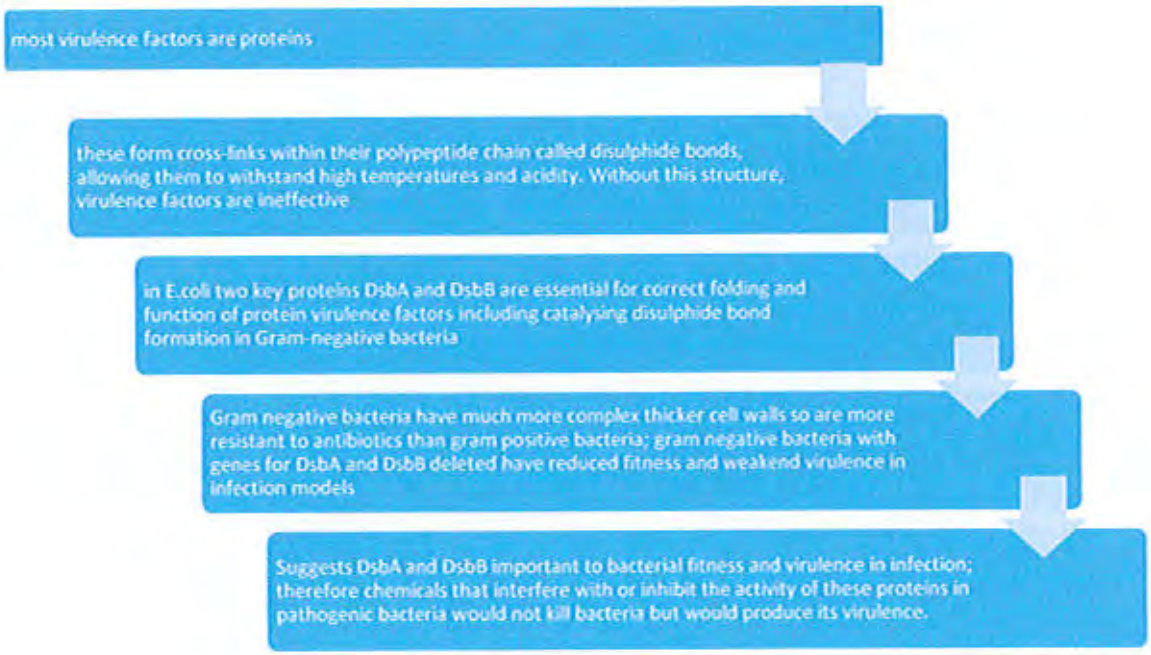
Diagram removed for copyright purposes

Diagram removed for copyright purposes

Source 8 – Bacterial Resistance Wars - article in digital magazine by Phillip Allan

Notes:

- Ancient bacteria dug up recently from permafrost found to be resistant to modern antibiotics
- Shows 'superbugs' were around long before antibiotics were developed
- To overcome:
  - Disarm bacteria instead of killing them; bacteria cause disease by producing virulence factors 'molecular weapons' eg toxins, enzymes that dissolve tissue and so on
  - Drugs could deactivate molecular weapons without giving rise to antibiotic resistance as less selective pressure to develop resistance as not killing the bacteria
  - So bacteria no longer a threat to health although treatment doesn't affect growth of population and immune system can deal with them
- Each bacteria = own virulence factors which vary enormously
  - Some researches are targeting specific high priority targets from individual bacteria eg developing chemicals which lock the activity of injector of bacterial secretion systems which inject host with toxins and poisons
  - Target 'weapons assembly factory' – drugs target machinery which makes virulence factors



Source 9 – Podcast by Richard Stabler

https://soundcloud.com/lshtm/richard-stabler-the-threat-of-antibiotic-resistance

These notes are taken whilst listening to a podcast, they are quite rough and abbreviated but record the overall picture of the podcast. The overall impression I got from the podcast was that ABR is a major problem and little action is being taken at the moment with few drugs being developed, but there is hope as people become more aware and more careful about using antibiotics.

- 'certainly is a very big problem'
- Urinary tract infections – E.coli – untreatable due to antibiotics – can be fatal
- Due to limited arsenal of antibiotics and misuse of ones we have; expectation of public to have medication even when unnecessary
- Misuse in veterinary – same as used for human infection
- Misuse is overuse – 'magic bullet' people don't take the whole course of antibiotics – ones left alive multiply and pass on resistance
- Travel – people from countries with lower stewardship – India, Peru – treat yourself, own doses, fake or weak drugs, not monitored, highly resistant strains develop and global travel spread it globally
- Developing new drug – intensely difficult and expensive – 1-2 billion pounds; identify – screen thousands of compounds, trials, tests
- Very few being produced – very little profit – more in anti-cancer jobs; neglected diseases – not in Western countries so not priority
- Not looked after tools we had; lack of investment
- We won't get to the point of no antibiotics
- Green tea novel technique s- extract sensitise resistance MRSA so sensitive to methicillin and be able to treat it but very long time off
- Gone back to Celestin or nothing – last resort from 1950s toxic effects
- evolutionary in action
- Some destabilise cell wall bacteria proteins made block binding sites of antibiotics so antibiotic cant bind; efflux bacteria, pump out drugs
- How worried are you personally how much time before time bomb goes off?
- Have to be concerned, more funding and research; slightly optimistic to find things
- Is it an apocalypse size of climate change terrorism why public not as concerned?
- Longitudinal prize – more awareness – especially as becomes worse – hits home
- Longitudinal prize – which most pressing problem ten million pounds to develop rapid diagnostic test or doctors and which resistance bacteria level it was
- Best case scenario – be able to pick up problem and type of micro-organism quickly so can still use old antibiotics
- Worst case scenario – strains develop multidrug can't treat
- Atm – gram negative particular problem, promise of new and different problems, survived before antibiotics and can survive even if they are gone.

The references to the Longitudinal prize and how aware the public has made me want to find out the level of awareness and concern amongst the public with antibiotic resistance; I want to know if the media and headlines have made people worried about antibiotic resistance – if people are more aware and concerned they are more likely to act and put pressure on governments to take action, this would lower the threat of ABR as more investment would go into reducing it.

Source:
Source 10 – Article 'Strength of Selection Pressure is an Important Parameter Contributing to the Complexity of Antibiotic Resistance Evolution' in Oxford journal Molecular Biology and Evolution.

CUES headings, themes, questions that connect points, main ideas	NOTES and content, quotations, references
Isogenic – having same or closely similar genotypes (genetic constitution of organism) – phenotype is set of observable characteristics Fits in with section 2 and which factors affect the rate of ABR emergence.	Strength of Selection Pressure Is an Important Parameter Contributing to the Complexity of Antibiotic Resistance Evolution – understanding and developing strategies to combat cross-resistance; and how selection strength effects evolution of cross-resistance • Intro: - Evolved 88 isogenic E. coli populations against 22 antibiotics from 7 drug classes for 3 weeks - For each drug two populations were evolved under strong selection; two under mild - Bacterial populations evolving under strong selection acquired high levels of cross-resistance against several antibiotics where as other = relatively weak resistance - **Selection strength is important parameter in complexity of a r problem and use of high doses = promotes cross-resistance** • Drug combinations used – slow down evolution as likelihood of developing simultaneous resistance against two or more drugs would be several orders of magnitude lower than the likelihood of developing resistance against a single drug • Would it be possible to use antagonistic drug pairs to slow down evolution of resistance in clinics • Bacteria can develop resistance to antimicrobials they have never been exposed to - Caused by efflux pumps; multiple pathway-specific mutations that confer cross-resistance to multiple drugs; **extra mutations compensating for bacterial fitness** • Performed whole-genome sequencing for 96 strains isolated from evolved populations to find genetics changes responsible for cross-resistance Findings - Strongly selected populations acquired higher number of mutations although acquired similar levels of resistance to drug they were evolved against - Mutations found in strongly selected and mildly selected populations were often found in diverse sets of genes, reflecting the plasticity of bacteria for developing antibiotic resistance - Strongly selected populations acquired higher numbers of mutations of genes that were specific to the target pathways of the drugs used for selection compared with the mildly selected populations - Diversity of pathway-specific gene mutations was largest for strongly selected populations • Variations between cross-resistance and antibiotic susceptibilities of strongly selected and mildly selected strains were largely due to the presence of the higher number of pathway –specific and off-pathway mutation in strongly selected populations - Strength of selection pressure in an evolving population is an important factor that affects the phenotypic and genotypic diversity - If mild – several sub-populations with diverse genotypes can coevolve; as dose in increased, populations have opportunities to acquire resistance-conferring mutations with relatively lower fitness costs, such as mutations in multidrug resistance genes or transcription factors instead of costly mutations in enzymes • Cross-resistance is an obstacle for designing effective drug therapies as its limits possible antibiotic options following an unsuccessful drug treat meant of a patient • Selection strength contributes to evolution of resistance, cross-resistance and susceptibility

SUMMARY including reactions, cross-references, ideas, confusions, questions

Overall: The higher dose of stronger antibiotic can promote the evolution of cross-resistance in bacteria. This means we are increasing the threat of antibiotics by mis-using them. In other sources like source 2, a rapids diagnostic test was suggested to find pathogen and strength of resistance of pathogen, this seems to fit in with the idea form this source as it would mean drugs that were just strong enough to kill the pathogen would be used, instead of using unnecessarily high doses; this method would reduce the speed of resistance occurring.

Notes – Source 12 – Antibiotic Resistance Threats in the United States 2013 report by the CDC

This report has lots of statistics relating directly to each individual antibiotic resistant microbe; I have decided not to include all the information here as I can easily refer back to the whole report to pick out specific statistics if relevant. Also, these notes are a condensed summary of the report, it means I am now familiar with the source so referring back to section if I need more detail for a particular aspect is easy. There were also lots of good diagrams and timelines in this source which I can incorporate into my dissertation

List of most significant resistance threats:

Urgent Threats: Clostridium difficile; Carbapenem-resistant Enterobacteriaceae (CRE); Drug-resistant Neisseria gonorrhoeae

Serious Threats: Multidrug-resistant Acinetobacter; Drug-resistant Campylobacter; Fluconazole-resistant Candida (a fungus); Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs); Vancomycin-resistant Enterococcus (VRE); Multidrug-resistant Pseudomonas aeruginosa; Drug-resistant Non-typhoidal Salmonella; Drug-resistant Salmonella Typhi; Drug-resistant Shigella; Methicillin-resistant Staphylococcus aureus (MRSA); Drug-resistant Streptococcus pneumonia; Drug-resistant tuberculosis

Concerning Threats: Vancomycin-resistant Staphylococcus aureus (VRSA); Erythromycin-resistant Group A Streptococcus; Clindamycin-resistant Group B Streptococcus

Facts and statistics:

- Estimated minimum no of deaths by a r = 2 million
- And 23,000 deaths
- Illnesses due to C. difficile – unique bacterial infection although not significantly resistant to the drugs used to treat it is directly realated to antibiotic resistance and use – 250,000 illnesses, 14,000 deaths

Commented [RN1]: Some threats are more urgent that others and thus have greater consequence for human health

Commented [RN2]: These are underestimates, the report says there are limitations with estimating as it is difficult to state the level of resistance of microbes and whether the death was due primarily to the resistance of microbes or to an underlying cause

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Diagram removed for copyright purposes

Timeline of antibiotic resistance

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Commented [RN3]: This timeline illustrates that as new antibiotics are introduced, within years resistance strains are identified; this suggests antibiotic resistance is an ongoing threat

Commented [RN4R3]: Also, from the timeline we can see that there are more antibiotic resistance strains identified in the last twenty years than in the previous fifty; this shows antibiotic resistance is an increasing threat

Commented [RN5R3]: Furthermore, this timeline shows very few new drugs have been developed despite the increase in resistance strains emerging in the last twenty years – illustrating as other sources have suggested that there is a 'perilously thing pipeline of new drugs' as in source 14.

ntibiotic prescriptions per 1000 people

Commented [RN6]: This chart shows that the frequencies of prescriptions are not consistent within the US; showing doctors are not systematically prescribing antibiotics the same way across all states

Tomorrow's Antibiotics: The Drug Pipeline

Image removed for copyright purposes

Image removed for copyright purposes

Commented [RN7]: This graph shows that very few new antibiotics have been developed in the most recent years, showing antibiotic resistance is a threat because there are very new drugs being manufactured to treat antibiotic resistant related illnesses.

