Literature review

by Sagari Muraliegaran

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MAST5952 Understanding and Synthesising Research

The Impact of Agricultural Antibiotic Usage on Antibiotic Resistance: Pathways, Public Implications and Policy Considerations

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Introduction

Antibiotic resistance is becoming increasingly severe as a public health concern with the environment, agriculture and human health all being seriously threatened by it. It is a phenomenon that occurs when bacteria resist and become immune to antibiotics, making them ineffective and increasing the likelihood of prolonged sickness and mortality. Antibiotic resistance has been causing one million deaths, at the very least, every year since 1990. This figure is set to rise with predictions stating the number of drug-resistant infection deaths to surpass 39 million by 2050 if nothing is done. *(Antibiotic Resistance Has Claimed at Least One Million Lives Each Year since 1990 | University of Oxford 2024)*.

As antibiotics are not solely used for medicinal purposes but also as growth boosters and preventative agents, their extensive use in agriculture, especially in cow husbandry is a significant reason why this is a worldwide issue *(Manyi-Loh et al. 2018)*. Approximately 80% of antibiotics in the US are used in agricultural and subcultural settings. Subtherapeutic antibiotic administration is one practice that worsens things when selecting resistant bacterial strains in animals used for food and consumption. There are many ways in which these resistant bacteria and their resistance genes spread with the most common ways being direct contact, contaminated food or environmental pathways such as water systems and manure runoff. The widespread distribution of antibiotic resistance genes (ARGs) throughout our ecosystems highlights the importance of addressing agriculture's contribution to this growing issue of antibiotic resistance *(Chang et al. 2015)*.

Understanding how agricultural antibiotic usage and the formation of antibiotic-resistant bacterial infection are linked is pivotal given the complex relationship that exists between human, animal and environmental health. This involves assessing the effects of public health, looking into the process of resistance transmission and putting strong risk reduction measures into place.

Nevertheless, many developing countries lack strict regulations controlling the use of agricultural antibiotics despite the known risks. Due to socioeconomic circumstances and poor regulatory framework, practices such as subtherapeutic doses, selling of over-the-counter antibiotics and the use of antibiotics that are prohibited in certain regions continue. For instance, there is an increased chance of cross-resistance because antibiotics that are often used in animals such as tetracyclines and macrolides share structural similarities with those used in human medicine. This is made worse due to the lack of cross-border monitoring and enforcement.

This report's objective is to examine the connection between the use of antibiotics in agriculture and the development of bacterial pathogens that are resistant to them, investigate the mechanisms by which resistance spreads from agricultural settings to human populations, evaluate the implications for public health in terms of treatment effectiveness, disease burden and mortality rates and suggest possible changes to agricultural practices to slow the emergence and spread of resistance. This study aims to support current international efforts to reduce antibiotic resistance and protect public health by tackling these important topics.

Method

Search Strategy

A systematic literature search was conducted using PubMed to identify relevant studies. Keywords were used to provide thorough coverage of the topic. Search phrases such as:

- “Antibiotics resistance AND agriculture”
- “Antibiotic residues AND bacterial pathogens”
- “Antimicrobial resistance genes AND livestock”
- “horizontal gene transfer AND foodborne pathogens”

The inclusion criteria were:

1. Studies published between 2010 and 2024 to ensure recent and relevant findings.
2. The study focuses on the relationship between agricultural antibiotic usage and antibiotic resistance.
3. Studies on the spread of resistance from agricultural settings to humans or the environment.
4. Peer-reviewed articles, articles, reviews and meta-analyses.

The exclusion criteria included:

1. Unrelated studies on agriculture or resistance to bacterial pathogens that are transferable to humans.
2. Research focused exclusively on clinical antibiotic use without an agricultural context
3. Non-English language articles
4. Grey literature, such as unpublished reports or conference proceedings.

