An investigation into factors affecting the implementation of Antimicrobial Stewardship (AMS) before and during the COVID-19 pandemic in two acute care settings

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Summary

Background: Antimicrobial resistance (AMR) is a global crisis that requires urgent attention and action. Antimicrobial stewardship (AMS) is a set of actions that aims to promote the effective use of antibiotics. According to the UK report in 2016, it was estimated that, by 2050, 10 million people will die every year due to antimicrobial resistance (AMR). For this reason, the Public Health England (PHE) emphasised the need for AMS implementation in the acute care settings to maintain the appropriate, effective, and safe use of antibiotics. AMS is important to reduce inappropriate antibiotic prescribing and tackle the threat of AMR. It is essential to investigate AMS strategies that could be used effectively in any crisis. COVID-19 challenged all aspects of healthcare, especially appropriate antibiotic use. This research project aims to explore AMS implementation in Bedfordshire Hospitals NHS Foundation Trust before and during the COVID-19 pandemic. It includes three sequential studies.

- **The first study** was conducted last year as a systematic literature review. It aimed to explore AMS interventions before and after the COVID-19 pandemic.
- **The second study** will investigate the practice of AMS implementation in Bedfordshire Hospitals NHS Foundation Trust (Luton and Dunstable hospital and Bedford hospital).
- **The third study** will explore healthcare professionals' (doctors, pharmacists, and nurses') knowledge, attitudes, and perceptions toward antibiotic prescribing and AMS implementation before and during the COVID-19 pandemic.

The proposed measures are to measure AMS implementation using the proportion of inappropriately prescribed antibiotics at the time of admission, 48-72 hours after admission. Additionally, it will review the antibiotic prescribing behaviour of healthcare professionals (HCPs) and identify factors that impact AMS intervention before and during the COVID-19 pandemic. The expected outcomes of this research project are to identify AMS implementation and measures that were used before and during the COVID-19 pandemic based on PHE toolkit of AMS (Start Smart – then Focus), which will provide the gold standards for this research project. Additionally, this research project will help to understand the knowledge, attitudes, and perceptions of healthcare professionals towards antibiotic prescribing and AMS implementation before and during the pandemic.

Abbreviations

AMS	Antimicrobial Stewardship
CI	Chief Investigator
AMR	Antimicrobial Resistance
PHE	Public Health England
NICE	National Institute for Health and Care Excellence
WHO	World Health Organization
L&D	Luton and Dunstable
RTIs	Respiratory Tract Infections
KPIs	Key Performance Indicators
CINAHL	Cumulative Index to Nursing and Allied Health Literature
MED-LARS	Medical Literature Analysis and Retrieval System Online
EMBSE	Excerpta Medica Database
MIDIRS	Maternity & Infant Care Database
CASP	Critical Appraisal Skills Program
CAG	Confidentiality Advisory Group
PI	Principal Investigator
REC	Research Ethics Committee
UH	University of Hertfordshire
HCPs	Healthcare Professionals
PIS	Participant Information Sheet
MAXQDA	Qualitative Data Analysis Software
NIHR	National Institute of Clinical Research
GCP	Good Clinical Practice
NRES	National Research Ethics Service

Table of Contents

Summary ……..……..……
Abstract ……..……..……..
Abbreviations ……..……..…….
Table of Contents ……..……..……..
Research Synopsis ……..……..……
1. Introduction ……..……..……
2. Research Project Stages ……..……..……
2.1. Systematic literature review ……..……..……
2.2. Observational study of hospital retrospective data ……..……..…….
2.3. Online survey questionnaire ……..……..……...
3. Study 1: Systematic Literature Review ……..……..……..
3.1. Objectives ……..……
3.2. Method ……..……..…….
3.3. Search strategy ……..……..……...
3.4. Inclusion and exclusion criteria ……..……
3.5. Information sources ……..……..……
3.6. Data extraction and synthesis ……..……..……..
3.7. Classification of outcomes ……..……..……
3.8. Assessment of quality ……..……..……
3.9. Results ……..……..…….
4. Study 2: Observational Study of Hospital Retrospective Data ……..……..…….
4.1. Aim and Objectives ……..……..…….
4.2. Setting ……..……..……..
4.3. Methodology ……..……..……
4.4. Inclusion criteria ……..……..……..
4.5. Exclusion criteria ……..……..…….
4.6. Data source ……..……..……..
4.7. Access to identifiable patients' data during the study ……..……...
4.8. Confidentiality Advisory Group (CAG) ……..……..……..
4.9. Data Confidentiality ……..……..…
4.10. Exit strategy and length of time support required ……..……..…….
4.11. Data Anonymization ……..……

4.12. Data collection: ……
4.13. Quality checks for data extraction ……
4.14. The Expected outcomes ……
4.14.1. Primary Outcomes ……
4.14.2. Secondary Outcomes ……
4.15. Sample size ……
4.16. Method of analysis ……
5. Study 3: Online Survey Study ……
5.1. Objectives ……
5.2. Methodology ……
5.3. Inclusion criteria ……
5.4. Exclusion criteria ……
5.5. Study Participants ……
5.6. Access to participants' data during the study ……
5.7. Data Confidentiality ……
5.8. Expected outcomes ……
5.8.1. Primary Outcomes ……
5.8.2. Secondary Outcomes ……
5.9. Sample Size ……
5.10. Method of analysis ……
6. Timelines ……
7. Ethical Consideration in Both Phases ……
7.1. Good Clinical Practice ……
7.2. Risk of Bias ……
7.3. Risk assessment ……
7.3.1. Risk of exposure to patients' sensitive data ……
7.3.2. Risk of identification of evidence of clinical negligence ……
7.3.3. Research Ethics Committees ……
7.3.4. Validity ……
7.3.5. Reliability ……
8. Data Protection and Confidentiality of Study Data ……
9. Regulatory Considerations ……
9.1. Discontinuation/Withdrawal of participants from the study ……
9.2. Approval ……

10. Peer Review ……..……..…….
11. Finance ……..……..……..
12. Publication Policy ……..……..
13. Reference: ……..……..
14. Appendices: ……..
14.1. Appendix 1: Research Development Training ……..
14.2. Appendix 2: Detailed Gantt Chart for the three sequential studies…….
14.3. Appendix 3. The flow chart for the research project (Phase 1 and Phase 2)
14.4. Appendix 4: AMS intervention strategies and their related outcomes……
14.5. Appendix 5: PHE antibiotic prescribing behaviour in acute care settings….
14.6. Appendix 6: University of Hertfordshire Conference Poster Presentation….
14.7. Appendix 7: Innovative Strategies for AMS During COVID-19
14.8. Appendix 8: Global Pharmacists' Contribution in AMS During COVID-19.
14.9. Appendix 9: European Congress of Clinical Microbiology…….
14.10. Appendix 10: Good Clinical Practice (GCP) certificate from NIHR ……
14.11. Appendix 11: Clinical Research Certificate ……...
14.12. Appendix 12: Royal Pharmaceutical Society Membership …….
14.13. Appendix 13: American Board of Pharmacy Specialities Certificate …….
14.14. Appendix 14: Antimicrobial Stewardship Program Certificate…….
14.15. Appendix 15: Data Collection Tool ……...
14.16. Appendix 16. Participant Information Sheet ……..
14.17. Appendix 17. Survey for knowledge, attitudes, perceptions and practices questions
14.18. Appendix 18: The need for ongoing AMS during COVID-19 pandemic
14.19. Appendix 19: Data anonymisation detailed flow chart

Research Synopsis

Title of Research	An investigation into factors affecting the implementation of AMS before and during COVID-19 pandemic in two acute care settings.
Aims	To explore the factors affecting AMS interventions before/during the COVID-19 pandemic in two acute care settings.
Research Questions	1. How was AMS implemented before and during the COVID-19 pandemic? 2. What factors affect the AMS implementation before and during the COVID-19 pandemic?
Research Objectives	1. To ascertain from the literature, the strategies, tools, and measures used for AMS implementation to decrease the AMR threat. 2. To evaluate AMS implementation before and during the COVID-19 pandemic. 3. To identify AMS intervention strategies used before and during the pandemic. 4. To explore health care professionals' prescribing behaviour, attitudes, perception, and knowledge of AMS practice before and during the pandemic. 5. To make recommendations to support healthcare providers regarding effective AMS intervention to minimise AMR.
Research Design	1. Systematic literature review. 2. Retrospective study from patient medical records after anonymisation of all identifiable data (quantitative study) 3. Prospective online survey study.
Settings	Bedfordshire Hospitals NHS Trust: ● Luton and Dunstable University Hospital (L&D) ● Bedford Hospital
Duration	September 2022- September 2024
Sample Size	● Hospital: 640 Patients' medical records. ● An online survey of about 240 health care practitioners
Resource, Tools, Forms	1. Data collection forms 2. Hospital Antimicrobial Guidelines. 3. Public Health England (PHE), Start Smart - then Focus toolkit of Antimicrobial Stewardship (AMS). 4. NICE guidelines for AMS. 5. British National Formulary (BNF). 6. PHE antibiotic prescribing behaviour toolkit

Pilot study	1. Phase 1 pilot: To maintain the reliability of the data extraction. 2. Phase 2 pilot: 5% of the survey respondents to maintain the validity and reliability of the survey. This will be conducted by using IBM statistical package for the social sciences (SPSS) version 22
Data Analysis	● Quantitative data analysis: Descriptive and inferential statistics will be applied in analysing quantitative data. This will be conducted by using IBM statistical package for the social sciences (SPSS) version 22. ● Qualitative data analysis: Data will be organised using NVivo and coded using thematic analysis.
Ethics	1. REC ethical approval 2. UH ethical approval 3. CAG provisional support and approval 4. Implied consent from all survey participants 5. Personal data will remain confidential and anonymous 6. Data will be processed in line with University of Hertfordshire policy

1- Introduction

The prevalence of antimicrobial resistance (AMR) has risen significantly over the last 40 years, and a few novel antimicrobials have developed [1]. AMR has increased the pressure on existing antibiotics and more significant challenges in treating patients. Inappropriate use of antimicrobials increases the risk of infection with resistant organisms and subsequent transmission to other patients. AMS is an essential element of the UK's five-year antimicrobial resistance strategy from PHE [2]. AMS is a set of actions that aims to promote the effective use of antimicrobials. Such stewardship initiatives aim to contribute significantly to the reductions and spread of AMR. Additionally, AMS intervention strategies seek to improve antimicrobial prescribing and decrease AMR (Appendix 4). The National Institute for Health and Care Excellence (NICE) produced AMS guideline in 2017 and recommended its implementation in acute care settings [1]. Additionally, PHE toolkit of AMS, Start Smart - then Focus provided an impressive outline of evidence-based AMS implementation within the secondary healthcare settings (Figure 1) [2].

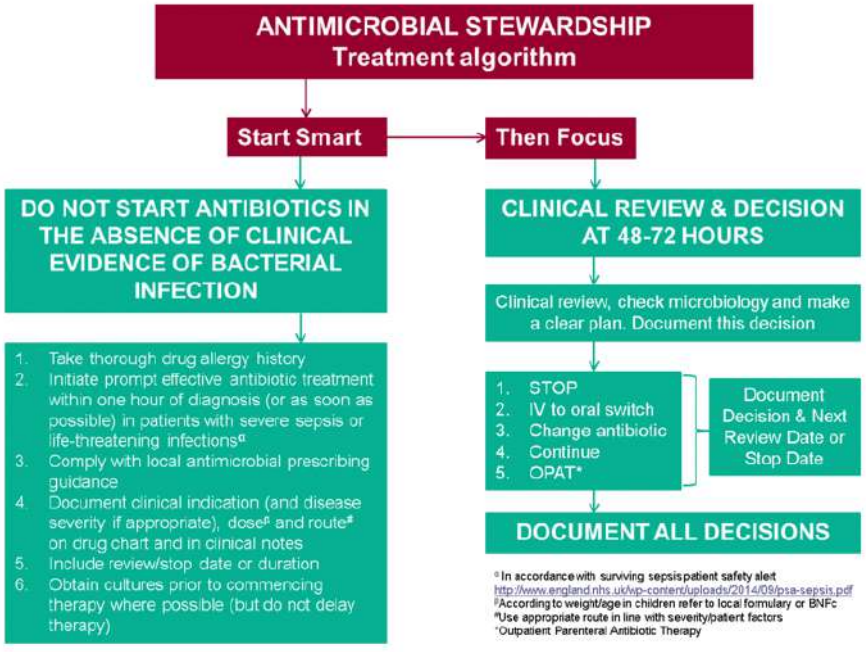


Figure 1 Public Health England AMS treatment algorithm [2]

Start Smart - this means:

- do not start antimicrobial therapy unless there is clear evidence of infection.
- take a thorough drug allergy history.
- initiate prompt effective antibiotic treatment within one hour of diagnosis.
- avoid inappropriate use of broad-spectrum antibiotics.
- comply with local antimicrobial prescribing guidance.
- document clinical indication (and disease severity if appropriate), drug name, dose, and route on drug chart and in clinical notes.
- include review/stop date or duration.
- obtain cultures prior to commencing therapy where possible.
- prescribe single-dose antibiotics for surgical prophylaxis where antibiotics have been shown to be effective.
- document the exact indication on the drug chart (rather than stating long term prophylaxis) for clinical prophylaxis.