Source:
Source 15 – Global Surveillance Report
produced in collaboiration with member states and other partners provides as accurate a picture as is presently possible of the magnitude of AMR and the current state of surveillance globally
This report attempts to map ABR surveillance status in Member States, and specifically the availability of data from national o´cial sources.
http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1

CUES headings, themes, questions that connect points, main ideas	NOTES and content, quotations, references
Introduction statistics –	• 'A post-antibiotic era—in which common infections and minor injuries can kill—far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century.' • There is a major gap in knowledge about the magnitude of this problem and such information is needed to guide urgent public health actions. • yearly cost to the US health system alone has been estimated at US $21 to $34 billion dollars, accompanied by more than 8 million additional days in hospital. Because AMR has e ects far beyond the health sector, it was projected, nearly 10 years ago, to cause a fall in real gross domestic product (GDP) of 0.4% to 1.6%, which translates into many billions of today's dollars globally. – link with source 12 Figure 9 Survival after pneumococcal pneumonia with bloodstream infection before and after penicillin treatment became available. Graph removed for copyright purposes
Penicillin increased survivial rates of pneumonia infections from 20% to 85%	Section 4 Figure 15 Proportion of new TB cases with multidrug resistance (MDR-TB) worldwide Image removed for copyright purposes
	TB case study :

Shows Global Spread of TB	Drug-resistant TB threatens global TB control and is a major public health concern in several countries. In 2012 it was estimated that, on a global level, 3.6% of new tuberculosis cases and 20.2% of previously treated cases had multidrug-resistant TB (MDR-TB). Frequencies of MDR-TB are much higher in Eastern Europe and central Asia than elsewhere in the world – page 49 of report - Current status of resistance to antibacterial drugs: • National data – E.coli, K.pneumoniae, S.aureus showed 50% were resistant to commonly used antibiotics • K.pneumoniae resistant to carbapenems – reported in all who regions – last line of treatment • Limitations cause uncertainty about representativeness and considerable gaps in coverage, the magnitude of the problem at both population & global levels is unclear and needs to be clarified • unclear to what extent differences in reported data for some bacteria–antibacterial drug combinations reflect real differences in resistance patterns, or are attributable to differences in sampling of patients, laboratory performance and methodology. Surveillance standards and international - Burden of resistance to antibacterial drugs • ABR has adverse impact on clinical outcomes of patients and leads to higher costs - Coordination and coverage • Lack of structures for coordination and info sharing to provide up to date overview of ABR • Most complete in more economically developed countries – EU and US

SUMMARY including reactions, cross-references, ideas, confusions, questions

Key findings:

- Major gap in knowledge about magnitude of problem and info is needs to guide urgent public health actions
- ABR is complex and multidimensional; involves range or resistance mechanisms affecting ever-widening range of bacteria, most of which can cause wide spectrum of diseases in humans and animals
- Surveillance of ABR neither coordinated nor harmonized so making it more difficult to assess and monitor the situation
- Resistance to common bacteria has reached alarming rates in many parts of world – many treatments becoming ineffective
-

Mutation Rates and Bacterial Growth

Even if only a single *S. aureus* cell were to make its way into your wound, it would take only 10 generations for that single cell to grow into a colony of more than 1,000 (2^{10} = 1,024), and just 10 more generations for it to erupt into a colony of more than 1 million (2^{20} = 1,048,576). For a bacterium that divides about every half hour (which is how quickly *S. aureus* can grow in optimal conditions), that is a lot of bacteria in less than 12 hours. *S. aureus*has about 2.8 million nucleotide base pairs in its genome. At a rate of, say, 10^{-10} mutations per nucleotide base, that amounts to nearly 300 mutations in that population of bacteria within 10 hours!
With a genome size of 2.8×10^6 and a mutation rate of 1 mutation per 10^{10} base pairs, it would take a single bacterium 30 hours to grow into a population in which every single base pair in the genome will have mutated not once, but 30 times! Thus, any individual mutation that could theoretically occur in the bacteria will have occurred somewhere in that population—in just over a day.

Thus, although you are on antibiotics and you are otherwise healthy, a total of 600 mutations have accumulated by the time you go to bed that night. Any one of those mutations could give your staph infection the capacity to continue replicating, even in the presence of the antibiotic. When that mutant cell replicates, it will pass on its resistant phenotype to its daughter cells, and they to theirs. Thus, a rapidly growing proportion of the replicating bacteria still present in your body will be drug resistant.

Spread of Drug Resistance

According to the U.S. Centers for Disease Control (CDC), in 2004, 63% of all reported staph infections in the United States were caused by MRSA (CDC, 2007). That figure represents a remarkable 300% increase in just 10 years' time. (In 1995, about 22% of all reported staph infections were MRSA, compared with only 2% in 1974.) The irony is that methicillin, a chemically modified version of penicillin, was developed in the 1950s as an alternative treatment for the growing proportion of staph infections already resistant to penicillin. At that time, about 60% of all staph infections were resistant to penicillin.

If a drug-resistant phenotype were to evolve and there were no antibiotic present, then that phenotype would fare no better than any other bacterial phenotype. In other words, it wouldn't flourish, and it might even die out. It is only when antibiotics are used that drug-resistant phenotypes have a selective advantage and survive.

http://www.nature.com/scitable/topicpage/antibiotic-resistance-mutation-rates-and-mrsa-28360

Genetic Signatures of Drug Resistance

More insight for developing and maintaining an effective drug-deployment policy will come from advanced evolutionary genetic modeling. Policy components will require that the models incorporate key parameters that may determine how fast the resistance spreads. Important factors are geographically-specific variables (e.g., the transmission/migration rate and host immunity) and the evolutionary genetic structure of resistance (e.g., the number and fitness effects of mutated genes and their interactions). Currently only limited information regarding these parameters is available, which severely limits efforts to analyze and evaluate models. One promising approach to obtain the necessary information is to reconstruct the actual events of drug-resistance evolution that recently occurred in various endemic areas. Then scientists can investigate which geographically-specific and genetic variables are associated with the rapid spread of drug resistance.

http://www.nature.com/scitable/knowledge/library/evolution-of-drug-resistance-in-malaria-parasite-96645809

Chinese pig farms breed drug –resistant Bacteria

Half of all pigs live in China – and well over half of them eat feed laced with antibiotic "growth promoters" - this practice is spawning a tide of antibiotic-resistant bacteria.The European Union banned antibiotic growth promoters for this reason in 2006. But they are still permitted in the US, where recently released figures show around half of all samples of the food-poisoning bacterium salmonella, taken from retail poultry meat, are resistant to at least three antibiotics.
To investigate, Yong-Guan Zhu of the Chinese Academy of Science in Xiamen,James Tiedje of Michigan State University in East Lansing, and colleagues tested soil along with fresh and composted manure at three big Chinese pig farms in different provinces. They also tested compost and manure from Chinese pigs not fed antibiotics, and soil from a remote forest. Using a quantitative PCR assay to pick up specific DNA sequences, the researchers measured the amounts of 244 different ARGs in their samples. They used the amount of a gene common to all bacterial in the sample as a measure of the total bacteria present, to establish how many ARGs

there were for a given number of bacterial cells. In the farm samples, the team found 149 ARGs that, between them, confer resistance to all classes of antibiotics – and the levels of some were "enriched" 28,000-fold compared to those in the soil samples not taken from farms. "Composting the manure and spreading that on soil reduced the load of some, but not all, types of ARGs," says Tiedje. Worryingly, the samples also contained enzymes that help ARGs move between bacteria. They even contained the antibiotics themselves, so selection pressure for the resistant bacteria continues outside the pig. Some would be expected to migrate to human pathogens." Antibiotic use is not monitored on Chinese farms, and Tiedje fears some sites where very large amounts are used could be resistance hotspots.

http://www.newscientist.com/article/dn23168-chinese-pig-farms-breed-drugresistant-bacteria.html#.VC69mPldW1S

http://planetearth.nerc.ac.uk/accessibility/transcripts.aspx?t=0&id=284

Source 16 - Impact of sewage treatment on ABR

- Two scientists researching ABR – Professor Elizabeth Wellington and doctor Greg Amos
- Warnings of 'post antibiotic era'
- 'right to be scared' 'significant problem' 'treatment and the way in which we do operations – rely on antibiotics'
- 'hazards' harbouring large numbers of very resistant bacteria
- Pollution selects for these genes – located on mobile transposons or plasmids – heavy metals, detergents, low levels of biocides, start to select bacteria
- Analysed ABR communities before effluent from treatment plant – more resistant downstream – to new and old antibiotics – genes found in clinical
- Genes are coming from animals from food chain, run off from farms and land, CTXM-15 – indicative of humans – coming from feaces from resistant bacteria in peoples gut
- Biological pollution – not so concerned with biological pollution; or resistant genes – can get to land or other native bacteria, can get to wildlife, food chain
- Reducing environmental load of antibiotics and resistant bacteria to reduce the cycle – use anaerobic digestion on farms, reed beds, new treatment plants
- Huge increase in number of resistance genes found in downstream river compared to pristine, a lot in E-coli, and related K. pneumonia predicted to be next superbug overtaking MRSA - finding them in the environment is definitely a cause for concern.