Study Selection

The initial search produced a wide variety of articles. Titles and abstracts were reviewed for relevance and duplicates were deleted. Full-text articles were then evaluated, and those that met the criteria were selected. Priority was given to research that used rigorous approaches, such as genetic study of resistance mechanisms or big datasets from several locations. Studies on transferable antibiotic resistance in foodborne pathogens such as *Escherichia coli, Campylobacter spp.,* were highlighted.

Data Extraction

Data from the selected papers were extracted systematically using a standardised extraction template. The extracted data contains:

1. Study design (e.g., experimental, observational, meta-analysis)
2. Antibiotic types (e.g. tetracyclines, macrolides, fluoroquinolones).
3. Resistance genes (e.g. blaCTX-M, mcr-1 and tetM).
4. Study setting (e.g. geographical location and whether the country was a developed or developing country).
5. Pathogen focus (e.g. *E.coli, Campylobacter* and *Salmonella*).
6. Mechanisms of resistance transmission (e.g. horizontal gene transfer and environmental mechanisms).

7. Key findings include prevalence rates of resistance and reported implications on public health.

Data Synthesis

The information obtained was analysed to detect common themes and trends across studies. The studies were classified by geographic location, agricultural technique (intensive and extensive), and the kind of antibiotic used. Data Synthesis aimed to investigate the link between agricultural antibiotic use and resistance development, as well as transmission paths to humans and public health concerns.

Results

In this section, presents the results categorised by types of farming systems and a detailed table summarising each article's key focus.

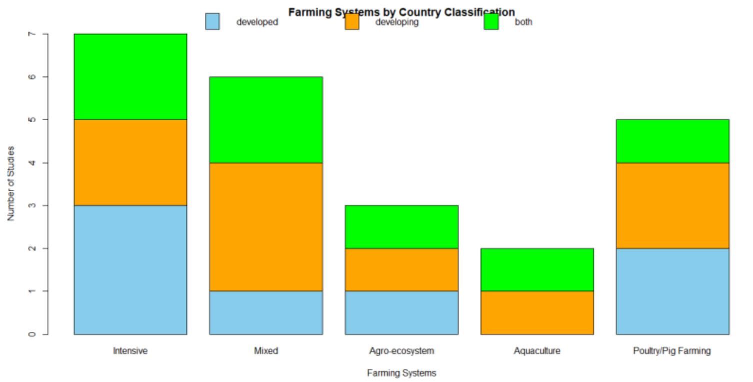

Figure 1 shows a bar graph showing the number of studies on different farming systems by country classification. The code for this figure is shown in Appendix 1.

Most of the studies look at intensive farming systems, which rely heavily on antibiotics for growth promotion and disease prevention which therefore increases resistance. Mixed Farming systems, which combine crop and livestock farming are ranked second. Their impact on soil and water through manure runoff is important in resistance studies. There are fewer studies for Agroecosystems and aquaculture, highlighting the shortage of study despite their importance in resistance spread through water systems and environmental pathways. Developed countries dominate intensive farming however in developing countries are represented in all types of farming systems. This highlights the differences in regulatory framework and antibiotic overuse. By analysing the farming systems particularly intensive and mixed are at high risk of resistance which can spread to food and water, posing serious harm to human health.

Table 1 provides an overview of studies investing in antibiotic usage in agriculture and its role in the development of antibiotic resistance across different farming systems and geographic regions. (page 7-8)