Then Focus – this means:

- reviewing the clinical diagnosis and the continuing need for antibiotics at 48-72 hours and documenting a clear plan of action - the 'antimicrobial prescribing decision'.
- the five 'antimicrobial prescribing decision' options are 1. Stop antibiotics if there is no evidence of infection 2. Switch antibiotics from intravenous to oral 3. Change antibiotics – ideally to a narrower spectrum – or broader if required 4. Continue and document the next review date or stop date 5. Outpatient Parenteral Antibiotic Therapy (OPAT).
- it is essential that the review and subsequent decision are clearly documented in the clinical notes and drug chart where possible, for example stop the antibiotic.

The COVID-19 pandemic has accelerated the threat of AMR. Inappropriate antibiotic prescribing has increased during the COVID pandemic. The World Health Organization (WHO) discourages antibiotics for mild cases of COVID-19. WHO was concerned about the inappropriate use of antibiotics, particularly during this pandemic [3]. AMR was responsible for 700,000 annual deaths worldwide. In the shadow of COVID-19, antimicrobial resistance (ABR), one of the world's worsening pandemics, has been 'silenced'. Inappropriate antibiotic prescribing within the hospitals has increased as the number of severely unwell COVID-19 patients increased. Diagnostic uncertainty and concern about secondary bacterial infections may have contributed to this adverse change in antibiotic prescribing [4]. It is essential to learn from the COVID-19 pandemic and prepare for any upcoming emergencies or future pandemics. This study will focus on AMS as a practical way to improve the safety and quality of patient care. Additionally, it will contribute significantly to the reduction of AMR (figure 2).

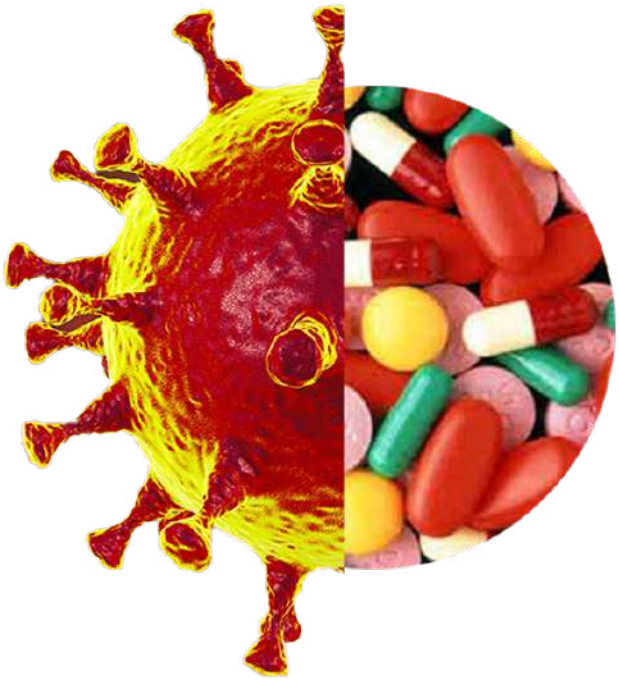


Figure 2 COVID-19 pandemic and antimicrobial resistance (AMR) silent pandemic

2. Research project:

This research project investigates AMS implementation before and during the COVID-19 pandemic. It includes three sequential studies (Figure 3).

1. Systematic literature review: The first study was undertaken on the published information available in scientific journals and reports to obtain evidence about antibiotic use and AMS intervention in acute care settings. It aimed to explore the practice of AMS in acute care settings before and during the COVID-19 pandemic, using a range of explicit strategies and measures, which showed promising outcomes in improving antibiotic prescribing and maintaining the rational use of antimicrobials, especially during COVID-19. Effective AMS implementation is linked to the improved overall health of adult patients and positively influences reducing AMR. Nonetheless, further studies are required to investigate AMS intervention strategies and the factors affecting AMS implementation in the future.

2. Phase 1: Observational study of hospital retrospective data: It will review the medical records of patients with RTIs or pneumonia who were admitted to Bedfordshire Hospitals before and during the COVID-19 pandemic.

3. **Phase 2: Online survey:** It aims to understand their perceptions, attitudes, practices and identify the factors that affected AMS implementation among Healthcare Professionals (HCPs) before and during the COVID-19 pandemic.

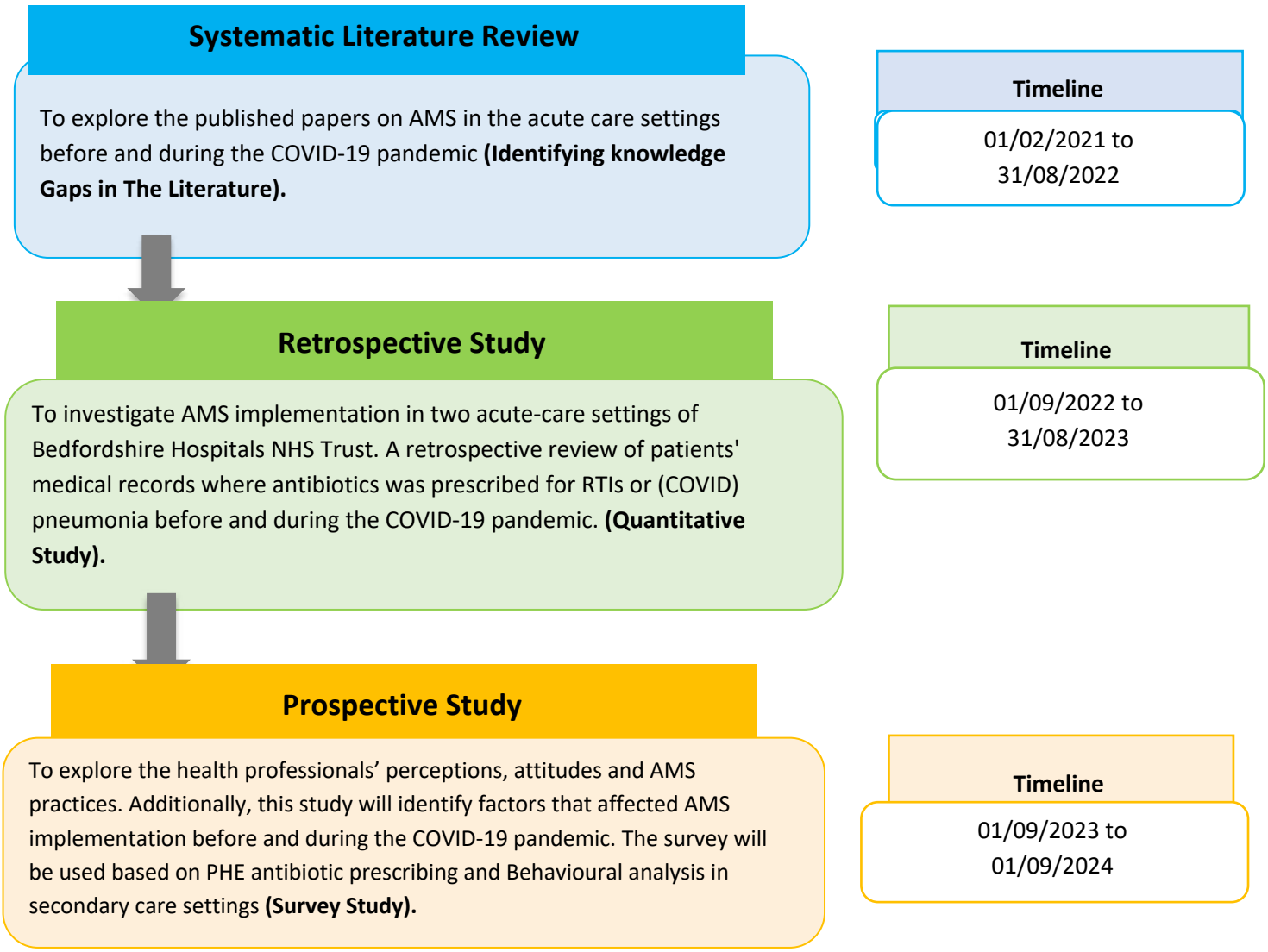


Figure 3 Description of the research project

4. Systematic literature review

A systematic review of antimicrobial stewardship intervention before and during the COVID-19 pandemic in the acute care settings

Introduction:

Antimicrobial resistance (AMR) is a global crisis that requires urgent attention and action. More than 1.2 million people died worldwide in 2019 from infections caused by bacteria resistant to antibiotics [9]. COVID-19 challenged all aspects of healthcare, especially the appropriate antibiotic use. AMS is a set of actions to promote the effective use of antibiotics. PHE emphasised the need for AMS implementation in acute care settings to maintain the appropriate, effective, and safe use of antibiotics. It is essential to find out AMS strategies that could be used effectively in any crisis. This systematic review explored AMS implementation strategies in acute care settings before and during the COVID-19 pandemic.

Method: A systematic literature search on MEDLINE, Embase classic, OVID, International Pharmaceutical Abstracts, Psychosocial Instruments, MIDIRS, PubMed, Scopus, Web of Science, CINAHL PLUS, OpenGrey, and Google Scholar was undertaken. The inclusion criteria were: (i) research studies focusing on antibiotic use in acute care settings; (ii) AMS intervention; (iii) AMS implementation strategies during the COVID-19 pandemic; (iv) adult patients of any gender; and (v) studies reported in the English language (Table 1).

Table 1: Inclusion and exclusion criteria of the systematic literature review

	Inclusion criteria	Exclusion criteria
Participants	Studies targeting the public/patients' use of antibiotics. HCPs responsible for prescribing, dispensing, or administering antibiotics (doctors, pharmacists and nurses)	Non-HCPs (patient family or community or nursing or long-term care patients)
Intervention	Studies describe an intervention to improve antibiotic prescribing or AMS implementation strategies as iv- oral switch, and de-escalation, antibiotic review and discontinuation.	Studies that do not describe an AMS intervention.

Comparison	Comparison with a control group/a group that carried out usual care without an AMS intervention.	
Context	Interventions are carried out in adult inpatient settings in acute care settings.	Interventions are carried out in nursing homes, care homes or long-term healthcare facilities; community settings; pediatric setting/hospital; and animals/ veterinary practice.
Outcomes	Primary outcomes: reviewing the effectiveness of AMS intervention and strategies prior to the COVID-19 pandemic and during the pandemic.	
	Secondary outcomes: HCPs' knowledge, attitudes or behaviours related to antibiotic prescribing; rates of AMR; length of stay in hospitals; other measures, metrics, quality improvement, KPIs and COVID-19 pandemic impact on AMS intervention.	
Study design	RCTs, non-randomized trials, CBA studies, interrupted time series designs, case-control studies and cohort studies, cross-sectional studies, qualitative studies	Systematic reviews, meta-analysis, single case studies, case reports, conference abstracts.

Results: Sixteen articles met the inclusion criteria from an initial result of 8,763 identified article titles. A range of AMS interventions was identified based on AMS toolkit that was developed by PHE. Prior to the COVID-19 pandemic, the most reported AMS strategies in 67% of studies were prospective audit, feedback, and AMS Multidisciplinary Team (MDT). AMS education was also reported in 50% of studies. During the COVID-19 pandemic, AMS education and MDT were the most written strategies implemented in 25% of studies. These were followed by antibiotic review, streamlining/escalation and formulary restriction reported in 17% of studies. The antibiotic review was implemented equally before and during the COVID-19 (Figure 4). This systematic review showed the global pharmacists' role in leading AMS implementation in acute care settings (Appendix 6). In addition, it showed some promising new innovative AMS implementation strategies, such as Procalcitonin (PCT) measurements, quality improvement initiatives and antibiotic dashboard that showed promising outcomes in AMS intervention during the COVID-19 pandemic (Appendix 7).

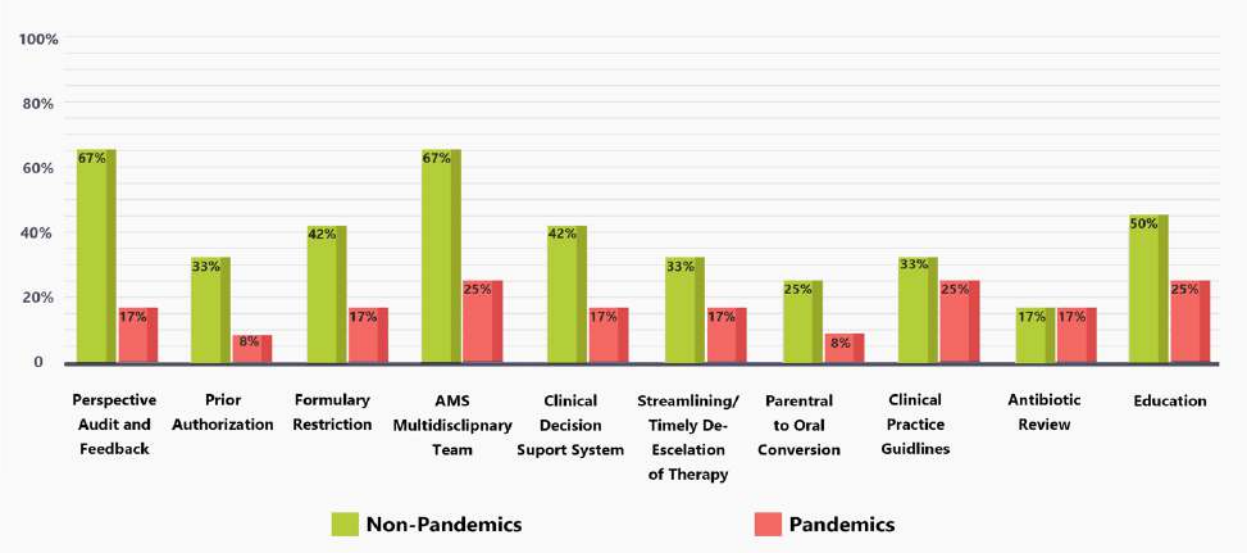


Figure 4 AMS intervention strategies before and during the COVID-19 pandemic (Total studies 16)

Conclusion: This systematic literature search support findings that show promising outcomes in selecting the right AMS implementation strategies in acute-care settings. The COVID-19 pandemic is a significant and new public health threat, putting tremendous pressure on all HCPs. However, the ongoing global crisis of AMR must not be neglected. Although urgent actions are required to continue measuring AMS implementation and practices during the COVID-19, to be prepared to any future pandemics. Other recommendations include ensuring access to effective antimicrobials and upholding the principles of AMS strategies in the acute care settings. Finally, advocacy for AMS must continue in the post-pandemic era to maintain the safety and quality of patient care.