PRIMARY RESEARCH

23

Collecting Primary Research

- My plan to collect primary research is as follows:
- Draft a pilot questionnaire
- Get two people to fill in and see which questions need changing
- Do final version
- Give to 20 different people
- Collect results into a table/graph
- Write interview questions for uncle
- Carry out interview
- Summarise results

Pilot Survey:

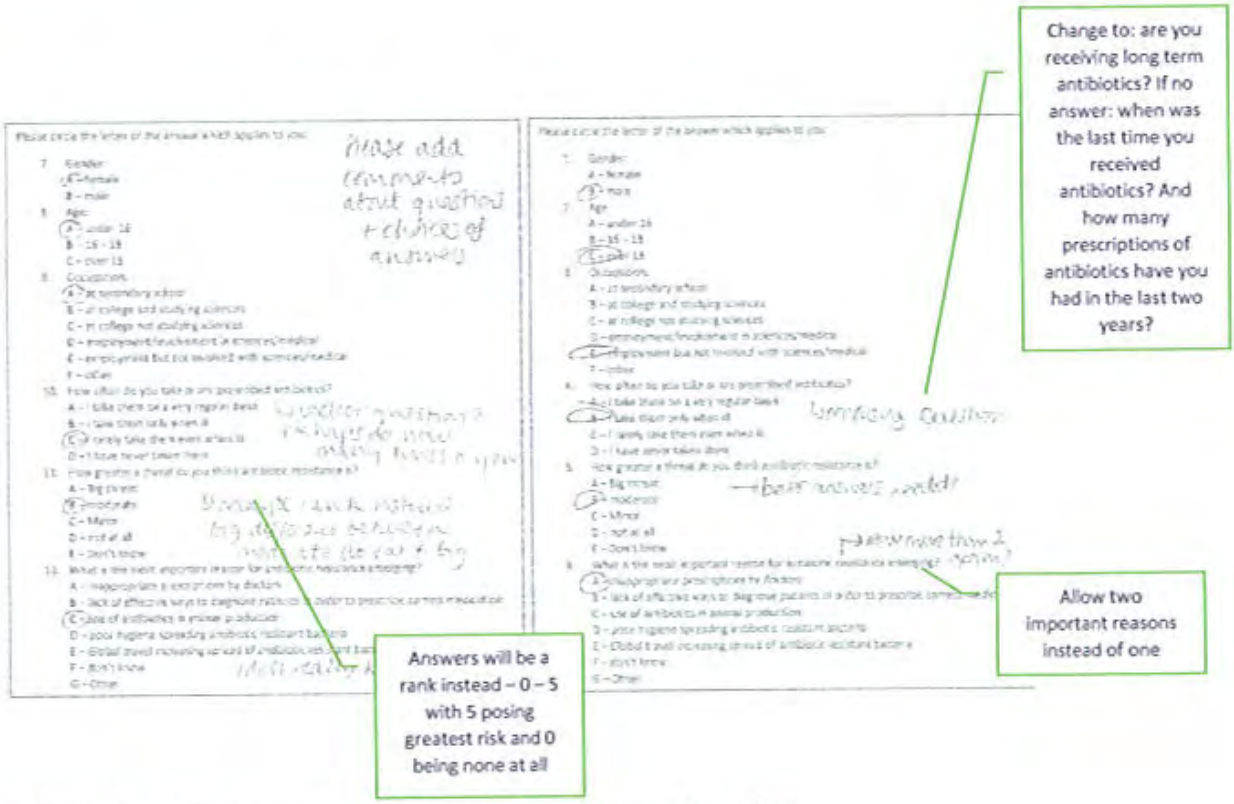
From initial research I discovered that most companies or large scale surveys have a pilot survey first to test out question to see if they get the required responses, before handing out the final version of the survey; this saves time and money if the original draft of survey was not effective. From my survey the main thing I wanted to find out from the public was whether they were aware of antibiotic resistances and the consequences of it. I also wanted to know if they were willing to take antibiotics when unnecessary.

Please circle the letter of the answer which applies to you:

1. Gender:
   A – female
   B – male
2. Age:
   A – under 16
   B – 16 – 18
   C – over 18
3. Occupation:
   A – at secondary school
   B – at college and studying sciences
   C – at college not studying sciences
   D – employment/involvement in sciences/medical
   E – employment but not involved with sciences/medical
   F – other
4. How often do you take or are prescribed antibiotics?
   A – I take them on a very regular basis
   B – I take them only when ill
   C – I rarely take them even when ill
   D – I have never taken them
5. How greater a threat do you think antibiotic resistance is?
   A – Big threat
   B – moderate
   C – Minor
   D – not at all
   E – Don't know

6. What is the most important reason for antibiotic resistance emerging?
   A – Inappropriate prescriptions by doctors
   B – lack of effective ways to diagnose patients in order to prescribe correct medication
   C – use of antibiotics in animal production
   D – poor hygiene spreading antibiotic resistant bacteria
   E – Global travel increasing spread of antibiotic resistant bacteria
   F – don't know
   G – Other

I then sent this questionnaire to five people and asked them to put comments detailing if they found it easy and clear to answer and if the questions were leading and had the correct answer options. I also found out whether this questionnaire would collect the right data. These were two of the responses I received which I have scanned:



After I edited the pilot survey and sent this one out to about 50 people:

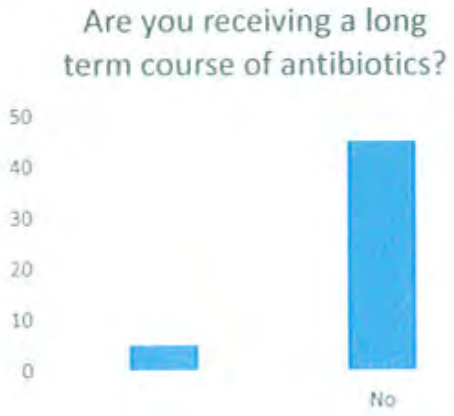
Please circle the letter of the answer which applies to you:

1. Gender:
   A – female
   B – male
2. Age:
   A – under 16
   B – 16 – 18

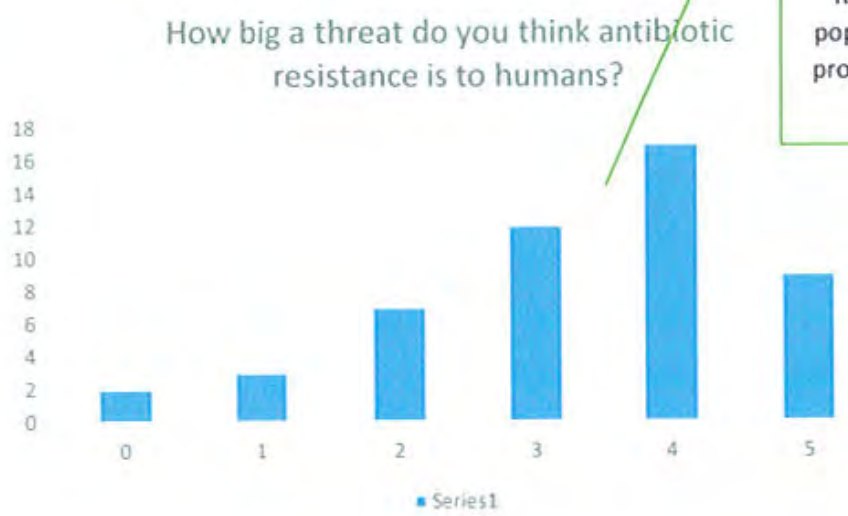
C – over 18

3. Occupation:
   A – at secondary school
   B – at college and studying sciences
   C – at college not studying sciences
   D – employment/involvement in sciences/medical
   E – employment but not involved with sciences/medical
   F – other
4. How big a threat do you think antibiotic resistance is to humans? Rate on a scale of 0 – 5, with 0 being no threat at all and 5 being a great threat:
   A – 0
   B – 1
   C – 2
   D – 3
   E – 4
   F - 5
5. Are you receiving a long term course of antibiotics?
   A – Yes
   B – No
6. If you answered Yes to Question 4 move to question 5. If you answered no to question 4: when was the last time you received a course of antibiotics?
   A – In the last month
   B – In the last six months
   C – In the last year
   D – In the last two years
   E – over two years ago (or never)
7. How many courses of antibiotics have you received in the last two years?
   A – none
   B – 1-2
   C – 3 - 4
   D – more than 4
8. What are the two most important reasons for the emergence of antibiotic resistance?
   A – Inappropriate prescriptions by doctors
   B – lack of effective ways to diagnose patients in order to prescribe correct medication
   C – use of antibiotics in animal production
   D – poor hygiene spreading antibiotic resistant bacteria
   E – Global travel increasing spread of antibiotic resistant bacteria
   F – don't know
   G – Other

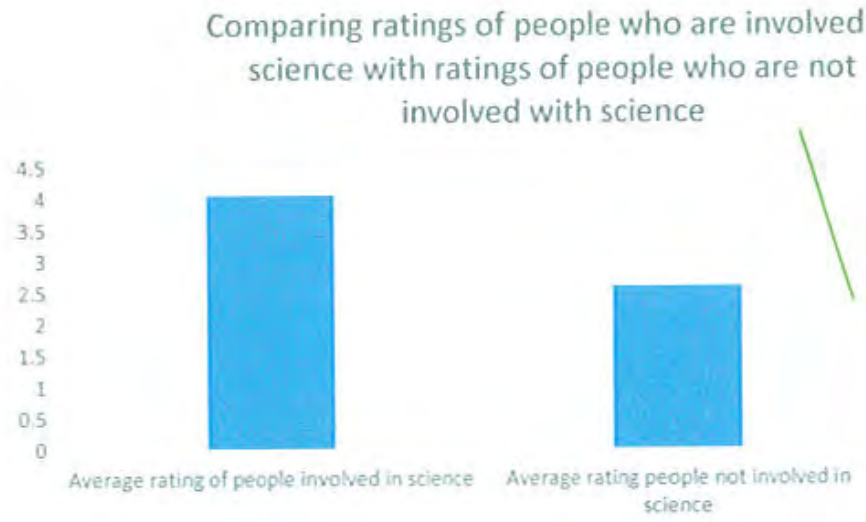
With the results I obtained I made charts and graphs on excel to display the data collected in an easier to understand format that I could interpret and then compare to my secondary research.



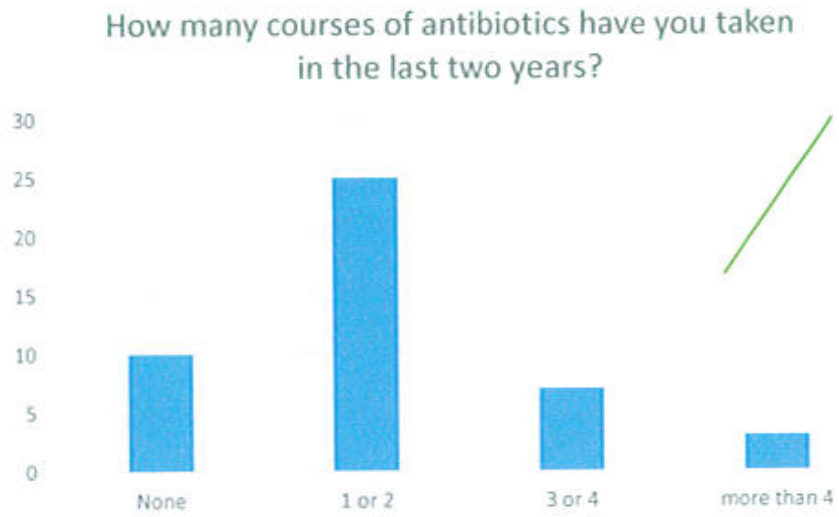
The vast majority of people were not on long term antibiotic treatment



The mean value calculated was 3.32 (calculated by multiplying the frequencies by the rating and dividing by 50). The mode value was however 4 which was the most popular answer, showing a greater proportion of people think ABR is a significant problem.



Comparing these ratings shows that people who are involved in science are more aware of the size of threat posed by ABR this shows that greater awareness needs to be raised against people who are not from a scientific background.



The modal value is between 1-2 with more than 3 being an exception. This shows that there is not a significant amount of overuse of antibiotics.

Summary of primary research:

- My primary research agrees with source 9 that the awareness of antibiotic resistance is growing among the public.
- It also suggests that people from a more scientific background are more knowledgeable and aware of antibiotic resistance, with the all people involved in science (in question 3) rating antibiotic resistance threat at least a 3 or more. It shows a distinct lack of understanding for people not from a science background
- My primary research doesn't necessarily agree with sources 13,9 and 12 that an over use of antibiotics is causing resistance as from my data this doesn't seem to be the case. As most people have taken maximum of two antibiotic treatments in the last two years.