Study + Study Design	Geographic Region	Farming System	Type of Antibiotic Usage	Resistance Development	Transmission Pathway	Public Health Implications
(Samutela *et al.* 2021) Observational	Zambia (Developing)	Intensive pig farming	Growth promoters, prophylactics (*tetracycline, penicillin)*	Methicillin-resistant *Staphylococcus auteus (MRSA), mecA, spa types*	Direct contact, contaminate meat	Increased infection rates in humans
(Pereira *et al.* 2018) Experimental	USA (Developed)	Dairy farming	Residual antibiotics in milk (*ampicillin, ceftiofur, oxytetracycline*)	Increased ARGs (*tetM, blaCTX-M*) in gut microbiota	Milk, manure runoff	Altered gut microbiota, potential ARG spread
(Mofo *et.* al.) Meta-analysis	Nigeria, Cameroon (Developing)	Aquaculture	Prophylactics, disease control (*tetracycline, ampicillin*)	High multidrug resistance (*E.coli, Salmonella spp*.)	Contaminated water, fish consumption	Increased risk of AMR infections
(Saha *et al.* 2024) Systematic review	Global (Developed and Developing)	Pig farming	Preventive antibiotics (*enrofloxacin, colistin*)	Resistance in diarrheal bacteria (*E.coli, Salmonella, Clostridium*)	Contaminated meat, direct contact	Economic losses, reduced antibiotic efficacy
(Talukder *et al.* 2023) Observational	Bangladesh (Developing)	Mixed animal farming	Veterinary antibiotics (*nalidixic acid, tetracycline*)	High AMR in Salmonella (*blaTEM, tetA, sul1*)	Foodborne transmission	Increased infection burden in humans
(Esfandiari *et al.* 2023) Observational	Iran (Developing), Germany (Developed)	Meat production	Veterninary antibiotics (clindamycin, ciprofloxacin)	Resistance in Clostridium difficile (cdtA, cdtB genes)	Meat products	Potential for CDI outbreaks
(Bastidas-Caldes *et al.* 2022) Meta-analysis	Ecuador (Developing), Spain (Developed)	Poultry, pig farming	Colistin use (*colistin, fluoroquinolones*)	High prevalence of colistin resistance (mcr-1, mcr-3)	Foodborne, direct contact	Last-resort antibiotic resistance threat
(Kaviani Rad *et al.* 2022) Observational	Poland, Netherlands (Developed), China (Developing)	Mixed crop-livestock farming	Fertiliser antibiotics (*tetracycline, streptomycin)*	Soil AMR gene accumulation (*tetX, sul2, blaOXA)*	Soil, water runoff	Environmental and human health risks
(Kalpana *et al.* 2024) Experimental	India (Developing), Australia (Developed)	Agro ecosystems	Agricultural antibiotics (*chloramphenicol, ampicillin*)	Resistance in produce-associated bacteria (*E. coli, Listeria)*	Fresh produce consumption	Food safety concerns
(Mshana *et al.* 2021) Observational	Tanzania (Developing), Canada (Developed)	Mixed food production	Veterinary antibiotics (*oxytetracycline, sulphonamides*)	High AMR in foodborne pathogens (*E. coli, Campylobacter*)	Food products, water	Increased AMR-related diseases

(Chang *et al.* 2015) Experimental	USA, Denmark (Developed)	Intensive animal farming (cattle, poultry)	Prophylactic antibiotics (*fluoroquinolones, tetracyclines*)	Fluoroquinolone-resistant *Campylobacter jejuni,* multidrug-resistant *Salmonella*	Contaminated meat, direct contact, water runoff	Increased burden of foodborne illnesses, reduced treatment efficacy
(Ahmad, Malak and Abulreesh 2021) Systematic Review	India, Brazil (Developing) UK (Developed)	Mixed farming systems (aquaculture, livestock)	Veterinary antibiotics (B-lactams, aminoglycosides)	ESBL-producing *Enterobacteriaceae*, colistin resistance (*mcr-1 gene*)	Environmental dissemination (soil, water), direct contact	Increased human exposure to AMR pathogens public health threat
(Manyi-Loh *et al.* 2018) Meta-analysis	South Africa, Vietnam (Developing) Sweden (Developed)	Livestock farming (poultry, cattle, pigs)	Growth promoters, therapeutic antibodies (*tetracyclines, macrolides, B-lactams)*	Multidrug-resistant *E. coli*, *Campylobacter spp.* With high resistance genes (*tetA, blaTEM*)	Foodborne transmission, environmental contamination via manure	High prevalence of AMR-related infections, increased risk of zoonotic diseases.