Results from the systematic literature review have been published at national and international conferences (Appendix 5). A research gap was found to identify how AMS was implemented in the acute care settings during the COVID-19 pandemic. Previous studies did not have the exact AMS toolkits or roadmap that could be used during the COVID-19 pandemic. They did not measure the proportion of inappropriate antibiotic prescribing, and HCPs' perceptions and attitudes toward antibiotic prescribing during the pandemic. This research project will investigate AMS implementation before and during the COVID-19 pandemic based on PHE toolkit of AMS (Start Smart – then Focus), which will provide the gold standards for this research project to identify how AMS interventions were implemented before and during the COVID-19 pandemic.

5. Retrospective study for the patient medical records

(Phase 1: Retrospective study at Bedfordshire Hospitals NHS Trust)

4.1. Aim and Objectives:

This research investigates AMS implementation before and during the COVID-19 pandemic in the Bedfordshire Hospitals NHS Trust (Luton and Dunstable University hospital and Bedford hospital).

Setting:

Bedfordshire Hospitals NHS Trust provides secondary care services for a population of around 400,000 people within the local catchment area covering Luton, South Bedfordshire and parts of Hertfordshire and Buckinghamshire. The hospital became a foundation trust in 2006. There are approximately 742 beds, of which 82 are maternity, and 18 are critical care beds and high dependency beds, with 18 contingency beds over 27 wards. In a twelve-month period, the Trust employed 7,982 (headcount) Health Professionals, the number of inpatient admissions 86,676 and 442,113 outpatient attendances. Permission and support for data collection were sought from the Chief Pharmacist and pharmacy team at Bedfordshire Hospitals NHS Trust.

4.2. Methodology:

This phase will include reviewing medical records of patients prescribed antibiotics for RTIs or pneumonia before and during the COVID-19 pandemic. Data collection will be undertaken at eight-time points, four before COVID-19 as baseline measures and four during the COVID-19 pandemic.

4.3. Inclusion criteria

1. Adult patients 25 years and older.
2. Adult Pregnant women and immunocompromised patients.
3. Patients admitted at Bedfordshire Hospitals NHS Trust.
4. Patient admitted in 2019 and 2020.
5. Patients who were prescribed antibiotics for RTIs or pneumonia.

4.4. Exclusion criteria:

1. Patients who were not prescribed antibiotics.
2. Children and patients admitted for less than 48-72 hours.

4.5. Data source

Data will be collected from the patient's electronic medical records in Bedfordshire Hospitals NHS Trust by the PhD student/PI according to the study inclusion criteria. The study includes two hospital research collaborators who work at Bedfordshire hospitals. The hospital collaborators will obtain the list of the patients from the coding team first, then communicate with from information governance team according to the study eligibility and the national NHS opt-out act exclusion. Then the PhD student/PI will collect the required study data from the data collection tool. The PI will use the data collection tool to extract the required data for validation and analysis. Each patient's medical record will take about one hour for the PhD student/PI to collect the necessary data.

Process of patient record identification and retrieval

The hospital collaborators for this study are part of the direct patient care team due to their roles within the hospital Trust. Sanil Patel is the lead AMS pharmacist. Patricia Edwards is a lead specialist pharmacist for education and training. Both work across the two Bedfordshire hospital sites, including Luton & Dunstable and Bedford hospitals. Both are part of the direct care team. Sanil Patel is the lead antimicrobial pharmacist who oversees AMS process for all patients. Patricia Edwards is the lead specialist pharmacist for education and training and has the responsibility to oversee all activities related to education and training, including the use of patient data by students who must all have an honorary contract or have employment by the trust.

The PI for this study is Rasha Abdelsalam Elshenawy, who has an honorary contract at Bedfordshire Hospitals NHS Trust. Patricia Edwards and Sanil Patel will contact the coding team to request a list of patient records using the specified codes and criteria for the patient records sample. The coding team will retrieve and produce the relevant patient list matching the study sample codes and criteria and send this to the two hospital collaborators. The coding team will also ensure that the list sent to the hospital collaborators aligns with the NHS opt-out process to ensure that patients who indicated this choice would not be included. The two hospital collaborators will review the patient list to validate its appropriateness with the study sample patient records. Following this process, the patient list will then be made available to the PI/PhD student. The list, which includes identifiable

patient information, will be maintained on the hospital computer system and will not leave the hospital system or site in this format.

4.6. Access to identifiable patients' data during the study

This phase will require assessing patients' data without prior consent. However, for this study, which is mainly retrospective, it will be impractical to obtain consent from the patients whose records are to be assessed due to the time required to seek and obtain consent from the relatively large sample. Patients may have moved residences. However, all data collection and processing will be fair and lawful in line with the principles of the General Data Protection Regulation (GDPR).

The PhD student/PI applied for the Confidentiality Advisory Group (CAG) Committee on 08th Match, 2022, with an application number (22/CAG/0039). CAG committee was provisionally supported, with satisfactory responses to the requests for further information and compliance with the standard and specific conditions of support. CAG is also supported for the duration of the retention of the key between confidential patient information and the pseudonymous study ID. The PhD student/PI will access the patients' identifiable data till the expected end of this study phase 1 which is 28th February 2023. Access to patients' identifiable data will be restricted only to the PI and external collaborators at both hospital sites (L&D and Bedford hospitals). Then the PI will anonymise the data and transfer it to the double secure University of Herefordshire (UH) system for analysis and results. The PI/PhD student who will conduct the data collection is a clinical pharmacist certified in AMS. The PI also obtained training certification in Good Clinical Practice (GCP) from the NIHR. In addition to the training modules in the research, data analysis in the UH, and the training modules in the NHS hospital portal, signed the confidentiality agreement and Honorary contract with the Bedfordshire Hospitals NHS Trust (Appendix 10).

The main ethical issues are data protection, confidentiality, and data anonymity. The PhD Student/PI has signed an honorary contract for the two years of study; the PI has an NHS secure email. In addition, the PI obtained a new user account to access the hospital's electronic system. The PI will protect the confidentiality of data; all patient identifiable data will be stored only in the hospital system under the supervision of the hospital collaborators. Then, the PI will anonymise the extracted data and store it on the University's secured network storage system, which requires a double security check for analysis. The external

collaborators (Patricia Edwards and Sanil Patel) are two pharmacists and part of the direct care team with limited capacity to undertake the necessary data extraction process for 640 patients. The PI/PhD student is trained in clinical research and data extraction and has over 20 years of experience in clinical pharmacy practice, research, data management, patient safety, quality improvement and AMS implementation.

4.7. Confidentiality Advisory Group (CAG) support

Confidentiality Advisory Group (CAG) support is required to allow the disclosure of confidential patient information to the PI, who is not part of the direct care team. CAG support was obtained while extracting a pseudonymous dataset for analysis from electronic patient records at Bedfordshire Hospitals NHS Trust. The CAG support was also assured for the duration between confidential patient information and the pseudonymous study ID. CAG support was retained for the PhD student/PI, who will have access to the patients' identifiable data until the expected end of this study phase 1. The PhD student/PI applied to the CAG Committee on 08th Match, 2022, with an application number (22/CAG/0039) and received the provisional support approval. The Confidentiality Advisory Group (CAG) category set has provisionally supported the following:

1. The CAG application allows the applicant/PI (Rasha Abdelsalam Elshenawy), who is not a member of the direct care team, to access confidential patient information. It will be held at Bedfordshire Hospitals NHS Foundation Trust. The PI will extract a pseudonymised dataset. CAG is provisionally supporting retaining the pseudonymisation key at the Trust. Additionally, CAG's satisfactory response supported the requests for further information and compliance with the standard and specific conditions of support.
2. Support to process the specified confidential patient information without consent is not in effect until a separate outcome letter is issued.

4.8. Data Confidentiality:

The external collaborators from the Bedfordshire Hospitals NHS Trust and part of the direct healthcare will identify the data initially. The data collection will be started after that by the research student. Only the PI will collect the required data from the patients' electronic medical records. The identifiable patient information will be stored only in the hospital system on the hospital. Personal data and clinical records will only be accessed through the PI's

secure hospital account with password protection. The data collection will be conducted from the trust computers with a password login protected on the hospital site itself.

4.9. Exit strategy and length of time support required

This phase obtained provisional support from CAG 's251' support, which refers to section 251 of the National Health Service Act 2006 and its current Regulations, the Health Service (Control of Patient Information) Regulations 2002. The exit strategy for the data extraction element is pseudonymisation. A member of the direct care team (Patricia Edwards) will identify patients who fit the criteria. This member will then review this to ensure patients with NHS opt-out are excluded. Patricia Edwards will then make this data available to the PhD student/PI. The PhD student will then extract the data and pseudonymise it in the hospital sites. The linked data will remain on-site in the custody of a member of the direct care team (Patricia Edwards). Only pseudonymised data will be stored on the university system to facilitate analysis. The PhD student/PI will no longer have access to the patients' identifiable data after the expected end of this study phase 1 – after 31st August 2023.

4.10. Data Anonymisation

1. After receiving the approval from the REC.
2. The PhD student/PI will supply the inclusion and exclusion criteria to the hospital collaborator.
3. The hospital collaborator will contact the 'Coding team' to look for the required list of medical records within the criteria and timepoints of the study.
4. The exported 'excel sheet' list of the patient will be generated for the hospital collaborator.
5. The hospital collaborator will contact the 'Information governance team' to apply the national opt-out act.
6. The hospital collaborator will provide the final list of the identified patient medical records.
7. The PhD student/PI has an Honorary contact in the NHS and will use the hospital computers, secure username and password, for data extraction.
8. Data will be extracted from a total of 640 medical records. Each medical record will take 45 – 60 minutes to extract the data (Appendix 19.

4.11. Data collection:

The PhD student/ PI will collect the data. The PI has an honorary contract in the Bedfordshire Hospitals NHS Trust from December 2021 until the expected end of the research project. As the seasonal variations affect antibiotic prescribing for RTIs or pneumonia. The highest incidence of pneumonia was noted in the winter season, followed

by autumn, and spring. However, a low incidence of pneumonia was noted in the summer season [10]. As this study will compare the impact of the COVID-19 pandemic on AMS implementation before and during the COVID-19 pandemic. Randomised data will be collected from eight Interrupted time series (four before the COVID-19 pandemic and four during the pandemic) as shown below:

Four-time points before the COVID-19 pandemic

1. 1st week of March (Spring 2019)
2. 1st week of June (Summer 2019)
3. 1st week of September (Autumn 2019)
4. 1st week of December (Winter 2019)

Four-time points during the COVID-19 pandemic

1. 1st week of March (Spring 2020): The first wave of COVID.
2. 1st week of June (Summer 2020): First lockdown.
3. 1st week of September (Autumn 2020): The second wave of COVID.
4. 1st week of December (Winter 2020): Vaccination Rollout.

Data extraction and processing

The PhD student/PI who has access to electronic medical records will extract the data. The PI will protect the confidentiality of data; the patient identifiable data will be stored only in both hospital sites. Data collection and extraction are based on PHE toolkit (Start Smart - then Focus). The PhD student will use the previously mentioned patient list to enable the review of the relevant hospital databases and systems to extract the required information in the data extraction tool based on PHE toolkit for AMS (Appendix 15):

- Demographic information (age and antibiotic allergy).
- Medical diagnosis
- Appropriateness of the antibiotics prescribed upon patient admission (drug initiation, dose adjustment, route of administration, duration and de-escalation).
- Appropriate use of short-duration of antibiotics (<72 hours) versus long-duration of antibiotics (>72 hours).
- Antibiotic(s) used after 48 -72 hours of admission; route, dose, frequency, and duration.

- Appropriateness of oral and IV antibiotics prescribed, antibiotic discontinuation, and antibiotic review
- Other chronic conditions increase the infection prevalence and affect the antibiotic selection, such as hypertension, diabetes, cardiovascular disease, kidney and liver diseases).
- Diagnostic methods, such as chest X-ray (CXR) and computed tomography (CT) scan.
- Laboratory inflammatory markers, such as procalcitonin (PCT), C-reactive protein (CRP), and Leukocytosis (WBC > 10,000/mm 3) that could indicate infection.
- Red flags for infection, such as fever as an oral temperature >37.8°C (>100.0°F).
- Bacterial culture results interpretation, including the timing of cultures, common culture sites, the potential for contamination, interpreting the Gram stain, use of rapid diagnostic tests, and conventional antibiotic susceptibility testing.