INTERVIEW

To continue my primary research, I am going to interview a family friend, Debbie Stringer, who is senior nurse at the local hospital – Addenbrookes, in Cambridge. She is in charge of after surgery care for patients. As a member of the frontline team fighting ABR in clinical settings I wanted to have her opinion on how severe the problem of antibiotic resistance is in hospitals and what are the consequences she has experienced in her career as a result of it. I wanted to know if the threat that the media and scientific reports are hyping up is having consequences in the hospital. This is a neat version of the questions I asked and answers she gave:

1. In your opinion, is antibiotic resistance a significant problem nationally?
   Increasingly so, it seems more far more of a problem the last few years than it was when I started working in hospitals 30 odd years ago.
2. Is it a significant problem in your hospital?
   Not that I am aware of, obviously we are all aware that if for instance hygiene was of a lower standard then antibiotic resistance may cause more of a problem and I suppose it's in the back of our minds however with strict hygiene and prescriptions we encounter it less often than some other hospitals. Its not to say that we don't have cases of antibiotic resistance, they're definitely not uncommon but to say it's a major problem in my hospital is an

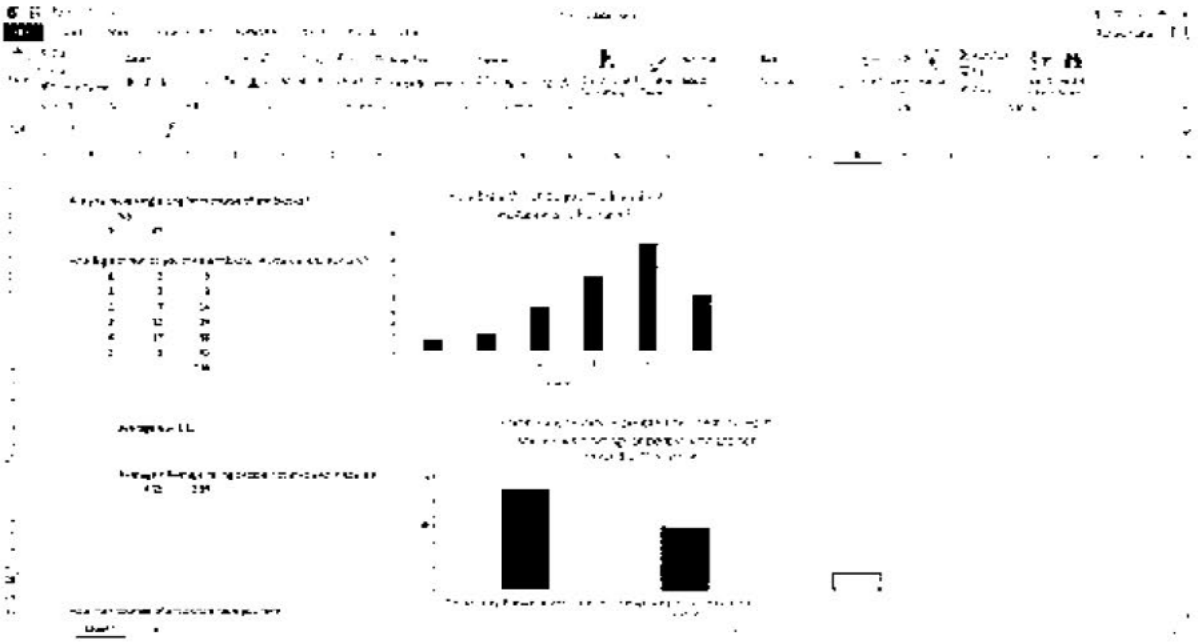
exaggeration. In general it is older or weaker patients who are already very ill which are most affected by antibiotic resistance.

3. So are there regular occurrences of infections caused by ABR micro-organisms?
   Erm, not really really often but they're not uncommon, in younger less ill patients it is far less common for them to be seriously affected by resistant strains, but more ill patient's condition can deteriorate rapidly if affected by antibiotic resistant strains as their immune system is already compromised so they are reasonably common in older weaker patients. Before we started screening patients for MRSA before planned surgery cases were much more common.
4. What is the level of awareness and knowledge of health care providers and the public?
   It is generally high and everyone working in my clinical setting is aware of how to prevent ABR spreading. It is normally a case of strict hygiene to stop us spreading microbes from patient to patient. Doctors and consultants prescribing the antibiotics have always been aware of the consequences of inaccurate or unnecessary prescriptions, but now in more recent years take more action to purposely refuse patients asking for prescriptions of drugs they don't need.
5. Do you think the hospital might be missing cases of ABR here and there? For instance because of poor monitoring and using broad spectrum antibiotics?
   In the vast majority of cases no, samples of microbes from the patient are sent to the lab for testing if the patient does not see immediate improvements or are significantly ill especially if infection is found after an operation; this means unless the patient makes an immediate recovery, we catch cases of ABR strains. Broad spectrum antibiotics are being used less frequently now in favour of more narrow spectrum, specific ones as well as increasing use of combinations of drugs. I think the monitoring of levels of resistance could be improved, however with financial cuts and the hospital exceedingly busy there is not enough resources or man power to take the numerous samples and collect the data needed. We have an overall awareness of the level of antibiotic resistance but this is often more form practical experience in discovering that a stronger dose or more combinations of drugs are needed to fight an infection.
6. Are you aware of any local, national or regional AMR containment efforts?
   Within our hospital there are guidelines and these are based on reports and initiatives ordered by the government and minister of health. I'd say they're more general hygiene practises that should be carried out regardless to ensure recovery of patients but obviously they help stop the spread of ABR too. I think local level efforts have far more effect and are more impacting as they work closer to home; the government sets the overall goals but it should be up to local hospitals which have their unique set of frequencies of ABR stains occurring exactly what action to take.
7. Are there efforts to improve hygiene to avoid the spread of ABR?
   Hygiene levels are quite high already and everyone tries their best to do their bit, for most people it's in their interest to wash hands and wear scrubs etc as they don't want to get till either so I'd say nearly everyone follows the hygiene standards to a high level.
8. How often in general do prescribers send samples to the lab for culture and sensitivity testing?
   Quite often, probably not as often as should happen but there are limited resources and man time to handle the number of samples should every patient get a culture grown. Probably about 75% of the time and in the patients that don't get a sample the doctor already has an accurate idea of what is causing the infection.
9. Do you think a rapid diagnostics test would help doctors prescribe more appropriate drugs?

Yes, there's been talk of that and I think it would really help because at the moment there's a lag between the time of prescribing a drug and when a doctor gets the sample taken back from the lab. This means often the wrong drug has been prescribed meanwhile, which obviously helps to develop ABR. Also if it told what level of resistance, doctors could prescribe drugs they know would be effective on the microbes.

SUMMARY OF FINDINGS:

- ABR is an increasing problem in hospitals – more cases are arising
- There is a lack of monitoring the levels of resistance occurring – often going on experience rather than scientific knowledge
- Diagnostics tests would be useful and could be practical



To interpret my primary data, I used excel to make bar charts so that the results of the data could be seen and understood easily.

CONNECTING SOURCES TOGETHER

24

Analysing Sources with Connect-Extend-Challenge

Section 1.1 – How does antibiotic resistance occur?

- Where does it come from?
- Where do resistance genes come from? – does this make them a larger threat

CONNECT new material to other sources and prior knowledge, relate:

- In common with other researchers, Source 4, Microbes and Man, shows random mutation in the sequence of bases in the DNA of an organism causes DNA of microbe to change and can be beneficial, resulting in ABR.
- Sources 1 and 7 and others agree that these mutations are rare, however man made selection pressures are responsible for creating a 'pandemic problem' as stated in source 1.
- These resistance genes (R genes) often come from the environmental gene pool – the origins of R genes - as Source 2 suggests, can be 'captured and expressed' as resistance in any microbe. An e.g. of this in Source 2 was when actinomcytes were screened for resistance against 21 antibiotics, significant numbers of strains were resistant to 7 or 8 antibiotics showing naturally occurring multi-drug resistance genes occur in nature, this is backed up by source 1 – 'some soil bacteria are naturally resistant to most known antibiotics'; and by source 8 – 'ancient bacteria dug up recently from permafrost found to be resistant to modern antibiotics' as well as source 11, these show that the genes are in the environment to begin with, making antibiotic resistance inevitable when selection pressure is applied – so this threat will always be there. Furthermore to support this inference, source 11 agrees the r genes are found in the environment because the mechanisms, genes and pathways of antibiotic production and resistance help microorganisms compete for niches in nature, therefore they represent normal evolutionary phenomena.

EXTEND the story so far, say what's new:

- Biofilms
- Source 17 goes further to detail the rates of bacteria mutation and reproduction to support the ideas in Source 1 that this is a serious problem as source 17 shows the rate of bacteria mutation is rapid as 300 mutations can appear in a population of bacteria within 10 hours.
- Source 5 agrees with other sources about mutations causing bacteria to become resistant to drugs, it goes further to explain these types of mutations which make it drug resistant; for instance losing the target for the antibiotic or making it inaccessible or chemically damaging or pumping out (using efflux pump) the drug. Some are more general adaptations – efflux pump – and being gram negative bacteria as thicker cell wall and work for a range of antibiotics, this matches with source 2 that bacteria can be naturally resistant to several antibiotics – an efflux pump could be responsible.
- Furthermore to support this inference, source 11 agrees the r genes are found in the environment because the mechanisms, genes and pathways of antibiotic production and resistance help microorganisms compete for niches in nature, therefore they represent normal evolutionary phenomena.

CHALLENGE the position, note the issues which remain or arise:

- Source 2 says there is little evidence that r genes found in the environment have been mobilised into pathogenic bacteria and expressed as resistance phenotypes. Source 11 agrees with Source 2 that the 'ecological impacts and roles of these r genes and mutations [found naturally] are not well understood'. However sources 1, 10, 7 and others all suggest the genes can be transmitted across to pathogenic bacteria and this is where the r gene come from as well as mutations. However in another part of the source, source 2 suggests B-lactamases enzymes (destroy B-lactam antibiotics) have been found in 'remote and desolate environments' and 'implies novel B-lactamases...occur in environment' so overall there is limited evidence but it can be interpreted that r genes to originate from environment. Moreover, source 11, fully supports this as it explains that B-lactamases enzymes are forms of penicillin binding proteins, suggesting that the enzymes that destroy antibiotics can be part of the existing machinery of wild type bacteria.
- Source 2 says that acquisitions of resistance is not a serious energy cost to microorganism so strains, however this contradicts with source 10 that mutations with resistance can 'compensate for bacterial fitness'. These sources are in direct contradiction however source 10 seems more accurate as it carried out experiments to prove this so would have access to primary and secondary research.
- Source 2 disagrees with source 17 as it suggests mutations are rarer than suggested by source 17 – in study with S.aureus only 35 mutations were identified in 3 months, source 17 suggests in a strain of microbe 600 mutations can have occurred in one day. Source 17 also disagrees with source 7 which says 'mutations...do not occur very often' in bacterial chromosome. However, I know from my as level studies in biology that bacteria reproduce rapidly so mutations although not common, because there are so much bacteria in a given population mutations are common – say 300 mutations in a population sounds common but in a population of 1 billion bacteria the percentage is very low.

Section 1.2 – How does antibiotic resistance occur?