Developing countries like Bangladesh and Zambia dominate the study which highlights weak regulations and widespread antibiotic misuse. However, in developed countries like the United States and Germany highlights stewardship gaps despite stricter policies. Intensive farming and aquaculture appear as key contributors to resistance, owning to the usage of growth promoters and prophylactic such as colistin and tetracycline, with resistance genes such as mcr-1, blaCTX-M and tetA often identified.

Multidrug resistant bacteria, such as *E. coli, Salmonella* and *MTSA*, have been related to inappropriate antibiotic usage. Resistance spread through contaminated food, manure runoff and direct animal contact providing risk to human health, especially in placed with poor biosecurity. These resistant bacteria lead to more infections, greater treatment costs and death, which is caused by resistance to last-resort medicines such as colistin. The findings highlight the critical need for stricter laws, greater biosecurity, and a worldwide One Health strategy to combat resistance.

Discussion

Analysis of Results

Significant findings have been recorded in both developed and developing countries, showing a clear link between the development of antibiotic resistance with the use of agricultural antibiotics, as shown by the evaluated studies. The overuse or inappropriate use of antibiotics in agricultural systems saw a rise in multidrug-resistant (MDR) bacteria such as *Salmonella*, *Campylobacter* and *E.coli*. Studies conducted in developing countries such as Bangladesh, Zambia and India showed a notably high usage of MDR bacteria, which is worsened by weak regulation. This is evident in Table 1 which highlights the necessity to combat resistance in areas with insufficient antibiotic regulations by showing that the majority of research was conducted in developing countries.

Widespread use of antibiotics in Bangladeshi chicken farms *(Ibrahim et al. 2023)* leads to a rise in resistance within agricultural environments. Selection for resistance increases when antibiotics such as tetracyclines and fluoroquinolones, are regularly given to poultry farms in Bangladesh for a considerable period of the animal's life cycle. Resistant bacteria infecting humans through contaminated food and direct contact is just one example of how the lack of sufficient biosecurity protocols leads to an increased chance of transmission.

In developed countries such as the United States, misuse of colistin and other last resort leads to MCR genes becoming resistant. The connection of this problem is demonstrated by a worldwide spread of these genes, which is supported by trade environmental transmission. Similarly, veterinarians on Australian dairy farms still prescribe essential medicines like cloxacillin for common illnesses like mastitis, despite the widespread awareness of antimicrobial resistance (Tree *et al.* 2022). The likelihood of chronic resistance is increased by the lack of proper care which is limited by the absence of systematic diagnostic testing. Figure 1 shows the frequency of intensive and mixed agricultural farming systems in resistance research, which shows the importance of focused intervention in these high-risk settings.

The study of European pig husbandry also emphasises how economic forces influence the use of antibiotics (Ibrahim *et al.* 2023). Despite having ARM awareness farmers are often left with no choice but to put profitability ahead of lowering antibiotic usage due to financial limitations. With a lack of sufficient financial incentives as well as a lack of regulation, farms often see themselves relying on antibiotics. However strict regulations alone aren't enough to solve the problem as even in countries like Sweden and Germany that have stricter rules, inadequate diagnostic procedures continue to be dangerous. These farms' resistant bacteria can spread through direct contact, contaminated meat and environmental exposure raising the risk to the public's health.

Antibiotic Resistance has severe implications on public health. Infections caused by resistant bacteria raise the risk of foodborne diseases, reduce the effectiveness of therapy and have a significant impact on cost. Such infections have the potential to increase death rates, admittance to hospitals and raise healthcare expenses if left untreated. Resistance to antibiotics used as a last resort, like colistin, poses serious risks as it restricts available treatment which might have catastrophic effects on human health.