Each patient record will be given a study ID during the extraction process. A list that matches patients' records and their study ID will be maintained on the hospital systems. Patricia Edwards will be responsible for maintaining this list as part of her role. It will be saved as a password-protected document that is only accessible to Patricia Edwards and the PhD student on the hospital sites. The PhD student will only be allowed to export anonymised data to the university's double security data storage system for input into the data analysis software (SPSS). Only patient anonymised data will continue to be fed into the SPSS database until the end of data extraction. Following data extraction, the analysis will then be undertaken. The PhD student will be able to liaise with Patricia Edwards if she needs access to the linked patient record/study ID list. The PhD student will no longer have access to patient identifiable data after the end of Phase 1, which is 31st August 2023.

4.12. Quality checks for data extraction:

A standardised data extraction instrument comprising of an excel sheet based on PHE toolkit (Figure 1), includes all the previously mentioned measures that would help to identify how AMS was implemented before and during the COVID-19 pandemic (Appendix 15). The PhD student/PI and the Sanil Petal, AMS pharmacist lead on the study sites, will independently undertake data extraction from 10 medical records. Inter-rater reliability will be determined

by examining the percentage of agreement in the data extracted independently by the two using Cohen's Kappa. Disagreements will be resolved via dialogue. Agreements of ≥80% will be considered as an indicator of the reliability of the process.

The pilot test will be conducted as follow:

a) The hospital collaborator will select one medical record for every 64 records, for a total of 10 medical records.
b) The PhD student/PI will extract the data from these 10 records in the data extraction form.
c) The AMS pharmacist in the Trust will extract the data from the same 10 records in the data extraction form.
d) Inter-rater reliability will be determined by examining the percentage of agreement in the data extracted independently by the two using Cohen's Kappa.
e) Disagreements will be resolved via dialogue. Agreements of ≥80% will be considered as an indicator of the reliability of the process.

4.13. The Expected outcomes

Primary outcome:

- AMS implementation before and during the COVID-19 pandemic, such as Parenteral-to-Oral switch, antibiotic discontinuation, de-escalation, dose adjustment, and antibiotic review based on the local guidelines.

Secondary outcome:

- Measured the proportion of inappropriately prescribed antibiotics at admission, and after 48 to 72 hours.
- Laboratory and other diagnostic methods, such as chest X-ray (CXR), procalcitonin (PCT), C-reactive protein (CRP), Leukocytosis (WBC > 10,000/mm 3), and fever measured using the proportion of their use in patients infected with RTIs or pneumonia before and during the COVID-19 pandemic.

4.14. Sample size:

The sample size was determined based on the literature and the percentage of inappropriate antibiotic prescribing. According to PHE and the NICE guidelines, at least 20% of all antibiotics are inappropriately prescribed in the UK. The stats package Minitab was used for the sample size calculation. The PI obtained the figures on the total number of inpatient admissions in both hospitals mentioned above, to ensure the feasibility and accuracy of the calculated sample sizes. The Sample size was estimated according to the population size, the margin of error (ME) of 10%, and the confidence interval (CI) of 95 %. Then the sample size calculation was verified with the UH statistician. Data will be collected from 320 patient records prior to the COVID-19 pandemic and 320 patient records during the COVID-19 pandemic. Each time series will include the review of 80 medical records. The total sample size for this phase will be 640 patient records. The PhD student/PI will conduct a pilot test for two samples and discuss their results with the academic supervisors to ensure the validity of the data collection and extraction. So data will be collected from 80 records per time point.

4.15. Method of analysis

The process of antibiotic use in the hospital consists of 5-stages, which are (1) prescribing, 2) transcribing and documenting 3) dispensing, 4) administering, and 5) monitoring. The appropriateness of antibiotic prescribing is measured based on the hospital antimicrobial prescribing guidelines. The rest of the antibiotic use process or antimicrobial stewardship will be measured based on Public Health England Antimicrobial Stewardship Toolkit and NICE Antimicrobial Stewardship guidelines.

Quantitative data: Statistical analysis will be performed. Descriptive statistics will be employed to ascertain the distribution of data. Inferential statistics employing parametric (if data is normally distributed) and non-parametric (if data is not normally distributed) tests to explain relationships within data will be performed. Means and standard deviations will be calculated for continuous variables, while percentages and proportions will be computed for categorical variables. Descriptive statistics for interval-level and ratio-level variables will be applied to report the results. Inappropriate antibiotic prescribing percentages prior to the COVID-19 pandemic will be compared with antibiotic use during the pandemic. Additionally, the ratio of AMS implementation strategies will be measured, including AMS strategies, such as IV-to-Oral switch, antibiotic discontinuation, de-escalation, dose adjustment, and antibiotic review based on the local guidelines measured. Further, measure antibiotic utilisation and consumption before and during the COVID-19 pandemic. Laboratory and other diagnostic

methods, such as chest X-ray (CXR), procalcitonin (PCT), C-reactive protein (CRP), Leukocytosis (WBC > 10,000/mm 3), and fever in patients infected with RTIs or pneumonia before and during the COVID-19 pandemic among infected patients treated with antibiotics, will be analysed using the ANOVA test for multiple variables.

5. Prospective Online Survey

(Phase 2: Online Survey at Bedfordshire Hospitals NHS Trust)

Though the first phase of this research study will measure AMS implementation before and during the COVID-19 pandemic, there consequently remains a strong need to determine the antibiotic prescribing behaviours among HCPs. For this reason, this second phase is essential to explore the factors that affect AMS implementation before and during Covid.

5.1. Objectives:

In this phase, the survey will use closed and open-ended questions based on PHE antibiotic prescribing literature review and behavioural analysis [6]. The survey aims to explore the HCPs' perceptions, attitudes towards antibiotic prescribing and AMS implementation before and during the COVID-19 pandemic (Appendix 16).

5.2. Methodology:

This study will use a cross-sectional online survey based on PHE behaviour change and antibiotic prescribing in secondary care settings [6]. A mixed open and close-ended questionnaire survey will be conducted through a secured and UH trusted survey platform, Qualtrics XM. This survey aims to explore perceptions, attitudes, and AMS implementation among HCPs (doctors, nurses, and pharmacists) before and during the COVID-19 pandemic.

5.3. Inclusion criteria:

1. Health Care Professionals (doctors, nurses, and pharmacists).
2. Adults 25 years and older.
3. Registered with the relevant professional regulatory body; GMC, GPhC and NMC.
4. HCPs who were working before/during the COVID-19 pandemic at Luton and Dunstable hospital and/or Bedford hospital and still working in one or two of these hospitals' sites.

5.4. Exclusion criteria:

1. HCPs (doctors, nurses, and pharmacists) who are not currently working at the Bedfordshire Hospitals NHS Trust.

5.5. Study Participants:

After receiving approval from the Research Ethics Committee (REC) and the University of Hertfordshire (UH) ethics, the survey link will be disseminated by the local research office (R&D) to the study participants from HCPs working in the Bedfordshire Hospitals NHS Trust. Potential participants will be identified by the hospital collaborator (Patricia Edwards) according to the study inclusion criteria and sample size calculations. The research and development (R&D) office will send the initial original email electronically to the HCPs' secure emails first. This email aims to invite health professionals to participate in the survey. It will include the invitation letter that consists of the Participant Information Sheet (PIS) and the survey link (Appendix 17). After four weeks from the initial email, the R&D office will send the second email, as a reminder, inviting health professionals to participate by clicking on a survey link. Submitting responses after completing the online survey will be taken as implied consent to participate in the survey (Appendix 18). Participants can also decide whether or not to participate as long as the survey link remains live. Participants will be advised on the survey closing date in the reminder email after which an opportunity to participate will no longer be possible as the link will become inactive. Only the research team will have access to this data. All collected data will be anonymised once the submission is completed.

5.6. Access to participants' data during the study

The study will involve a survey of doctors, pharmacists and nurses engaged in antibiotic use and prescribing during the COVID-19 pandemic. The survey is based on PHE antibiotic prescribing behaviour literature review and behavioural analysis. All collected data will be anonymised with no participants' identifiers and all data will be kept confidential in password-protected files. It will not be possible to link any comment to any participant. Only the PI/PhD student will access the respondent's data, analyse, and interpret the results. This anonymised data will be stored on the University's secured network storage system, which requires a double security check.

5.7. Data Confidentiality:

Only the PI/PhD student will access the respondent's data, analyse, and interpret the results. The results interpretations will be discussed with the UH Academic Supervisors (Dr Zoe

Aslanpour and Dr Nkiruka Umaru) listed in this protocol. The anonymised data will be stored on the University's secured network storage system, which requires a double security check.

5.9. Expected outcomes

Primary outcome:

- Antibiotic prescribing behaviour of HCPs will be explored using the range of knowledge, attitudes, and perceptions questions.

Secondary outcome:

- Factors affecting AMS implementation will be explored using the range of AMS implementation before and during the COVID-19 pandemic.

5.10. Sample Size:

To ensure the feasibility and accuracy of the calculated sample size, the PhD student/PI obtained the figures on the total number of employed registered pharmacists as 206, the total number of employed registered nurses as 2,140 and the total number of employed registered doctors as 5,636. Additionally, the PI obtained the total number of health professionals (headcount) which is 7,982. The sample size n and margin of error E are given by:

x	=	$Z(^{c}/_{100})^{2}r(100-r)$
n	=	$^{Nx}/_{((N-1)E^{2}+x)}$
E	=	$\mathrm{Sqrt}[^{(N-n)x}/_{n(N-1)}]$

Where N is the population size, r is the fraction of responses that you are interested in, and $Z(c/100)$ is the critical value for the confidence level c. The sample size for the survey will be 240, with a margin of error is 5%, a confidence interval is 95%, and a response rate of 20%. All sample size calculations for both phases were verified by the University of Hertfordshire (UH) statistician support.

5.11. Method of analysis

The PhD student/PI will collect, extract, and analyse the results. The academic supervisors will also discuss with the PI the emerging themes, categories, and concepts. An iterative data analysis process will be employed to identify and categorise ideas into key themes and their relationships. The quantitative data will be analysed using Qualitative Data Analysis

Software (MAXQDA) to facilitate the categories process. The textual material will be analysed in terms of categories. Any disagreements will be resolved through discussion.

6. Timelines:

This study will start on 01st September 2022: After receiving approval from the NHS and UH ethics.

End of Study: This study will be continued until the required data sample is extracted before 31st August 2024. It will end when the last survey response is received from the last participant.

7. Ethical Consideration in Both Phases:

7.1. Clinical Neglicance:

The research student undertook a training course provided by the National Institute of Clinical Research (NIHR) on Good Clinical Practice (GCP) (Appendix 10).

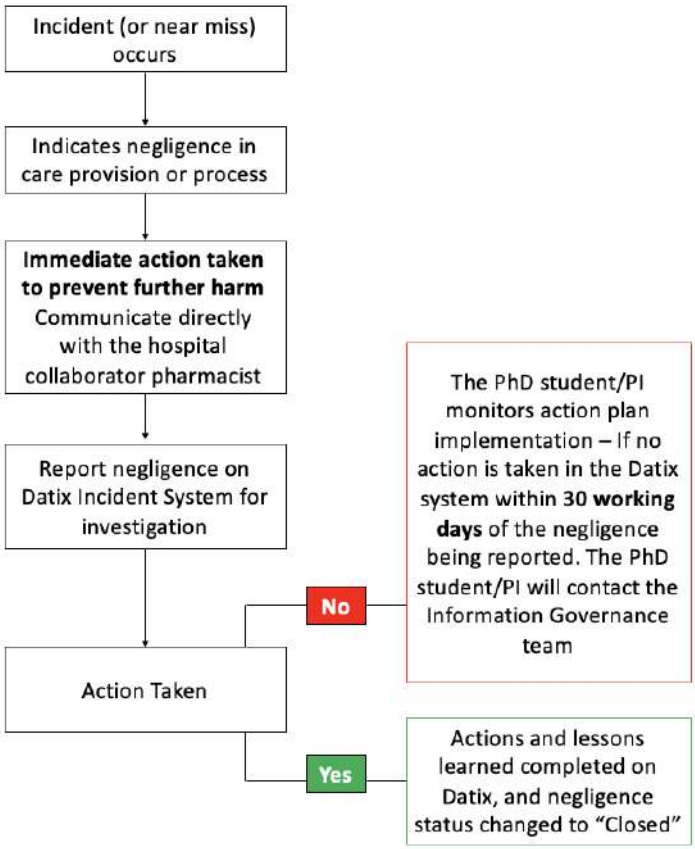
In line with the learning from the above course, potential harms found in patients' notes in the Trust will first be flagged with the team involved in patients' care if considered reasonably appropriate to do so. This is because any findings of potential harm by the research student, if not handled with diplomacy, may impact negatively on good relationships, which is very necessary for the success of the research at the Trust. Negligence in care provision or process which is also considered as patients' safety related matter of concern due to care provision. A detailed procedure is established, with the proposed guidance for dealing with any clinical negligence or incident. It includes the description of each potential deficiency. Hence the first-place concerns will be raised with the hospital collaborators within the Trust.

The following steps will be considered:

1. If the PhD student/PI discovers any negligence, she will communicate with the hospital collaborators to discuss the negligence issue.
2. Immediate action taken to prevent further harm. The PhD student/PI will communicate directly with the hospital collaborator pharmacist.
3. Report the negligence on Datix System for investigation.
4. The PhD student/PI monitors action plan implementation – If no action is taken in the Datix system within **30 working days** of the negligence being reported, the PhD student/PI will contact the Information Governance team.