- **How does antibiotic resistance genes spread between organisms and why does this make antibiotic resistance such a threat?**

CONNECT new material to other sources and prior knowledge, relate:

- According to source 1 and 11 state these mutations can be spread either parent to offspring (producing genetically identical offspring) or by using plasmids, circular pieces of DNA called plasmids, to transfer genes horizontally ('neighbour to neighbour'). In line with source 2, Source 1 and source 11 suggest horizontal gene transfer is the most common mechanism through which ABR arises and this 'unique ability makes bacteria an even greater threat', which agrees with source 2 which says 'r genes with efficient horizontal gene transfer...are next to impossible to control.' This supports source 3 which explains that plasmids are 'highly mobile' so can transfer genes to many different bacteria, making ABR a greater threat as hard to control and happens quickly. It seems this property of bacteria makes it easy to spread resistance genes across organisms of the same and even different species (including between gram positive and gram negative bacteria) as Source 7, 4 and 11 suggest, making in a large threat as one species can pass resistance to one another.
- All sources agree that methods of transferring genes and acquiring genetic variation between organisms are conjugation, transmission, and transduction.
- What makes the mutation become so dominant within a population is when selective pressure is applied (using antibiotics); as Source 17 gives the impression of, if there were no antibiotic present, the drug-resistant phenotype would fare no better than any other bacterial phenotype so wouldn't flourish, when antibiotics are used they have selective advantage and survive, this agrees with source 11 and other researchers that humans apply a selective pressure encouraging resistance to emerge favouring both 'naturally resistant' and 'acquired resistant' strains. Other sources support this idea that although bacteria can transfer genes between themselves, by applying a selective pressure (antibiotics) only the ones with mutations to survive the antibiotics survive and multiple and pass by HGT their genes on, as explained in a diagram in source 12.
- Further supporting this idea that this is an evolutionary process catalysed by the use of antibiotics is Source 2, which suggests that the slow, random evolutionary process of acquiring antibiotic resistance has been intensified by anthropogenic influence.

EXTEND the story so far, say what's new:

- Source 11 explains the importance of plasmids further, agreeing with other sources of the fact that plasmids make gene transfer very rapid, it also explains that many genes can be tolerated on the conjugative plasmids, this agrees with source 5.
- Source 4 and 6 explain further the process of horizontal gene transfer. Conjugation of bacteria means 'male' bacterium donate DNA (normally plasmids) to 'female' precipitant bacteria giving her new genes which become hereditary; transformation is rarer – bacterium in suitable state (e.g. abrupt cooling) take up raw DNA from surroundings and builds some of it into its own DNA; transduction is when bacterial virus carries some DNA from previous host into new host and later survives and uses imported DNA which becomes hereditory.

CHALLENGE the position, note the issues which remain or arise:

- For this section, sources agreed on vast majority of it.

Section 1.3 – How does antibiotic resistance spread globally?

- What are the selective pressures?
- Do resistant populations in environment have a relationship with those for hospitals?

CONNECT new material to other sources and prior knowledge, relate:

- Source 3 states that 50% of antibiotics used globally are in farming, this is supported by Source 1 which suggests that the overuse of antibiotics on farms, even on healthy animals, acted as an 'incubator for multidrug resistance' as bacteria in the guts of animals acquired strong resistance and therefore shortened the lives of antibiotics. This inference was strongly supported by source 19.

- In source 1, the over use of prescriptions is suggested as a selective pressure of antibiotic resistance, it claims 'half of antibiotic use in humans is unnecessary' and are used for viruses and cold/flue as well as being used 70% of time for acute bronchitis even though medical guidelines state it is not needed. Furthermore, inaccurate prescriptions are being given as consultants have to wait two days until proper diagnosis, increasing levels of resistance. These ideas are in agreement with source 12 and source 2; source 2 has a diagram showing the inconsistencies of antibiotic prescriptions per 1000 people in each state of the US – it showed that doctors in different places prescribed different amounts of antibiotics, this agrees with source 1 that unnecessary or incorrect prescriptions are given.
- Source 2 and 11 suggest the dumping of unnatural xenobiotic substances - non biodegradable – into the environment causes a rich reservoir of r genes: the genes are frequently carried as genomic islands on transmissible plasmids and provide ready sources of resistance genes. Diagrams in source 2 and source 12 show the cycle of r genes in world, go from animal to animal, meat, soil, water systems, commercial, human community etc. This is supported by source 11 which confirms that selection take place anywhere an antibiotic is present, including waterways, farming and also points out that antibiotics are stable substances (non-biodegradable as source 2 says) so remain present in an environment as a selective pressure for a long time.
- These ideas are illustrated in source 2 – water samples taken downstream from water treatment plant showed more resistant bacteria to new and old antibiotics and some of the genes found are in clinical settings so, it shows there is a relationship between resistant populations in the environment and ones in clinical. A lot of E. Coli and K. pneumonia found – predicted to the

next superbug after overtaking MRSA – so finding them in the environment is very concerning – big threat. Source 19 even says that 'we would expect some to migrate to human pathogens.'

- **PRIMARY RESEARCH** – my primary research – interview with nurse – agreed with sources 1,12, and 2 that inaccurate prescriptions are often given as there is no way of being able to tell immediately which microbe is causing the infection, this is very good supporting evidence as it is from someone that works in a hospital setting.

EXTEND the story so far, say what's new:

- In source 19, it explains that antibiotics in farming in US and other countries other than EU are still permitted. In china, using the amount of a gene common to all bacterial in the sample as a measure of the total bacteria present, a study established how many antibiotic resistant genes there were for a given number of bacterial cells. They found 149 ARGs in farm samples that between them are resistant to all classes of AB – levels were 28,000 fies compared to not taken from farms. This shows that antibiotic resistance is increased in levels by using antibiotics in farming, which agrees with source 1 and 3.

CHALLENGE the position, note the issues which remain or arise:

- Source 16 unlike any other sources, suggested that pollution in waterways and environment are also selective pressures for resistant bacteria, not just acting as reservoirs of genes as source 1,2 and others have agreed. From source 16 it says heavy metals, detergents and low level biocides – pollution selects for genes located on mobile transposons of plasmids.
- Unlike other source, source 9 suggests that the global travel of people from countries with lower stewardship like India and Peru spread highly resistant strains that have had no monitoring; in these countries people treat themselves fake or weak drugs and are not given prescriptions. This contradicts other sources, source 12 for instance, which suggests that strains of resistance differ regionally and geographically, implying that global travel and globalisation has less impact on spreading strains of all types across the globe.

Analysing Sources with Connect-Extend-Challenge, and notes on sources 13, 15 and 17.

Section 2 – IS THE RATE OF ANTIBIOTIC RESISTANCE INCREASING?

- Data and statistics to show antibiotic resistance is increasing and getting worse – shows threat is increasing
- What factors affect the rate of emergence of antibiotic resistance
  - Biological factors
  - Environmental factors
- How is the rate of antibiotic resistance emergence is measured and are these effective?
-

CONNECT new material to other sources and prior knowledge, relate:

- All three sources agree that the threat of antibiotic resistance is increasing. One of the most common resistant infections is cause by methicillin resistant S.aureus (MRSA) and Source 17 shows that the number of resistant infections has increased by 300% in 10 years time to 63% of reported staph infections in US were caused by MRSA, this factual statistic is repeated in source 12, so it should be fairly accurate. Source 12 continues by saying that VRSA (vancomycin-resistant S. aureus) is now a concerning threat (agreeing with source 13) which means S.aureus is becoming resistant to last line of treatment antibiotics. Source 13 supports source 15, 17 and 12 in that bacterial resistance is increasing at an 'alarming rate'. However my primary research indicates that it is not as alarming an increase as these sources suggest, these sources are written as reports to educate the public and people working in the health sector so they are likely to be exaggerating, this means that antibiotic resistance is definitely increasing but perhaps not as rapidly as sources 13 and 15 in particular give the impression of. Sources 13, 15 and 12 all agree on which are the most urgent threats caused by antibiotic resistance :
- ▪ Clostridium difficile – Source 13 goes further to explain the seriousness of c. dfficile in causing 14,000 deaths and being the most common cause of antibiotic resistant diarrhoea. This statistic is also used in source 12; and source 12 explains that deaths related to C. difficile increased 400% between 2000 and 2007, in part because of a stronger bacteria strain that emerged. Again strengthening the argument that antibiotic resistance in increasing.
- ▪ Carbapenem-resistant Enterobacteriaceae (CRE)
- ▪ Drug-resistant Neisseria gonorrhoeae

The table below from source 13 shows the consequences and seriousness of the antibiotic resistant infections, this information can be used in support of the earlier inferences that antibiotic resistance is a major threat

Minimum Estimates of Morbidity and Mortality from Antibiotic-Resistant Infections*

Table removed for copyright purposes

ction 2.2/3

- Source 13 - limitations of collecting data – for many species of bacteria, there are no standard definitions that allow for dividing the species into only two categories – resistant vs. susceptible without regard to a specific antibiotic
- The distinction between an antibiotic-resistant infection leading directly to death, an antibiotic reistant infection contributing to death, and an antibiotic resistant infection related to, but not directly contributing to a death are usually determined subjectively depending on each case
- The estimates for number of deaths are underestimates because the risk of death following infection with strain of resistant bacteria is greather than that folloing infection with a susceptible infection. But lacking data, lower estimate used
- For some pathogens only certain stats have been used, eg in acute care hospitals or requiring hospitalisation.

Source 15 states that MRSA is an increasing threat, however source 13 **disagrees and contradicts** this by suggesting that although MRSA infections can be very serious and the number of infections is among
the highest of all antibiotic-resistant threats, the number of serious
infections is decreasing and there are multiple effective antibiotics for treating
infections. If MRSA infection rates increase or MRSA strains become more resistant
to other antibiotic agents, then MRSA may change from a serious to an urgent
threat.

Bacteria commonly causing infections in hospitals and in the community

Table removed for copyright purposes

This chart from source 15 shows that a) only about half the member states contributed data showing a lack of integration and complete coverage of the pattern of resistance, and b) that the vast

majority of countries which did report data had high levels of resistance (over 50%). It is worth noting however that the countries missing data add to the concern.
Also, **In agreement with source 10**, it suggests that stronger, last resort drugs 'further accelerate development of resistance'.

I will further interpret this data to use in my dissertation.

CHALLENGE:
In source 10, it is made clear that a stronger selection pressure promotes cross-resistance more than a mild selection pressure does. However in Source 11, it infers that a lower concentration of antibiotic resistance makes bacteria more prone to develop resistance in the future.

MID PROJECT REVIEW

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Mid project Review

What have you achieved in you project so far?

- Skills learnt → I have learnt how to handle sources which are very long and quite technical. I did this by condensing the sources into keyfacts and quotations, using the Cornell method and by making bullet points. Furthermore, I have learnt how to compare sources and contrast them which enabled me to synthesise the material into one more reliable & stronger argument. Also, I have improved my self-motivation skills, as at the moment I have been completing EP every few days. I have really developed my knowledge in microbiology and immunology, both have been very interesting.
- Knowledge
- progress

What have been the main strengths and weaknesses of your planning, organisation and time – management?

- Strengths – adapting and overcoming problems – sources to complex/disorganised
- Weaknesses – time management, lack of direction in dissertation - aims

At the moment I am on target but behind with my timeline but have made lots of progress.