Policy Framework and Global Initiatives

Implementing an effective regulatory framework to regulate the use of antibiotics in agriculture is crucial to fight against antibiotic resistance. Antibiotic resistance rates have seen a significant decrease in countries that follow strict restrictions and reduce agricultural antibiotic usage (Jensen and Hayes 2014; Levy 2014; Speksnijder *et al.* 2015). For example, Denmark was successful in lowering livestock antimicrobial resistance by implementing laws that limit the use of essential antibiotics and requiring veterinarian prescriptions for their usage. Similarly, the Netherlands implemented a thorough antibiotic management program that reduced the use of agricultural antibiotics by 58% over ten years.

The World Health Organisation and other organisations encourage countries across the world to limit antibiotic use and track resistance trends through international programs such as the Global Action Plan on Antimicrobial Resistance (Administrator n.d.). However, the level of implication across the globe varies greatly, with a lack of funding and proper enforcement of laws seeing developing countries struggle greatly. Comparing regional regulatory methods can assist in identifying the best practices and create practical suggestions for enhancing antibiotic management in countries where antibiotic resistance is increasing rapidly.

Gaps in Content and Quality

Major Gaps in material and quality were seen when evaluating the articles. A major concern is the lack of representation of developed countries with rigid agriculture policies. While papers from some countries such as the United States, Germany and Australia were included there is little data on how rigorous controls affect antibiotic resistance. Comparative studies on regulatory differences may provide a fairer knowledge of resistance prevalence. As the majority of articles are cross-sectional and focus on a short time period, a lack of longitudinal research is another gap. Longitudinal research can potentially help track resistance development over time and increase evidence of the relationship between resistance expansion and antibiotic usage. Furthermore, different procedures being used across investigations means there is no standardisation in data collecting. The ability to compare data and make consistent conclusions was made almost impossible as some studies focused on phenotypic resistance while others did not include the genetic study of resistance genes. Addressing these outcomes will strengthen and increase the dependability of the future in this field.

Strengths of the Review

This study has exhibited geographic coverage incorporating studies from across the globe, including both developed and developing countries. This allows a thorough knowledge of how antibiotic usage habits differ throughout the world and how these variations impact resistance development. There is useful insight into how various agricultural methods contribute to antibiotic resistance, as the analysis covers a wide range of farming systems such as intensive pig farming, aquaculture and mixed crop-livestock operations. The study also offers vital direction for future intervention methods by identifying significant transmission paths, such as contaminated food and environmental routes, emphasising their importance in transmitting resistance from agricultural settings to human populations.

Limitations of the Study

The review has various limitations that could impair its comprehensiveness. As the study is mostly based on published literature, which favours studies with substantial or favourable findings, there is a concern for publication bias. Furthermore, there is a linguistic limitation as only publications published in English were considered thus omitting significant research in other languages that might provide valuable insights. Although the review emphasises the public health consequences, it does not provide a thorough analysis of the economic cost of antibiotic resistance or the efficacy of present policies in limiting antibiotic usage or the efficacy of present policies in limiting antibiotic resistance. This leads to insufficient attention to policy and economic settings which is another weakness. Addressing these constraints in the future would increase the depth of the results

Implications for Policy and Practice

This review has numerous major implications for policy and practice. Most importantly there is an urgent need for tighter regulatory frameworks to limit antibiotic usage in agriculture, especially within developing countries where antibiotics are readily available with over-the-counter sales still being prevalent. A counteractive measure for this would be to enforce veterinarian prescriptions and limit the use of last-resort medicines such as colistin. Tracking resistance patterns and antibiotic consumption in all contexts from agricultural usage to clinical contexts, allows for the early detection of resistance trends and guiding targeted responses, This can be achieved by implementing surveillance and monitoring systems. The study shows the significance of marketing antibiotic alternatives, such as probiotics and immunomodulators, to prevent bacterial infections in animals. Governments and agricultural sectors could take the initiative and increase investment in research and development in these alternatives.