5. Actions taken and lessons learned completed on Datix, and clinical negligence status changed to “Closed”.

Figure 5. Negligence Reporting Process Overview Flow Chart



7.2. Risk of Bias:

Bias to data extraction due to the PhD student’s professional role as a pharmacist will be minimised by maintaining the selection of samples and quality checks by the hospital collaborators (Patricia Edwards and Sanil Petal) of data extraction.

7.3. Risk assessment

7.3.1. Risk of exposure to patients' sensitive data

CAG was provisionally supported, with satisfactory responses to the requests for further information and compliance with the standard and specific conditions of support. CAG is also supported for the duration of the retention of the key between confidential patient information and the pseudonymous study ID. Access to patients' identifiable data will be only restricted to the PI and external collaborators at Bedfordshire Hospitals NHS Trust (L&D and Bedford hospitals). Data will be saved as a password-protected document accessible to Patricia Edwards and the PhD student on the hospital sites. The PI will anonymise the extracted data and store it on the University's secured network storage system, which requires a double security check for analysis. Identifiable data will be anonymised before leaving the research hospital site.

7.3.2. Risk of identification of evidence of clinical negligence

Phase 1: In the Retrospective study, the PI will flag any clinical negligence with the hospital collaborators who are part of the direct care team and who will take responsibility for dealing with this issue. They will follow up with the team involved in patients' care in both hospitals. These will escalate information if considered reasonably appropriate to do so.

Phase 2: In the survey study, the PI will be unable to address any survey responses directly because responders' details will be anonymised. However, if there is any notable evidence from the submitted responses, the hospital collaborators will be informed.

7.3.3. Research Ethics Committees

Ethics approval will be sought from the NHS Research and Ethics Committee (REC), the University of Hertfordshire Ethical Committee, and reviewed with Bedfordshire Hospitals NHS Trust Research and Development (R&D) department before starting the study. The PhD student/PI has signed an honorary contract until the end of this research project. The PI received an NHS secure email and a user account to access the electronic system in both hospitals. The PI will protect the confidentiality of data; all identifiable patient data will be stored only in the hospital system. The PhD student will be able to liaise with Patricia Edwards if they need access to the linked patient record/study ID list. The PhD student will no longer have access to patient identifiable data after the end of Phase 1, which is 31st August 2023.

7.3.4 Validity

In Phase 1, the PhD student/PI will extract data from the validated data extraction tool, generated from the literature.
In phase 2, the survey will be validated by piloting the survey among 5% of the sample size (pharmacists, nurses, and doctors), using SPSS program.

7.4. Reliability

In phase 1: Reliability will be determined by the percentage of agreement between the PI/PhD student and the hospital collaborators hospital collaborators, AMS pharmacist. Abdul Mohamed will extract data from 10 patients' medical records one week after the first extraction by the PhD student/PI. Agreement in the two extracted data will be ascertained using Cohens Kappa to check the intra-rater reliability. Agreements of ≥80% will be considered an indicator of the instrument's reliability and process. Any disagreements will be clarified via dialogue.

In phase 2: The results from the pilot test will be imported into SPSS software to check for reliability and validity.

8. Data Protection and Confidentiality of Study Data

In both studies, measures will be taken to maintain participant anonymity. The PI will protect the confidentiality of data; the patient's identifiable data will be stored in the hospital system. The anonymised data will be held on the University's secured network storage system, which requires a double security check. CAG supervision was obtained to access the patient's identifiable data in the retrospective study without consent. Then the hospital collaborator will anonymise the data and transfer it electronically to the online double secure University of Herefordshire system for analysis and results. No mobile devices are used for transferring data. The anonymised data will be kept on the University's secured network storage system, which requires a double security check.

9. Regulatory Considerations

All the participants will be treated by the ethical guidelines outlined by the National Research Ethics Service (NRES) and obtain the NHS ethics approval and the Health, Science,

Engineering and Technology ECDA (Ethics Committee with Delegated Authority) at the University of Hertfordshire.

9.1. Discontinuation/Withdrawal of participants from the study

Participants have the right to withdraw from the study or not participate without giving a reason before the survey has been completed. Though, once they are completed and submitted, participants will not be able to withdraw, as their data will be anonymised entirely at this stage. Furthermore, the response data of the withdrawn participants will be included in the analysis and dissemination.

9.2. Approval

The study protocol and all supporting materials, including the participant information sheet, will be submitted to seek Research Ethics Committee approval and the UH Ethics Committee. The Investigator will submit and, where necessary, obtain permission from the above parties for all substantial amendments to the original approved documents. The CI will ensure all the appropriate approvals from participating organisations will be undertaken before the study has been started.

10. Peer Review

The Research Information and Governance team has reviewed the research protocol at the University of Hertfordshire. In addition to the external review to maintain the scientific quality of this research study. The research protocol was reviewed and critiqued by an independent external academic consultant pharmacist from Hertfordshire University (Dr Andrzej Kostrzewski) to assess the quality of this research study. The research team consists of qualified academics considered field experts in pharmacy practice, AMS, and research.

11. Finance

This research is being conducted as part of a doctoral degree (Rasha Abdelsalam Elshenawy). There is no funding for this research project. However, there is no conflict of interest between the PhD student/PI and the study outcomes.

12. Publication Policy

The study results will be submitted for publication in a peer-reviewed journal. The PhD student/PI will prepare the manuscript in collaboration with the research team members, and mutual agreement will determine authorship. Additionally, the publication bias was avoided by publishing this research study in these public databases:

- The study's systematic review was published on the PROSPERO website [9].
- The research project will be published in ISRCTN under the WHO standards for study registration [11].
- This research project will be registered and published in the University of Hertfordshire public database.

13. References:

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11. *ISRCTN*. (n.d.). Www.isrctn.com. Retrieved May 31, 2022, from https://www.isrctn.com/ISRCTN14825813

14. Appendices:

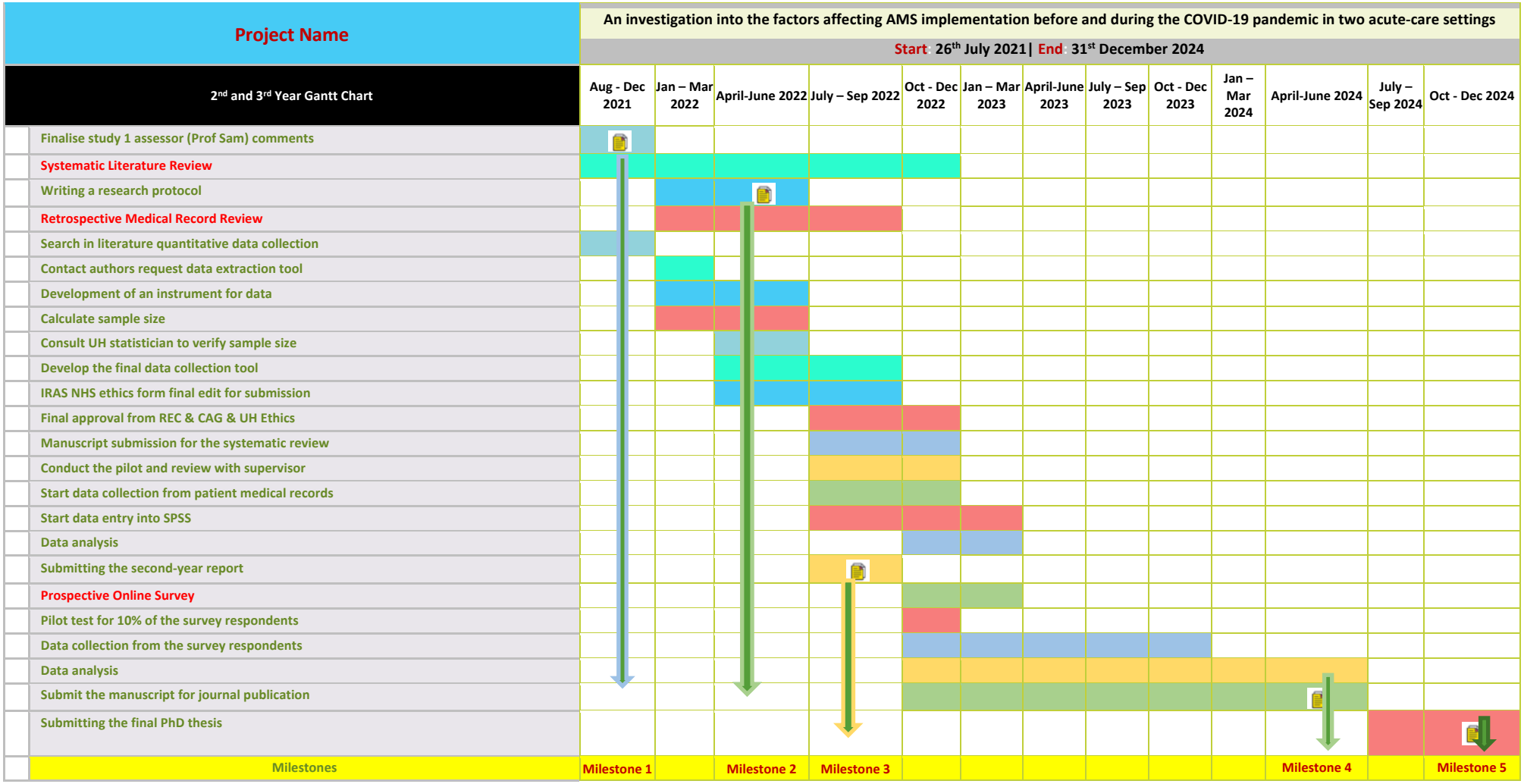
Appendix 1: Research Development Trainings

Date	Session
30/11/2020	The WHO Webinar of the Impact of COVID-19 and Antimicrobial Stewardship
20/01/2021	Writing for, and submitting to, a Journal
21/01/2021	Inferential Statistics
25/01/2021	Research Cycle and Writing a Manuscript
27/01/2021	Systematic Review Critical Appraisal
28/01/2021	Developing your impact plan
28/01/2021	How to Cope with Stress
18/02/2021	COVID-19 and Antimicrobial Stewardship
24/02/2021	Leading creatively across the NHS in 2021
27/02/2021	Project Management NHS Elect Training
15/03/2021	Healthcare Cultural Intelligence NHS Course
17/03/2021	Qualitative Data Analysis: Methods and Techniques
17/03/2021	CVs, Application Forms and Personal Statements
24/03/2021	Reference Management (Endnote, Mendeley and Zotero)
25/03/2021	Research Data Management| Working with Supervisors
25/03/2021	Writers Block &How to Overcome It
30/03/2021	How to give a presentation
15/07/2021	Introduction to Office 365 for UH Researchers
08/09/2021	The British PhD: some key steps to success
09/09/2021	Research Data Management
09/09/2021	Qualitative and Quantitative Research Methods

10/09/2021	Supporting your well being
10/09/2021	The Challenges of your research
15/09/2021	Critical Thinking
15/09/2021	Raising the visibility of your research
16/09/2021	Critical Reading & Writing
16/09/2021	The Writer's Block
17/09/2021	Conceptual Frameworks and concept mapping
17/09/2021	3-minute thesis
12/10/2021	Poster Presentation
04/11/2021	A Guide to Applying for External Research Funding
30/11/2021	Lean thinking methodology
01/12/2021	Quality Improvement projects
07/12/2021	Compassionate leadership
10/02/2022	Critical Reading & Writing
10/03/2022	Technical Writing Course
14/03/2022	Build a Research Website in Under 3 hours
14/03/2022	Social Media Bootcamp: Sharing and Connecting
24/05/2022	Conservational Analysis

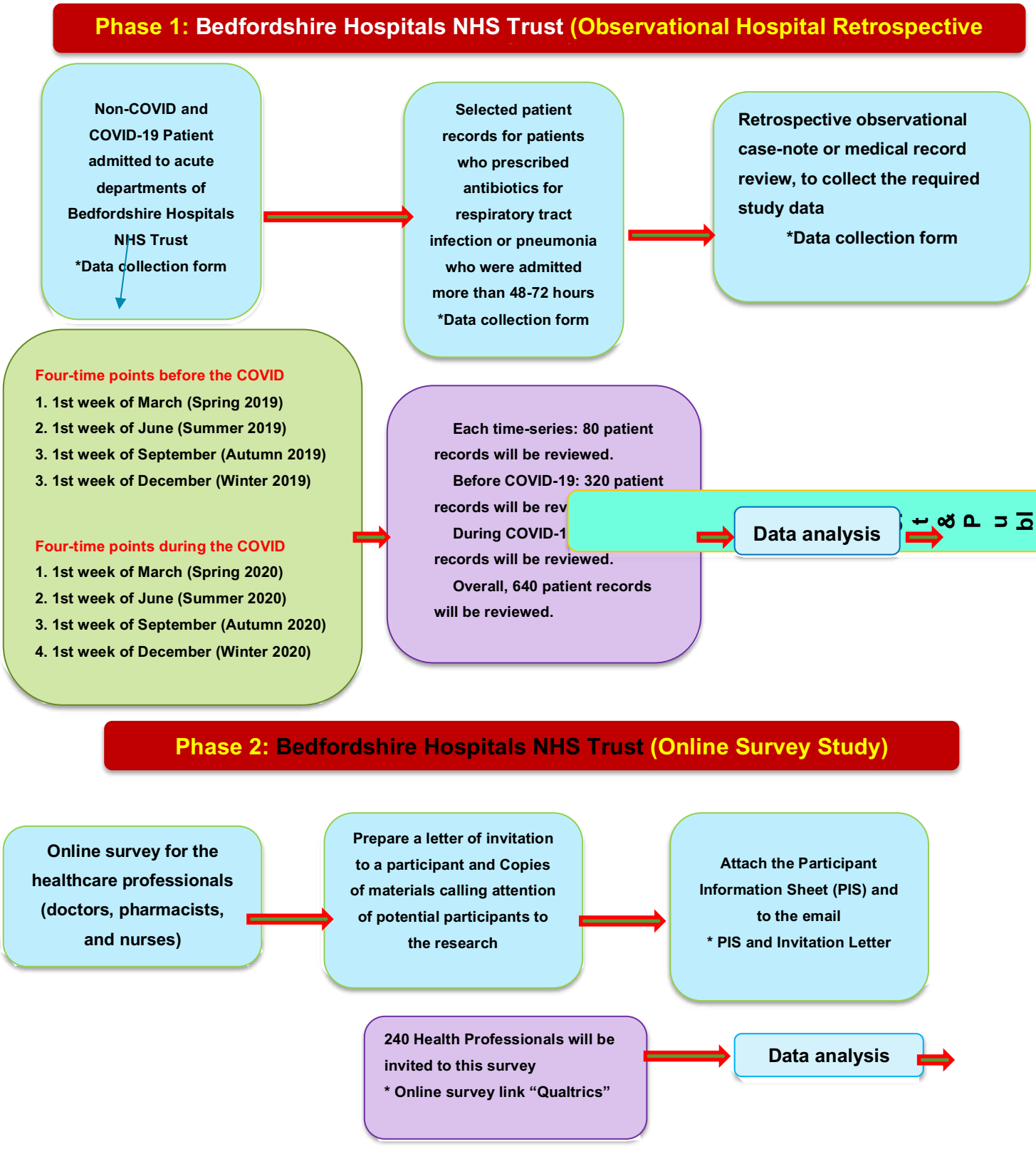
Appendix 2.