My strengths have been source work and organising my sources and dissertation according to sections of my dissertation. This was because I collected so much source material, that I had to sort it into relevent sections to make it easier to compare sources. I have managed to adapt to problems such as sources being too complicated by looking at easier sources first to gain foundation knowledge a the topic & looking up difinitions. I also overcame the problem that some of my notes were irrelevent + repeated in the connect-extend templates by incorporating both into one document.

What problems or difficulties have you encountered? How have you overcome them?

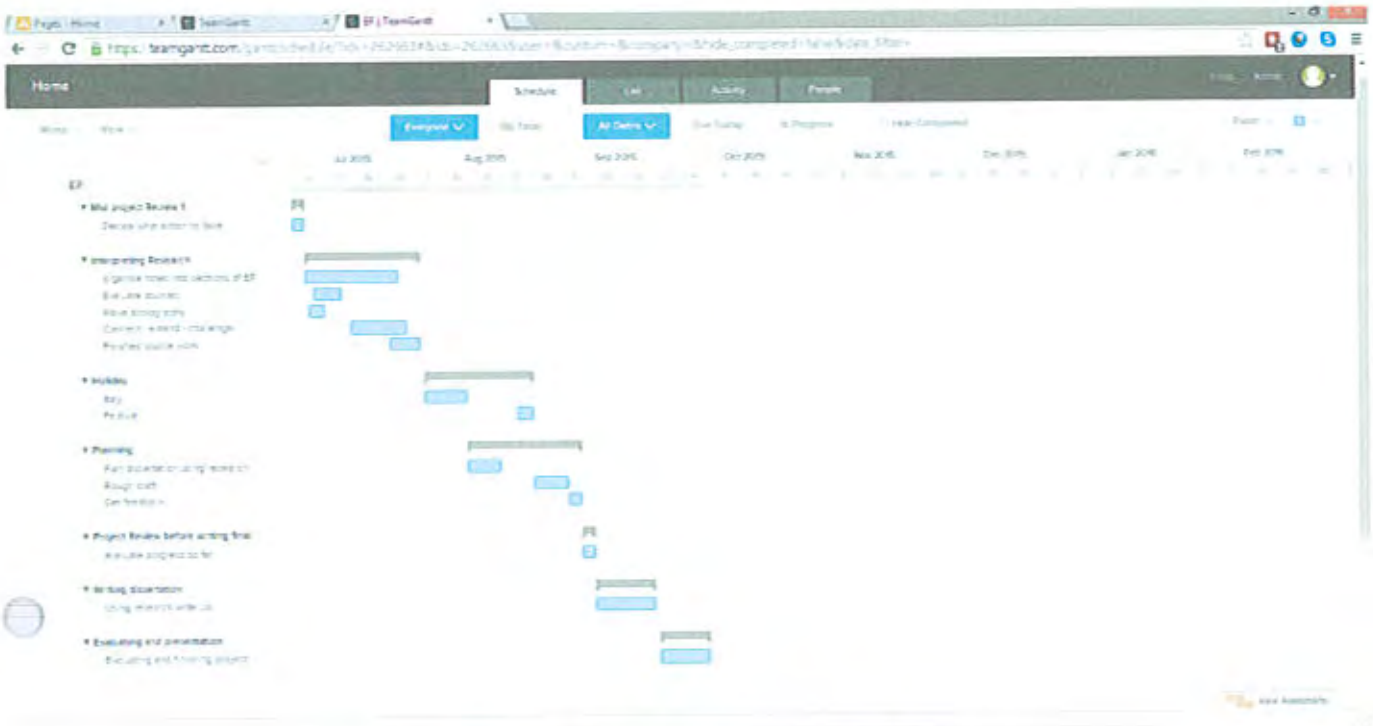
- Time management has been a weakness and something I have found difficult due to college + other non-college commitments. To overcome this, I have started a new time line with the areas I have left to complete and starting from now with re-adjusted timescales. This means I can now see where I am at and know whether I realistically going to finish on time. The newly adjusted timeline was made online & is on next sheet.

What is left to do on you project? How will you go about completing it and handing it in on time?

- So far I have completed the majority of source work; I still need to complete connect-extend-challenge templates but after that I will be ready to start composing my final dissertation.

Another problem I have encountered was that parts of my planned dissertation were lacking focus & structure, however, I overcame this by

DO24 ✓



This is my new timetable to complete E.P. on gantt.com.

PLAN OF DISSERTATION

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Dissertation Plan:

Now I have gathered research, I am going to thoroughly plan my literature review so it answers the overall question of 'how significant is the threat of antibiotic resistance to humans?' in a logical and thorough way.

Using my aims and objectives of the dissertation I thought of earlier, and slightly altering them, I have a brief overview of what each section will include and key points or questions to answer within it as well as references to sources I know contain the information.

INTRODUCTION:

- Introduce the problem of antibiotic resistance by explaining the importance of antibiotics and how they work and then explaining what antibiotic resistance is in basic terms
- Then go on to explain the consequences of antibiotic resistance and what impacts this could have on human society.
- Then introduce the fact that antibiotic resistance is increasing and is becoming major threat and 'unpack' the title and how I will approach the topic.

SECTION 1 – WHAT CAUSES THE EMERGENCE AND SPREAD OF ANTIBIOTIC RESISTANCE?

- Explain how antibiotic resistance occurs - mutations, explain that resistance genes can be found in the environment and this is often source of them – the threat is inevitable, and occurs in nature
- How does antibiotic resistance genes spread between organisms and why does this make antibiotic resistance such a threat?
- How does antibiotic resistance genes spread globally? – If bacteria can become resistant anywhere in the world they are a greater threat

SECTION 2 – IS THE RATE OF ANTIBITOTIC RESISTANCE INCREASING AND WHAT EFFECTS THIS?

- Data and statistics to show antibiotic resistance is increasing and getting worse – shows threat is increasing
- What factors affect the rate of emergence of antibiotic resistance
  - Biological factors
  - Environmental factors
- How is the rate of antibiotic resistance emergence is measured and are these effective?

SECTION 3 – SOLUTIONS TO OVERCOME ANTIBIOTIC RESISTANCE

- What can doctors and patients do to prevent resistance?
- What research and new solutions are being researched?
- What stage are these solutions – will it be too late?

CONCLUSIONS –

- How significant is the threat of antibiotic resistance?
  - Contrast and compare sources

After planning this outline I started to interpret my sources in more detail. I used connect-extend-challenge templates to connect sources together and compare them to each other. I brought the

interpretations of the sources together to make a final judgement of each section of the dissertation. So where it was appropriate, I compared sources together for each particular section. This meant it was focused and clear and can be used to write a draft of my dissertation. After interpreting and analysing my sources, I tweaked my essay plan to fit the research better and flow more easily and answer key questions. I also researched how to write a good literature review and found the following key concepts:

- Be critical of what has been written, raise key questions, and identify areas in need of more research
- A short clear intro should include outline of the review, including the main topics covered and the order of the arguments, with a brief rationale for this
- Each paragraph should be organized around and related directly to research question you are developing; there should always be a clear link between your own arguments and the evidence uncovered in your reading. Include a short summary at the end of each section
- Acknowledge opinions which do not agree with your thesis. If you ignore opposing viewpoints, your argument will in fact be weaker.
- Compare, contrast and evaluate sources
- Synthesis – bring together source material as an integrated whole – in this case structured review and coherent argument for the study that you are doing.

INTRODUCTION:

- Introduce the problem of antibiotic resistance by explaining the importance of antibiotics and how they work and then explaining what antibiotic resistance is in basic terms
- Then go on to explain the consequences of antibiotic resistance and what impacts this could have on human society.
- Then introduce the fact that antibiotic resistance is increasing and is becoming major threat and 'unpack' the title and how I will approach the topic. – Mini rationale

SECTION 1 – WHAT CAUSES THE EMERGENCE AND SPREAD OF ANTIBIOTIC RESISTANCE?

- Explain how antibiotic resistance occurs
  - Mutations – rate of mutation and reproduction of bacteria means antibiotic resistance occurs rapidly and easily under selective pressure
  - Naturally occurring R genes found in environment
- How does antibiotic resistance genes spread between organisms
  - Clonal replication
  - Horizontal gene transfer
  - Selection pressure
- How do antibiotic resistance genes spread globally?
  - What are the selective pressures
  - Do resistant populations in environment have a relationship with those in hospitals?

SECTION 2 – IS THE RATE OF ANTIBITOTIC RESISTANCE INCREASING AND WHAT EFFECTS THIS?

- Data and statistics to show antibiotic resistance is increasing and getting worse – shows threat is increasing
- What factors affect the rate of emergence of antibiotic resistance
  - Biological factors
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- How is the rate of antibiotic resistance emergence is measured and are these effective?

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- What can doctors and patients do to prevent resistance?
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- What stage are these solutions – will it be too late?

CONCLUSIONS –

- How significant is the threat of antibiotic resistance?
  - Contrast and compare sources

SOURCE EVALUATION

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DATE	SOURCE USED (numbers refer to bibliography)	BRIEF SUMMARY/DESCRIPTION OF SOURCE	WHAT WAS I HOPING TO FIND OUT?	SUMMARY OF WHAT I'VE LEARNT AND HOW HELPFUL IT IS	RELIABILITY OF SOURCE	CROSS REFERENCES WITH OTHER SOURCES	WHERE NEXT?
05/06/14	Source 1 – article in Harvard Magazine: Superbug: An Epidemic Begins	It describes the problems of antibiotic resistance and what can be done to solve it.	How does an antibiotic resistance epidemic begin, where does it originate from – animals/humans/clinical setting or community – and how does it spread.	Very useful source; learnt sources of resistance and how rapidly it can spread from animals to humans; about bacteria plasmids; good statistics; about overuse of antibiotics in farming and prescriptions and how these can be overcome. However, article covered broad topics, so aspects were quite general and not detailed enough, for example the paragraph on bacteria acquiring genes was very brief.	Source is very reliable as published by top medical school of top Harvard university in America so has scientific contributions and access to science journals to write article. Also is up to date published very recently (June 2014) so up to date information and statistics. It is written for a reasonably academic audience – readers of science magazine so should be accurate.		Find out more about the genetics behind how bacteria acquire mutations and spread these to other bacteria. Investigate biofilms and how these effect rates of resistance.
07/06/14	Source 2 – article from science journal *Microbiology and Molecular Biology* from 2010 – Origins and Evolution of Antibiotic Resistance	Article from science journal explaining in depth how resistance spread from genes in the environment to clinical settings	How bacteria evolve and spread resistance and where to the genes to do this come from	Details of how genes arise in natural environment meaning there is constant threat of pathogen developing resistance, however it is human selective pressure that has made resistance a problem; I learnt that the genes for resistance are abundant in nature.	Very reliable as has all sources referenced and accessible, it is written in 2010 so perhaps not as up to date as others but as there are few statistics in this the methods of gene transfer for example will be the accurate. It is written for an academic audience as in a science journal so information should be accurate.		I want to know how these genes arise in the first place – is it mutation? And the mechanisms of transferring genes briefly mentioned – conjugation eg;
07/06/14	Source 3 – book 'Deadly Companions' by Dorothy H. Crawford published 2007	Story of how human evolution is entwined with that of microbes and how we will never be able to overcome our 'deadly companions'	Why antibiotic resistance makes microbes so deadly – what abilities do they that enable them to adapt to antibiotics	Brief overview of process of requiring genetic resistance and uses of antibiotics in farming; also what affects the rate of antibiotic resistance emergence – is it economically or geographically decided? This source wasn't as useful as anticipated, very general and less about science behind resistance more on politics	The author is a Professor of Medical Microbiology at the University of Edinburgh; also a research Fellow of the Academy of Medical Sciences and others. This suggests the facts in this source are accurate as the author is of a scientific background.		More information but more science based about which factors affect the rate of antibiotic resistance emerging