Conclusion

The reviewed articles demonstrate a clear and troubling link between agricultural antibiotic usage and the increase in antibiotic resistance. This has significant effects on public health, food safety and environmental stability. The range of farming methods facilitates the spread of resistance through pathways. These findings highlight the critical need to address the rising threat of MDR bacteria which compromises the effectiveness of essential treatment as well as increase mortality rates.

Despite widespread understanding, there are still critical gaps. The primary focus on developing countries highlights the need for comparative studies in regions with strict regulations. The success of countries like Denmark shows its effectiveness. However, at the same time due to the range and diversity of global agricultural practices locally tailored solutions are more ideal. Furthermore, the lack of longitudinal research limits the ability to assess the sustainability of interventions and predict long-term trends.

Addressing antibiotic resistance will require more investment into research and development into alternatives, as well as specific support in marketing so that there can be more adoption of these products especially in those countries where over-the-counter antibiotics are still prevalent. On top of this, there needs to be more cooperation so that there can be coordinated global action to standardise surveillance and data collection/trends as well as facilitate knowledge sharing so that the issue can be combatted effectively.

In the future researchers must prioritise the economic dimensions of antibiotic resistance. Also integrating genetic analysis with phenotypic studies will provide deeper insights into resistance mechanisms allowing more precise interventions. By addressing these issues researchers and authorities can make significant progress in reducing the threat of antibiotic resistance, protecting both public, agricultural and environmental health.

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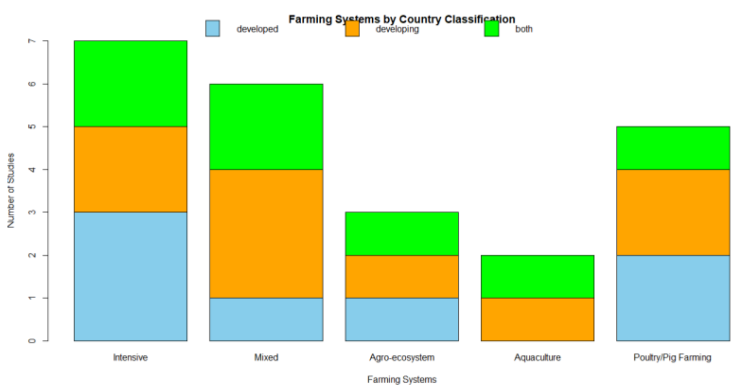
Appendix

Appendix 1: This is the code for Figure 2 which shows the Farming systems by country classification.

```
> #Second bar plot: Farming Systems by Country Classification
> farming_systems <- c("Intensive", "Mixed", "Agro-ecosystem", "Aquacultur
e", "Poultry/Pig Farming")
> developed <- c(3,1,1,0,2)
> developing <- c(2,3,1,1,2)
> both <- c(2,2,1,1,1)
>
> data_matrix <- rbind(developed, developing, both)
>
> barplot(
+   data_matrix,
+   beside = FALSE,
+   col= c("skyblue", "orange","green"),
+   main = "Farming Systems by Country Classification",
+   xlab = "Farming Systems",
+   ylab = "Number of Studies",
+   names.arg = farming_systems,
+   ylim = c(0,7)
+ )
>
> # Adding the legend below the second bar plot
> legend(
+   "top",
+   legend = rownames(data_matrix),
+   fill = c("skyblue", "orange", "green"),
+   bty = "n",
+   horiz = TRUE,
+   inset = c(0, -0.15), # Moves the legend below the plot in the middle
+   xpd = TRUE)
>
```

The code produced this figure:



Literature review

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41	E. A. R. Portal, K. Sands, C. Farley, I. Boostrom et al. "Characterisation of colistin resistance in Gram-negative microbiota of pregnant women and neonates in Nigeria", Nature Communications, 2024 Publication	<1%
42	Frédéric Moffo, Mohamed Moustapha Fokom Ndebé, Mildred Naku Tangu, Ranyl Nguena Guefack Noumedem et al. "Antimicrobial use, residues and resistance in fish production in Africa: systematic review and meta-analysis", BMC Veterinary Research, 2024 Publication	<1%

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Literature review

GRADEMARK REPORT

FINAL GRADE

78/100

GENERAL COMMENTS

Thank you for submitting this assignment. This was a very interesting read and it was clear that you understood this assignment. You have made good use of the resources provided to you and completed a throughout and in-depth literature review.