Detailed Gantt Chart for sequential studies (Version 3)



		Finalise First Report Comments		Final Version of the Research Protocol	2nd Year PhD Report						Submit the Manuscript for Publication		Complete the Final PhD thesis Report

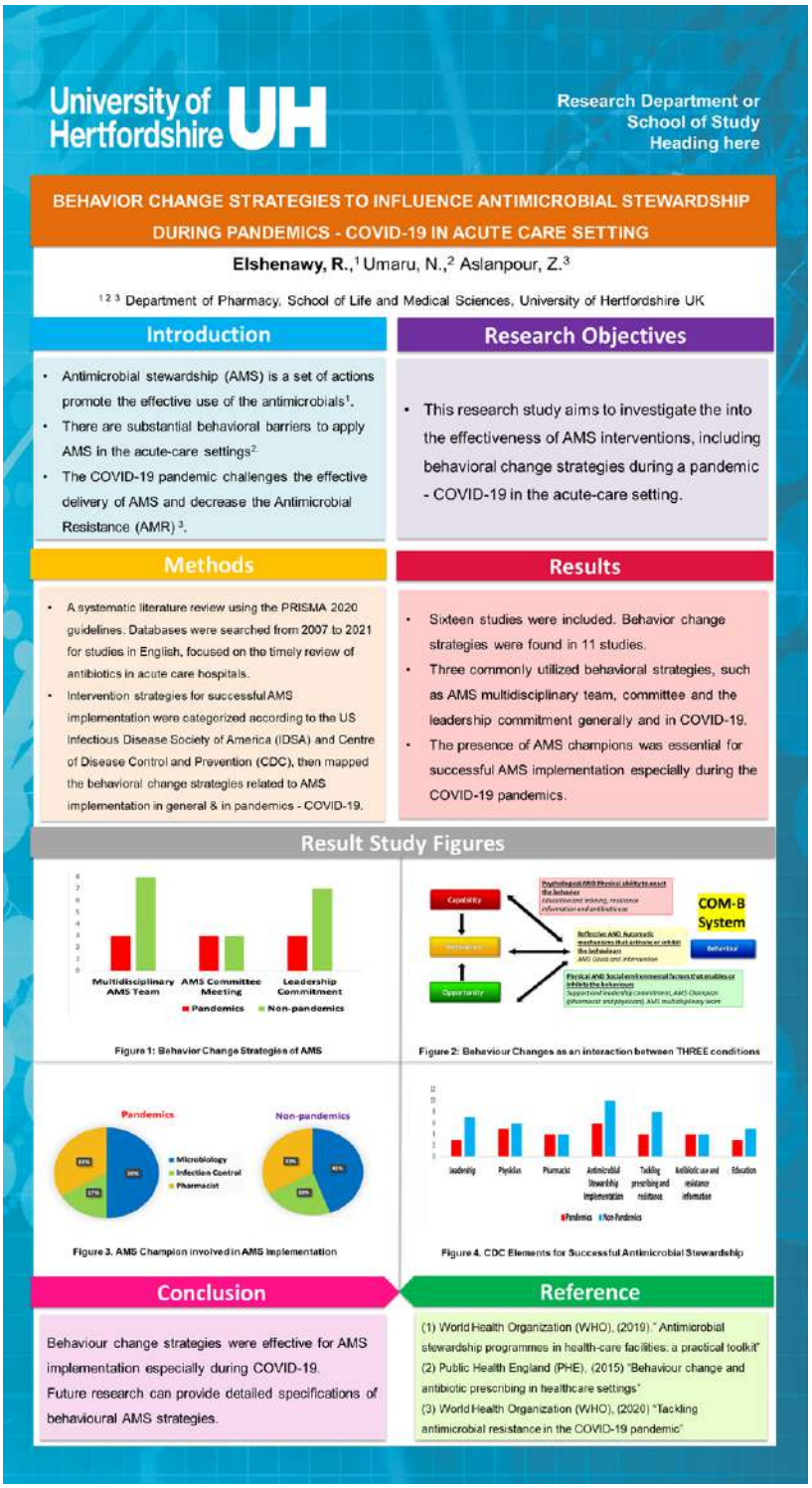
Appendix 3. The flow chart for the research project (Phase 1 and Phase 2)



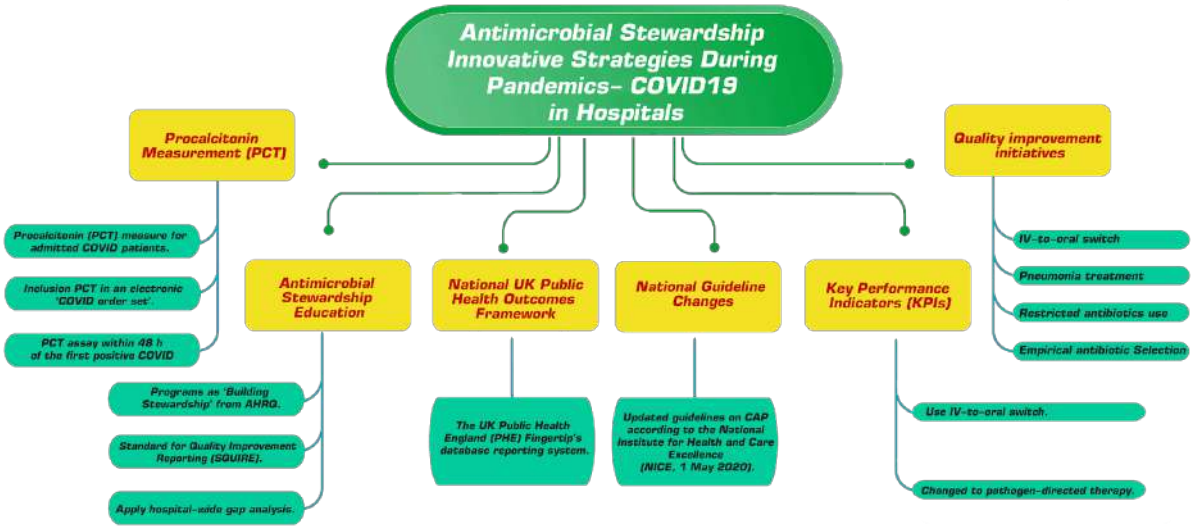
Appendix 4: AMS intervention strategies and their related outcomes (Systematic Review)

AMS Strategies	Evidence Support Outcomes
Formulary restriction	Clinical Outcome Economic Outcome Resistance Outcome
Formulary review/streamlining	Clinical Outcome
General antimicrobial order forms	Clinical Outcome
Inappropriate pathogen/antimicrobial combinations (bug-drug mismatch	Resistance Outcome
Improved rapid diagnostics	Clinical Outcome Economic Outcome Resistance Outcome
Intravenous to oral conversion	Clinical Outcome Economic Outcome Resistance Outcome
Prescriber education	Clinical Outcome Economic Outcome Resistance Outcome
Preventing treatment of non-infectious conditions	Resistance Outcome
Promotion of timely and appropriate microbiologic sampling	Resistance Outcome
Prospective audit with intervention and feedback	Clinical Outcome Economic Outcome Resistance Outcome
Scheduled antimicrobial reassessments ("antibiotic time-outs")	Economic Outcome Resistance Outcome
Strategic microbiology results reporting	Resistance Outcome
Surgical antibiotic prophylaxis optimization	Clinical Outcome
Systematic antibiotic allergy verification	Clinical Outcome
Targeted review of patients with Clostridium difficile infection	Clinical Outcome Resistance Outcome
Targeted review of patients with bacteraemia/fungemia	Clinical Outcome Resistance Outcome
Targeted review of therapeutic duplication	Economic Outcome
Therapeutic drug monitoring (with feedback)	Clinical Outcome

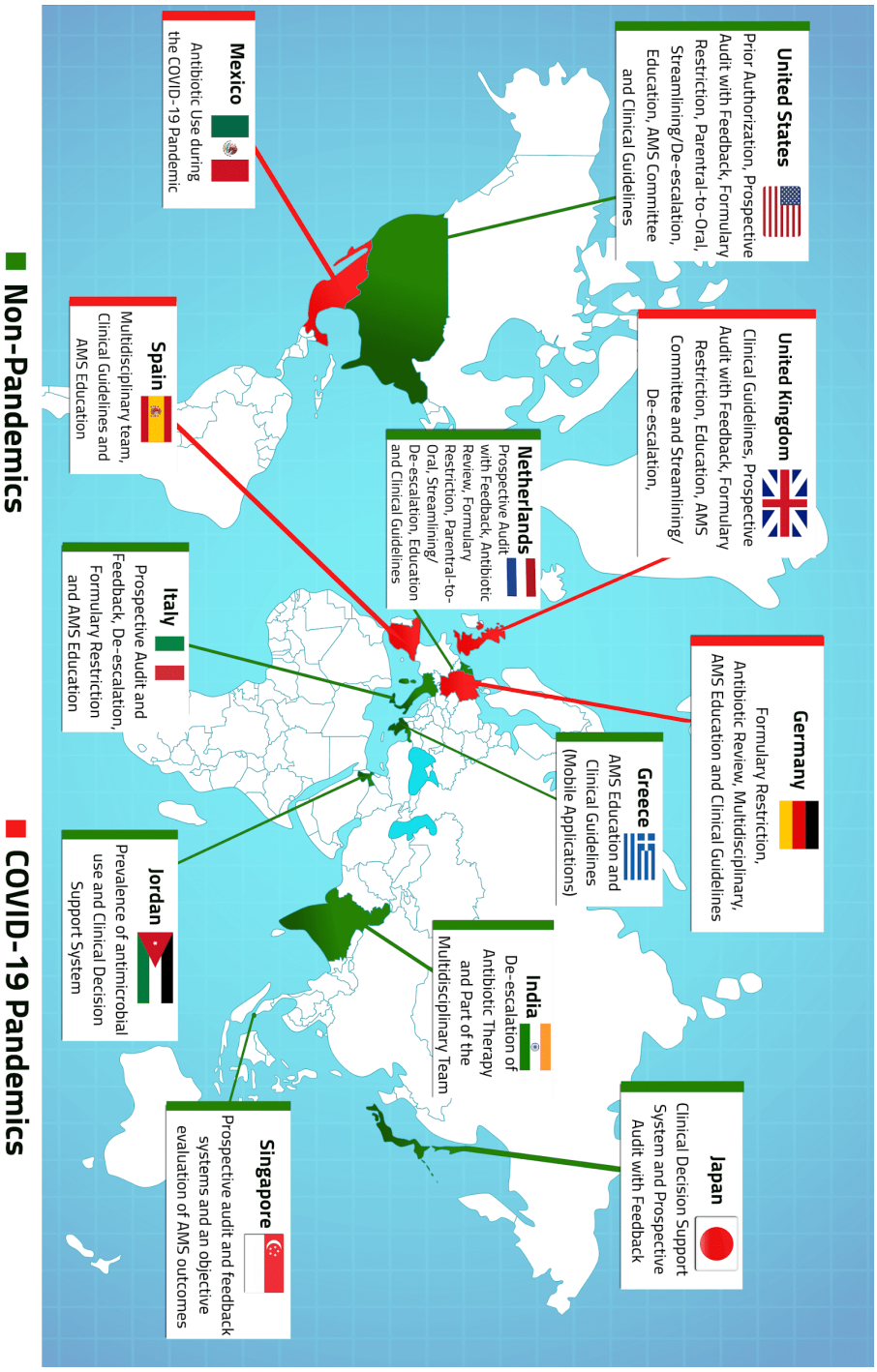
Appendix 5: University of Hertfordshire Conference Poster Presentation (Systematic Review)