12/06/14	Source 7 – A2 textbook 'Microbes and Disease'	Overall information on Microbes and Disease, quite general	This source is quite basic, I wanted to use it however as it has useful diagrams which describe and illustrate the process of genetic resistance spreading – conjugating etc as referenced in source 4	The diagrams gave me a far better understanding of the mechanisms of gene transfer between organisms, hopefully I can apply this to my dissertation.	The source diagrams are reliable as this is a book aimed at A2 students, it would have been proof read and had scientific input in writing it.		
16/06/14	Source 8 – digital magazine – Biological Review – by Philip Allan magazines	The magazine consists of reviews and articles on the important matters and discoveries in biology In the magazine; this article described ways we can fight back against antibiotic resistance.	Find out new solutions to how we can overcome antibiotic resistance, cross referencing with other sources to compare how close we are to a solution – closer means less threat from ABR	Very useful section on how we can stop virulence factors in bacteria, as suggested also in source 2. It identifies the stages of doing this and suggests the future is optimistic for lowering the threat of ABR.	Phillip Allan magazines are aimed at an audience of students and teachers, and are written by authors interested in the scientific field of biology, so the information provided should be accurate and not bias.		Need to find other ways to overcome ABR and also compare with this source and source 2 how likely these solutions are to being a reality and hence decreasing the threat of ABR
20/09/14	Source 9 – online podcast of interview with Richard Stabler of London school of hygiene and tropical medicine, September 2014	Richard Stabler talks about the implications of antibiotic resistance and how concerned should we be, and what can be done about it.	I want to find out the opinion of a scientist in the field and see if they are as concerned about antibiotic resistance as other articles and government reports suggest.	It was clear Stabler felt ABR is an increasingly significant problem but also that he did see light at the end and that he was optimistic that things are starting to improve as people become more aware of ABR and its implications	It does not say exactly if Richard Stabler is from a scientific background or government or pharmaceutical so as this podcast is entirely his opinion I must take it with caution as if he were from a pharmaceutical company for example his opinion would be that companies needed investment etc. He is accurate with his information as it compares well to other sources and as it is published so recently and by a well-known publisher – London School of hygiene and tropical medicine, I think this source is fairly reliable.		Richard Stablers interest in the growing awareness of the public made me want to carry out some primary research to see how people in my community know and feel about ABR.

25/07/14	Source 10 – article from Oxford Journal about how strength of selection pressure contributes to ABR published July 2014	Investigates how the strength of selection pressure contributes to the complexity of the ABR and whether it is cross-resistant; describes experiment proving that a stronger or larger dose of antibiotics makes bacteria more likely to evolve resistance and cross-resistance.	For my section 2 of dissertation, I need source material on what factors affect the rate of antibiotic emergence so I hope this source will answer these aims.	Selection strength is important parameter in complexity of a r problem and use of high doses = promotes cross-resistance. And bacteria can develop resistance to antimicrobials they have never been exposed to – causing a major threat to the use of antibiotics	This source should be very reliable and accurate as it is produced by scientists from across the globe and published by the university of Oxford Journals which is a world renowned university with the highest quality research. Also it is very up to date as was published about a month before I accessed it.		I think I need to find out some more factual statistics and evidence for how widespread ABR is globally

Name of mentor:

Teacher comment sheet for student presentation

Student name/Title of Project	Diss Antibiotic resistance.
Style and type of presentation	Prezi.
Communication and presentation skills (eg ability to communicate with a non-specialist audience; clear structure and focus; speaking with clarity; expertise in subject; balance between subject/process)	Clear & confident. Lots of text on some slides so difficult to read. Not very notes
Communication of the process of the Project (eg does the student talk about planning, time-management, the process of independent research, source analysis, problem solving and decision making)	Good overview of why done topic → uni application. Planning & time management discussed. Had to do 2nd Gantt chart to aid organisation. Research - primary / secondary. Had a variety of sources to see if agenda affected info.

Activity	Date	Detail	Supervisor's initials	Comments
16. What have you changed after reviewing your work?		I reorganised my notes from sources into more relevant sections and decided to disregard some sources as they were irrelevant and unreliable. This made it much easier to manage source material and meant I had less to sift through when writing up the dissertation.		
17. Final phase - Do you feel that you have achieved all of the outcomes/objectives of your project?		I feel I have achieved most of the skills and outcomes I wanted to achieve. I think my time management skills still need improving as I tend to leave bits to the near the deadline but my time keeping has improved. I do however feel that the final dissertation could have been improved – the middle section lacked direction. I have definitely improved my source skills and IT skills which I can use and apply to other situations and future projects, especially at university.		
18. Presentation of Portfolio • written section (compulsory, even if the outcome is a performance or artefact) • other evidence can be DVD, photographs, slides, CD, artefact, digital technologies etc		5000 word dissertation and accompanying planning and source material.		
19. Describe how you have presented your project to an audience		'Prezi' (presentation software); presentation displayed main points and no extra notes were used apart from a print out of the presentation.		

OCR Project Progression Record 08.01

Activity	Date	Detail	Supervisor's initials	Comments
20. Have you evaluated your project, taking into account any feedback from your audience?		The project and each section has been evaluated, looking at the parts which I did well and ones which I learnt from/would do better at next time. As well as identifying skills developed. I also took into account feedback from the audience, who said I seemed to have learnt a lot from completing the EP.		
21. Date of project submission to teacher		6th October 2014		

Notes

This form should be used to record the progress of each learner and may also assist in forming a basis and justification for the mark awarded under each assessment criterion (for example, by indicating the level of support needed by the learner).

At Level 3 it is not intended that the supervisor gives any written feedback to the learner in the comments section. *Verbal feedback may be given by the supervisor; this should not be recorded on this form. Learners may use the comments section for taking notes.*

A copy of this form must accompany each learner's work when it is submitted for Moderation.

OCR Project Progression Record 08.01

EVALUATION OF EP:

PLANNING

I think my planning of the project was not realistic at first, as sections took longer than I expected. However after changing my project to a dissertation after realising my artefact was too ambitious in the time scale and with science being more relevant to my future university application, I was able to reschedule my project timeline in a way that ensured it would be complete in time. The way I broke the stages of the project up in a Gantt chart worked well as it meant I could see if I was on target or not to finish by the deadline. Furthermore, my project diary was filled in weekly and recorded any changes to the project and gave me the next step I should do, this meant that each session spent on EP I knew exactly what needed to be done and what had already been completed which meant sessions were more focused so this worked well.

RESEARCH

My research was a strength of my project as I used a wide range of sources, including podcasts, articles and books. I also took high quality detailed notes of the sources using methods which were new to me such as the Cornell note making method. A lot of my research was in topics I had not covered before so they were quite challenging at time and I had to refer to textbooks and a teacher to fully understand them. To improve my research I would carry out more primary research using a larger sample population and of different backgrounds and ages as the population I sampled were not a very accurate representation of the population of the UK. I would want more specific data about how often and what type of antibiotics were used by people to see if this had a positive correlation with the antibiotics with highest resistance rates. Moreover, to improve my research, I would perhaps take less notes; although the notes I took were very useful and detailed, there was a lot of notes to sift through to find relevant information which meant it was harder to keep up with my projected timeline. I think I analysed how useful and how reliable each source was well and in detail. Some of the sources contradicted each other and I recorded this in my connect-extend-challenge sheets. This I believe was another strength of my project as I cross referenced many sources so I could gather a detailed picture of antibiotic resistance and how large a threat it is.

FINAL OUTCOME

I was pleased with the final dissertation but I think it could have been improved a lot. Unfortunately I did not have time to do more than one good draft of the dissertation, so next time I would (although I had factored it in to my timeline) complete at least two drafts instead of one. I feel I did overall meet my aims and objectives – to investigate and evaluate how serious the threat of antibiotic resistance is to society. I concluded that it was a significant threat although has the potential to become a very serious problem. However I found solutions to this problem, some were low cost and effective. I also met the aim of answering is the rate of resistance increasing, which was yes. But, I neglected to look into how human society suffered as a consequence, only briefly touching on economic and health implications of antibiotic resistance. I feel I learnt a lot about and wrote accurately about how antibiotic resistance arises and this was of particular interest as I would like to study biology at university, so learning about the evolution and genes of bacteria was a highlight.