Relevance

1. Very well-directed answer to the essay question - understanding the link between agricultural antibiotic Usage and antibiotic resistance. Please note you should not call this assignment a "report"; rather it is a "literature review", or, just an assignment.

Knowledge

1. You demonstrated evidence of comprehensive knowledge about this topic, providing illuminating perspective on the issues relevant for the topic and its context. Well done.

Analysis

2(1) Consistent analysis; sound argument; sensible use of evidence. Strengths include systematic approach and addressing the key issues. Your discussion on gaps, strenghts & limitations, and implications is excellent. Limitations are: you could have synthesised results more, combine/integrate results, either using counts or percentages.

Organisation

2 (I). The review follows a conventional structure. Table of contents at the start is helpful. However, some sections could be improved. For example, analysis should be presented in Results section, not Discussion. Good and clear tables and graphs.

References

2(I) Honest attribution of sources; consistent forms of reference. Well done.

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RUBRIC: RUBRIC YIDA UNDERSTANDING DATA

DIRECTION / R	FIRST 70+
FIRST 70+	Very well-directed answer to the question
2(I) 60-69	Essentially relevant and covers whole question
2(II) 50-59	Some lack of focus or incompleteness
THIRD 40-49	Partial answer, only moderately directed to question
FAIL 0-39	Not relevant to the question /module.

KNOWLEDGE / U	FIRST 70+
FIRST 70+	Evidence of comprehensive knowledge; illuminating perspective on the topic and its context
2(I) 60-69	Sound; evidence of critical reading
2(II) 50-59	Broad awareness but gaps. Evidence of reading.
THIRD 40-49	Superficial; limited evidence of reading
FAIL 0-39	Very poor.

ARGUMENT / AN	2(I) 60-69
FIRST 70+	Independent thought; consistent analysis, awareness of limitations of evidence and analysis
2(I) 60-69	Consistent analysis; sound argument; sensible use of evidence
2(II) 50-59	Limited argument and range of views covered, but defensible analysis
THIRD 40-49	Largely descriptive; Argument and analysis limited and largely rehearsed uncritically from reading
FAIL 0-39	Misleading or arbitrary argument.

ORGANISATION	2(I) 60-69
FIRST 70+	Structure clearly reflects and enhances argument
2(I) 60-69	Clear, if conventional, structure
2(II) 50-59	Structure dictated by treatment in books, etc read.
THIRD 40-49	Poor organisation
FAIL 0-39	Very poorly organised.

EXPRESSION	FIRST 70+
FIRST 70+	Clear, unambiguous writing
2(I) 60-69	Good, conventional English
2(II) 50-59	Limited but largely free from serious errors
THIRD 40-49	Errors and ambiguities
FAIL 0-39	Writing is very confusing or unclear.

REFERENCES AN	2(I) 60-69
FIRST 70+	Scholarly, well-organised treatment of references, bibliography, etc
2(I) 60-69	Honest attribution of sources; consistent forms of reference
2(II) 50-59	Some under-referencing
THIRD 40-49	Serious under-referencing
FAIL 0-39	Little or no referencing.

PRESENTATION	FIRST 70+
FIRST 70+	Thoughtful, effective
2(I) 60-69	Conventional
2(II) 50-59	Reasonable
THIRD 40-49	Poor
FAIL 0-39	Very poor presentation.