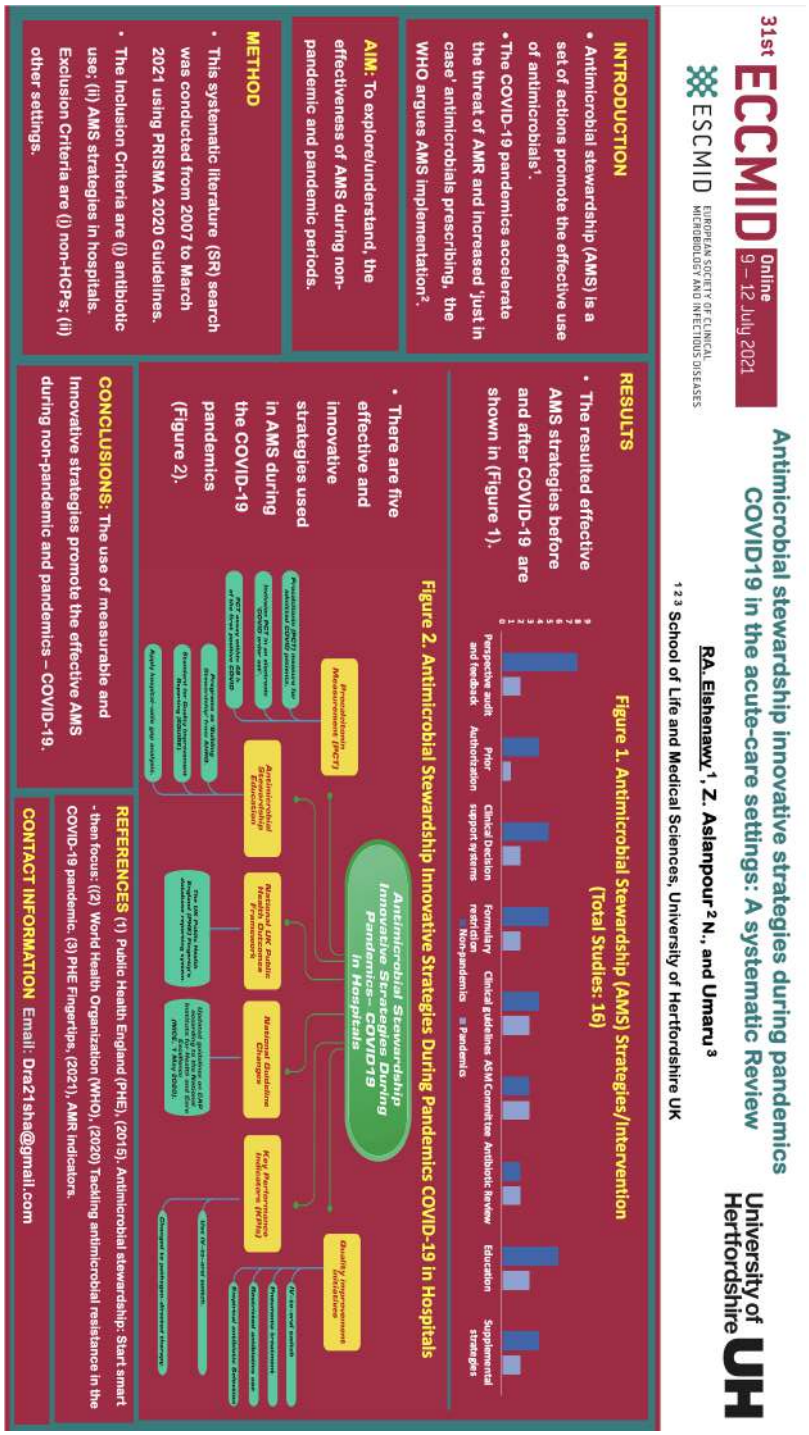
Appendix 6: Innovative Strategies for Antimicrobial Stewardship During COVID-19 (Systematic Review)



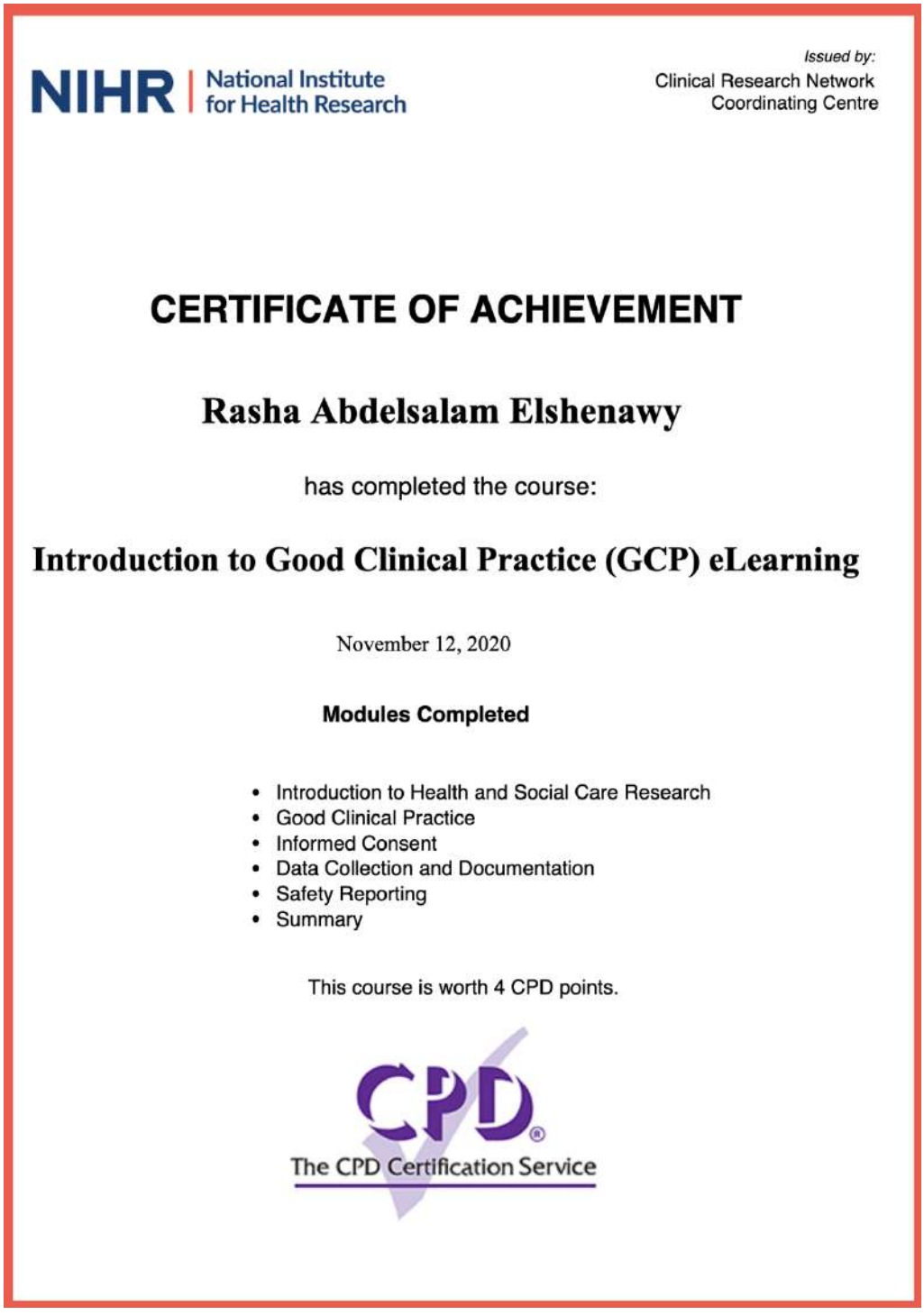
Appendix 7. Global Contribution of Pharmacists in AMS During COVID-19 in Hospitals - Worldwide map (Systematic Review).



Appendix 8. European Congress of Clinical Microbiology & Infectious Diseases Poster (Systematic Review).



Appendix 10: Good Clinical Practice (GCP) certificate from NIHR



NIHR | National Institute for Health Research

Issued by:
Clinical Research Network
Coordinating Centre

CERTIFICATE OF ACHIEVEMENT

Rasha Abdelsalam Elshenawy

has completed the course:

Introduction to Good Clinical Practice (GCP) eLearning

November 12, 2020

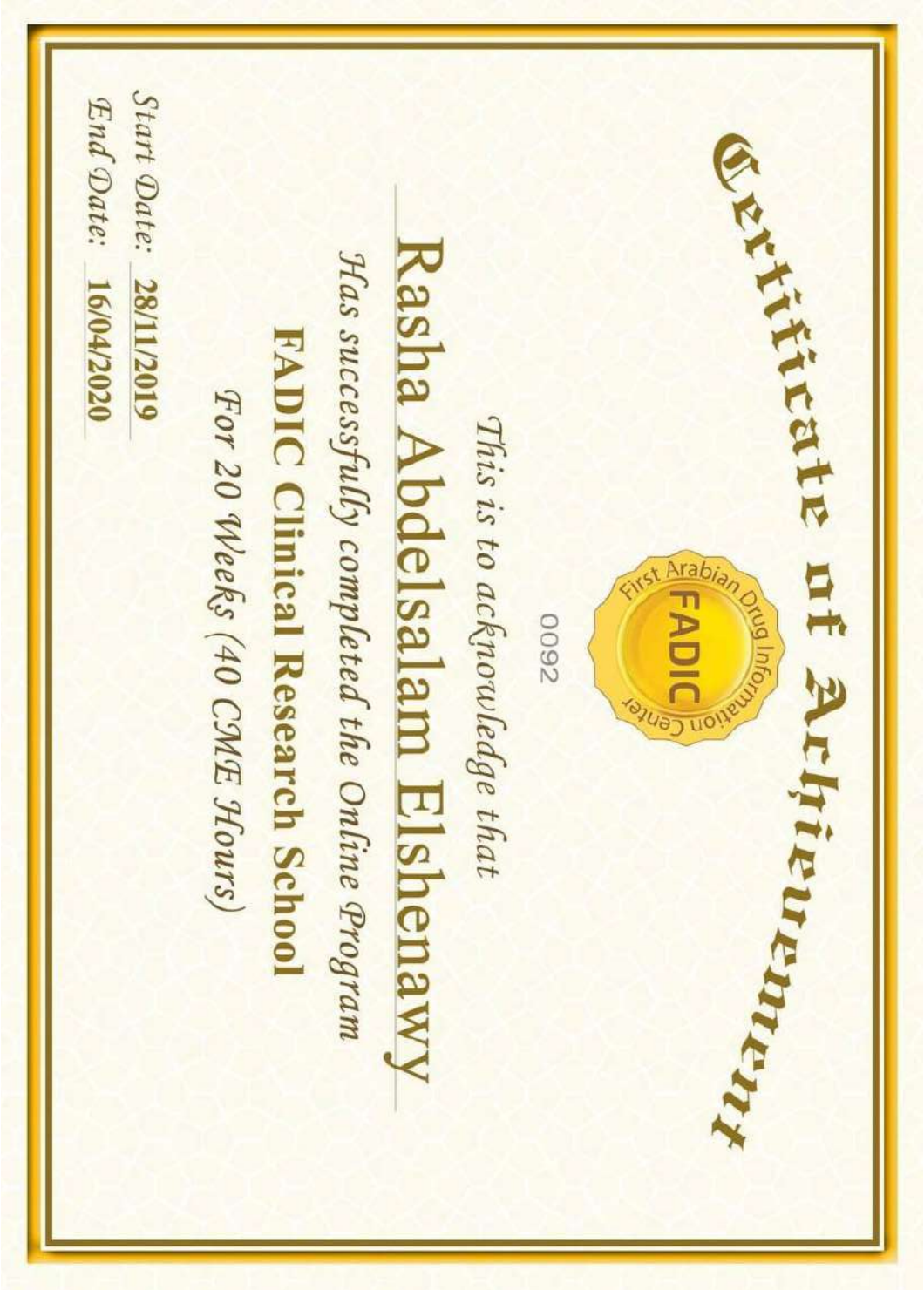
Modules Completed

- Introduction to Health and Social Care Research
- Good Clinical Practice
- Informed Consent
- Data Collection and Documentation
- Safety Reporting
- Summary

This course is worth 4 CPD points.