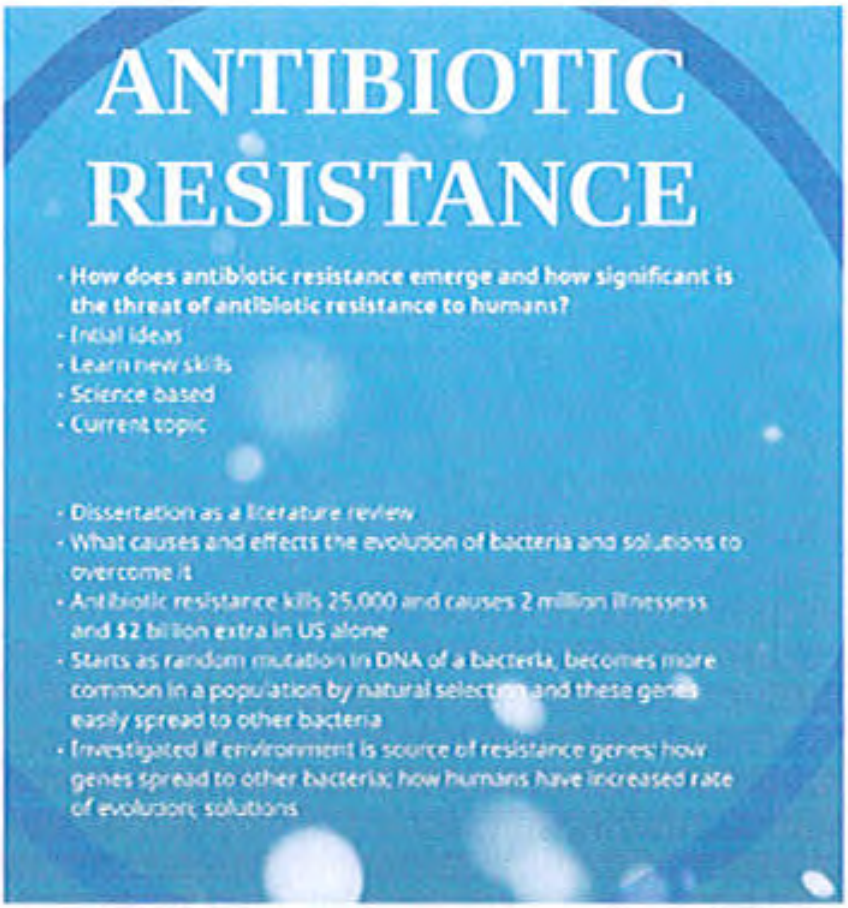
PRESENTATION

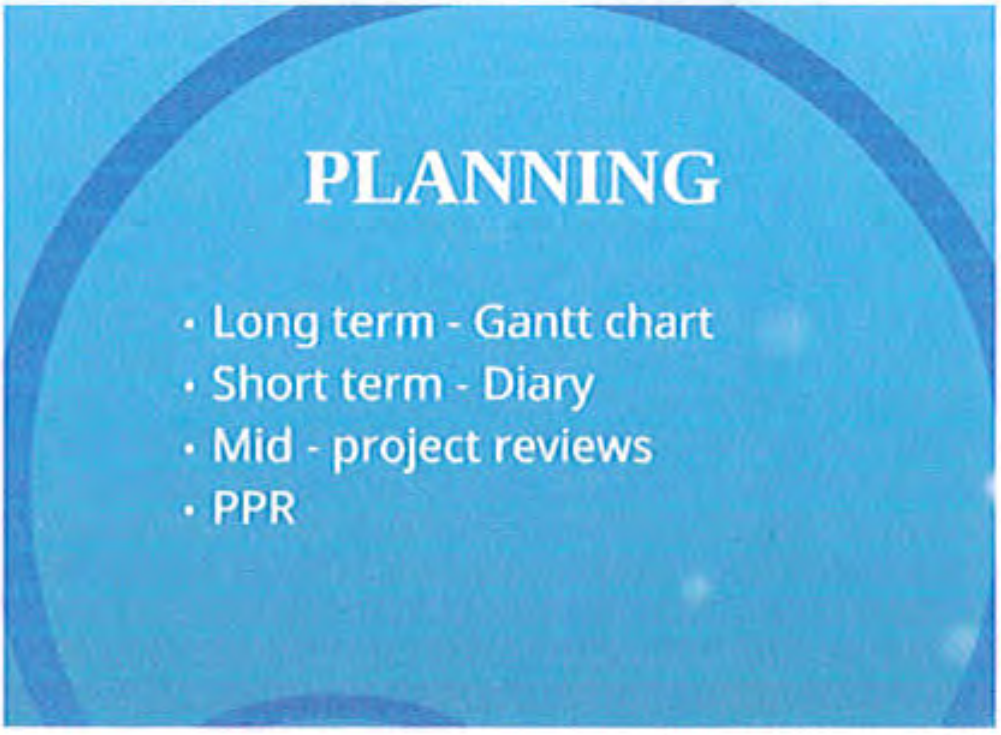
I chose to do my presentation in a prezi format, which is a type of free online presentation software. I chose this format as it has fun animations between slides to keep the audience interested and also effectively connect slides and ideas together so the presentation flows well. It enabled me to have bullet points outlining the main points from which I could improvise what I wanted to say. The audience reaction was overall very positive, commenting that I spoke clearly and loudly and the presentation was the correct length. I know that I could have answered the questions given more concisely as the answers I gave were quite long winded.

TRANSFERABLE SKILLS

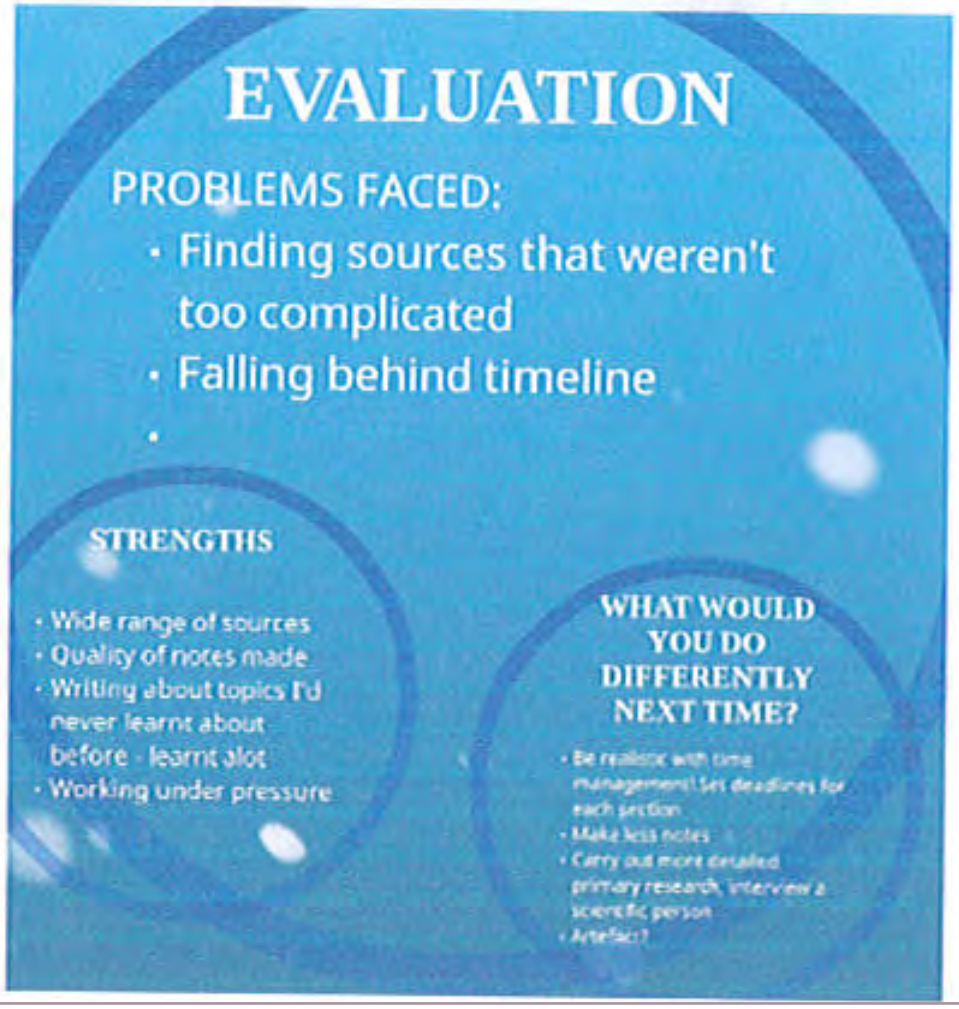
From completing this project I have learnt a range of transferable skills which will be useful beyond a level.

- IT skills
  - During planning I created a Gantt chart using online software I had never used before
  - I also created mindmaps showing how concepts and ideas were interlinked as a form of note taking as it showed key ideas without lots of writing
  - Creating a bibliography on word in the correct format
  - Annotating notes and drawing grids to take notes in using word
- Dissertation skills
  - Note taking was a key new skill learnt, at first I struggled to make detailed concise notes but after learning new ways to take notes like mind maps and the Cornell method I was able to condense large sources into easily manageable notes
  - Working with sources was in some cases challenging as I wanted to contrast and compare them using the connect extend challenge worksheets, this gave me several perspectives from which to write and conclude my dissertation
  - Primary research was also a skill I developed as I found writing questions to surveys and interviews in order to get the specific relevant data I needed hard
- Project management skills
  - Time management was a weakness of my project as at first I fell behind the schedule in place in my Gantt chart. However I managed to overcome this successfully, improving my time management skills by setting realistic targets and changing my Gantt chart according to this. I have learnt that I need to keep myself motivated in long projects like this or I lose motivation and make slower progress, not keeping up to date!


ANTIBIOTIC RESISTANCE
• How does antibiotic resistance emerge and how significant is the threat of antibiotic resistance to humans?
• Initial ideas
• Learn new skills
• Science based
• Current topic
• Dissertation as a literature review
• What causes and effects the evolution of bacteria and solutions to overcome it
• Antibiotic resistance kills 25,000 and causes 2 million illnesses and $2 billion extra in US alone
• Starts as random mutation in DNA of a bacteria, becomes more common in a population by natural selection and these genes easily spread to other bacteria
• Investigated if environment is source of resistance genes; how genes spread to other bacteria; how humans have increased rate of evolution; solutions


PLANNING
• Long term - Gantt chart
• Short term - Diary
• Mid - project reviews
• PPR


RESEARCH
• Primary research - survey, interview
• Survey - public awareness and average use of antibiotics
• Secondary research - articles, science journals, books, podcasts
• Note taking
• Planned essay


EVALUATION
PROBLEMS FACED:
• Finding sources that weren't too complicated
• Falling behind timeline
STRENGTHS
• Wide range of sources
• Quality of notes made
• Writing about topics I'd never learnt about before - learnt alot
• Working under pressure
WHAT WOULD YOU DO DIFFERENTLY NEXT TIME?
• Be realistic with time management! Set deadlines for each section
• Make less notes
• Carry out more detailed primary research, interview a scientific person
• Artefact?


WHAT WOULD YOU DO DIFFERENTLY NEXT TIME?
• Be realistic with time management! Set deadlines for each section
• Make less notes
• Carry out more detailed primary research, interview a scientific person
• Artefact?


NEW SKILLS DEVELOPED
IT skills: Gantt chart, mindmaps, bibliography on word, annotating notes on word, excel, prezzi
Dissertation skills: Source work, note taking, primary research
Project management skills: time keeping, self motivation, planning ahead
Subject knowledge

Commentary

Marks awarded

A01	A02	A03	A04	Total
12	12	22	10	56

What it is about

This is fairly typical example of a medicine/ biology dissertation based project. The topic was chosen as an area of study related to the student's university plans, but was not covered by the student's Biology A level course.

General comments on strengths and weaknesses

This is an excellent project based mostly on sophisticated use of extensive secondary research employing a wide range of academic journal articles that extends the student's knowledge of Biology well beyond A level. The project has been very well planned and monitored and there is ample evidence of critical reflection in a very well used PPR and reflective diary. The dissertation draws clear conclusions based on this research. The dissertation would have benefited from a glossary to explain technical terms. There is a good effort at primary research including a useful interview and a much less useful survey. The survey is the weakest area of the project. There are some limitations in the design, the sample and the analysis of this survey of which the student seems unaware.

Use of the URS and annotation

The teacher's comments on the URS are helpful and give a clear rationale for marks awarded including reference to the level of challenge beyond A Level. It would have been useful to see further reference to particular challenges faced by the student and personal triumphs.

A01

Why the marks were awarded

The mark of 12 given here reflects the degree of independence exercised by the student and the efficiency of both overall and responsive planning of all aspects of the project which is very clearly documented in the PPR and diary. The dissertation is well planned and executed.

Any weaknesses

The mark of 12 is slightly generous in the light of some minor time management issues and the weakness of the survey, although this does not seriously undermine the overall success of the project.

A02

Why the marks were awarded

Full marks were awarded and the comments on the URS are very helpful in supporting the rationale for this. The secondary research is a real strength and includes a very wide range of journal articles and government websites. The primary research interview was incorporated successfully. The student provided good evidence of successful note taking and cross-referencing of sources as well as sophisticated selection and collation of material in the dissertation.

Any weaknesses

There is some confusion about the nature of a bibliography and this is an area for development. The bibliography is actually an extensive list of references in order of use. The primary research has some flaws. A mark of 11 may have been more appropriate, but nevertheless the research element is very strong.

A03

Why the marks were awarded

The mark of 22 for this AO is realistic. Microbiology is a new field for the student and it is clear that she has learned a lot. Skills needed to complete the project successfully are identified early on, their development is well documented and they are used effectively to achieve a well-executed outcome.

A04

Why the marks were awarded

The mid project review and final evaluation are used effectively to evaluate progress and there is some critical reflection informing planning.

Any weaknesses

The teacher's comments on the URS and presentation are useful in supporting the mark of 10. Ongoing evaluation could have been more thorough and there were some minor issues with the presentation but generally, the evaluation of the project deserves its mark in the top band.

The small print

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