CPD
The CPD Certification Service

Appendix 11: Clinical Research Certificate



Certificate of Achievement

0092

First Arabian Drug Information Center FADIC

This is to acknowledge that

Rasha Abdelsalam Elshenawy

Has successfully completed the Online Program

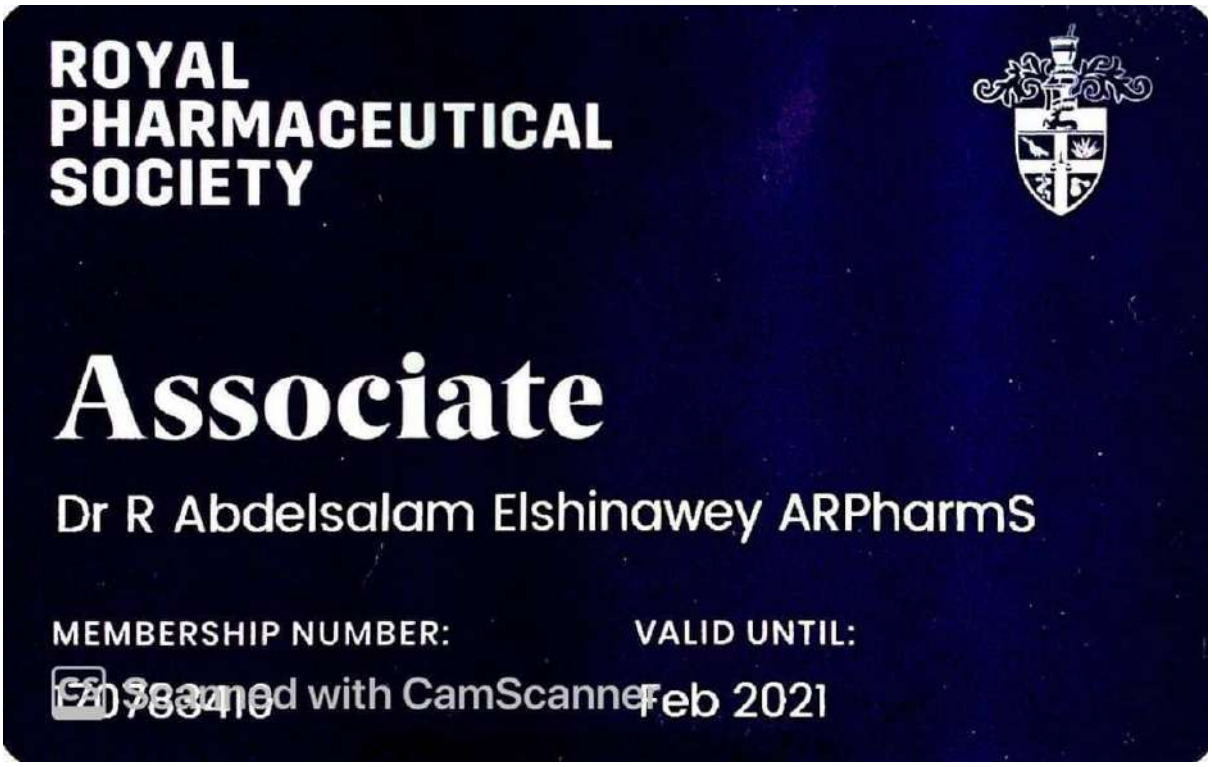
FADIC Clinical Research School

For 20 Weeks (40 CME Hours)

Start Date: 28/11/2019

End Date: 16/04/2020

Appendix 12: Royal Pharmaceutical Society Membership



Appendix 13: American Board of Pharmacy Specialties Certificate with added qualification of infectious disease

Board of Pharmacy Specialties

Hereby Certifies that

Rasha Abdelsalam Elshenawy

having satisfied all the requirements for re-certification in the specialty practice area of

Pharmacotherapy

and upon the recommendation of the Specialty Council on Pharmacotherapy and is is designated

Board Certified Pharmacotherapy Specialist

For the period of 2022-2028

Credential Number : 31401255

Given this 1st day of January 2022

First certified on the 31st day of July 2014

Founded by the American Pharmacists Association 1976

Appendix 14: Antimicrobial Stewardship Program Certificate

SIDP
SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

ProCE

CERTIFICATE OF ACHIEVEMENT

This acknowledges that

Rasha Abdelsalam Elshinawey

has, on ***January 20, 2017****, successfully completed the* ***SIDP Antimicrobial Stewardship Certificate Program,*** *a national program for pharmacists providing or implementing antimicrobial stewardship programs.*

Richard Lewis, Pharm.D., MBA.
President & CEO, ProCE, Inc.

Date: 1/27/2017

Jason Gallagher, Pharm.D.
President, Society of Infectious Diseases Pharmacists

Date: 1/27/2017

Appendix 15: Data Extraction Tool

Start Smart																
Empirical Antibiotics (on Admission)																
Abx Allergy	Clinical Indication	Stat Antibiotic	Empirical Antibiotics	indication	initial abx	start date	end date	Is comply with local guidelines (Y/N)	Did culture obtained prior to Abx (Y/N)	Is abx use reviewed? (Y/N)	If yes, who reveiw the abx ?	Day of review	Nature of intervention	abx changed before/after culture?	abx changed before culture results?	What AMS strategy/ intervention taken	Reason for continuation recorded (Y/N)

Targetted Antibiotics (After Culture) - Change Antibiotic						IV-to-Oral Switch		
Microbiology Check	Antibiotic used after cuture results	What is the culture results	appropriate abx choice	appropriate duration	appropriate indication	initial abx (Empirical)	abx changed to (Targetted)	Route of abx

Then Focus														
Abx Stop		Other Complication									Other Investigations			
Date of Start Abx	Date of Stop Abx	HTN	other CVD	Lung	Kidney	Liver	malignancy	Transplant	Others	Inpatient History	X-Ray	PCT test	WBCs	Fever

Appendix 16: PHE antibiotic prescribing behaviour in acute care settings reference form survey study

(Theoretical Domains Framework)	Barriers and facilitators	Issue
Knowledge	Evidence	Doctors are not sufficiently aware of the scale of AMR.
		Doctors are not aware of guideline or are sceptical if they suspect guidelines may not be up to date.
		Posters were felt to be effective when placed in front of junior doctors.
		Doctors omit to draw blood samples for microbiological evaluation (cultures) on admission.
	Proposed	Doctor understands basic microbiology and routine clinical therapeutics
		Doctor is aware of the threat of antimicrobial resistance.
Skills	Evidence	Medical school insufficiently prepares doctors for which antibiotic is appropriate; yet this may differ by hospital and specialty.
	Proposed	Doctor is able to appropriately balance clinical need with population risk
		All clinical staff (nursing staff in particular) are able to identify the early stages of infection (in particular surgical site infections).
		Nursing staff are able to identify a change in clinical trajectory and escalate situation as needed.
Memory, attention and decision processes	Evidence	In teaching hospitals, antibiotic prescribing decisions are frequently made by least experience.
		Doctors tend to exercise clinical judgment that takes precedence over guidelines.
		Decision-making is often challenged by pressures on time.
		Doctors rated resistance as the least important factor in their decision-making.
	Proposed	Doctor undertakes appropriate microbiological tests in a timely manner
		Doctor starts appropriate antibiotic therapy as required (in respect of agent, route and duration).
		Doctor reviews microbiological evidence at appropriate time point and amends therapy as required – likely best to coincide with ward round
		Doctor is conscious that, if having experienced a patient with a substantially bad outcome in the past (which may have been averted by timely antibiotics), this was the exception and not the rule.
		Doctor considers antimicrobial resistance when selecting an antibiotic.
Professional, social role and identity	Evidence	A staff group who perceived that they were disengaged from the development process tended to ignore the consequent guidelines.
		The medical hierarchy prioritises autonomy and deviation from guidelines.
		Junior doctors learn their practice from seniors.
		Nursing staff can be well-placed to request oral-IV switch.
		Desire for clinical microbiologist / pharmacist to support decision making.
	Proposed	All staff feel engaged in the antibiotic guideline and therefore act upon it.
		Senior doctors and pharmacists take opportunities to educate and demonstrate to juniors the appropriateness of antimicrobial therapy (including breadth of spectrum and route).
		Doctors duly consider the needs of society
		Doctors strike an appropriate balance between guidelines and clinical judgment
		Junior doctors are enabled to question management plans developed by their seniors and viceversa
		Staff witness senior leadership prioritising AMR as a challenge to be overcome
Beliefs about capabilities	Evidence	Doctors express greater confidence in using intravenous therapy over oral alternatives.
	Proposed	All clinical staff perceive stewardship as an area to which they can effectively contribute
		Doctors are confident of switching from intravenous to oral therapy in a safe and timely manner
		Clinical staff believe that their contribution is not over-shadowed by other factors such as veterinary prescribing or international trends.
Beliefs about consequences	Evidence	Guidelines may be insufficiently clear and doctors may have greater confidence in intravenous therapy.
		Clinicians accept AMR affects the system and institution
	Proposed	Clinical staff believe that appropriate rationing of antibiotics will not attract blame (if a patient comes to harm as a result of not receiving a prescription).
		Clinical staff believe that resistance affects their own practice.
		Clinical staff believe their actions are having a positive effect for society and future generations.
		Clinical staff believe that failure of stewardship may result in a pre-antibiotic era.
		Clinicians feel it is still valuable to switch intravenous to oral therapy

Appendix 17. Participant Information Sheet

Healthcare Professional Information Sheet

Title of Project: An investigation into factors affecting the implementation of Antimicrobial Stewardship (AMS) before and during the COVID-19 pandemic at Bedfordshire Hospitals NHS Foundation Trust.

IRAS Project ID: 314805

Name of Researcher: Rasha Abdelsalam Elshenawy

Research Ethics Committee…

Introduction:

UK health officials warned that antimicrobial resistance (AMR) was a "hidden pandemic" that could emerge in the wake of COVID-19 unless antibiotics were prescribed responsibly. This study aims to explore the views of clinicians, nurses and pharmacists toward antibiotic prescribing before and during the COVID-19 pandemic. You are invited to participate in this study to explore factors affecting AMS implementation and antibiotic prescribing behaviour perceptions and attitudes before and during the COVID-19 pandemic at Bedfordshire Hospitals NHS Trust. This study is about a topic known as “antimicrobial stewardship”, and we want to understand the factors that feed into how decisions to prescribe antibiotics were made both before and during the pandemic. We are doing this because we believe lessons could be learnt from COVID-19 pandemic, and we need your help to learn them. Your participation will help us understand the antibiotic prescribing behaviour, find the factors that improve the antibiotic prescribing and maintain the appropriate and judicious use of antibiotics.

This study will be undertaken based on the University of Hertfordshire’s regulation, UPR RE01; you can access UH regulation via this link: https://www.herts.ac.uk/about-us/governance/university-policies-and-regulations-uprs/uprs. After accessing this link, scroll down to Letter S, where you will find the regulation 'Studies Involving the Use of Human Participants’.

Please take your time to read the following information carefully before deciding to participate. Do not hesitate to ask us for anything that is not clear or requires further information.

Thank you for reading this.

What is the purpose of this study?

AMS was established to effectively use antibiotics, prevent antimicrobial resistance, improve patient safety, and reduce healthcare costs. The implementation of AMS was highly challenged during the COVID-19 pandemic. Public Health England (PHE) has always emphasised the need for AMS implementation in acute care settings to maintain the appropriate, effective, and safe use of antibiotics. We don't know AMS measures that improved the prescribing of antibiotics during the pandemic, nor what actually happened. This study is being conducted as part of a doctoral programme of study. It aims to explore factors affecting AMS implementation and antibiotic prescribing behaviours, perceptions, and attitudes before and during the COVID-19 pandemic in Bedfordshire Hospitals NHS Foundation Trust (Luton & Dunstable and Bedford hospitals).

Most of the deaths from AMR were caused by infections, such as Respiratory Tract Infections (RTIs) and pneumonia. **The first part of this study** involves the review of patient records, including those prescribed antibiotics for RTIs or (COVID) pneumonia, before and during the COVID-19 pandemic. It is also essential to identify the factors that feed into how decisions to prescribe antibiotics are made both before the pandemic and during it. **The second part of this study** will use an online survey to explore factors affecting AMS implementation and antibiotic prescribing behaviours, perceptions, and attitudes before and during the COVID-19 pandemic. Your participation in this survey will help us understand these factors, as we are certain that lessons could be learnt from the COVID-19 pandemic. We need your help to learn them, maintain the proper use of antibiotics and provide guidance to prescribe antibiotics appropriately.

Do I have to take part?

Your participation in this study is entirely voluntary, and there is no obligation to take part in it. Nevertheless, your participation is desirable for this study to achieve the objectives. Therefore, we would encourage you to participate. Your answers will be anonymised. The information collated in this study will only be used for research purposes. Data will be strictly confidential.

Is there any age or other restrictions that may prevent me from participating?

If you are one of the healthcare professionals (doctors, nurses or pharmacists) working before/during the COVID-19 pandemic at Luton and Dunstable hospital and/or Bedford hospital and still working in one or two of these hospitals' sites, you would be eligible to participate in this survey questionnaire.

How long will my part in the study take?

Completion of the survey is expected to take 20 minutes. No other time commitments are required from participants.

What will happen to me if I take part?

You will be invited to fill out the online survey. Access to the survey is via the link included in the email. Submitting your responses after completing the online survey will be taken as implied consent that you wish to participate in the study. Only the research team will have access to this data. All collected data will be anonymised once the submission is completed.

What are the possible disadvantages, risks, or side effects of taking part?

Other than the time required, there are no anticipated disadvantages to your participation. You can ask for further information or raise concerns directly to the study team (contact information provided further on).

What are the possible benefits of taking part?

There is no direct benefit to you, but your participation will help the study team, and a wider audience better understands the factors affecting AMS implementation in both hospitals during the COVID-19 pandemic. It is anticipated that the overall results of this study will inform the development of AMS policies and actions that could support effective and appropriate antibiotic use in future emergencies, to decrease the threat of antimicrobial resistance (AMR).

How will my taking part in this study be kept confidential?

All collected data will be anonymised entirely with no participant identifiers. It will not be possible to link any comment to any participant. It will be stored on the University of Hertfordshire (UH) secured network storage system, which requires a double security check to access. Only the research team will have access to this anonymised data.

Can I withdraw from the study after completing the survey?

Participants have the right to withdraw from the study or not participate without giving a reason before the survey has been completed. Though, once they are completed and submitted, participants will not be able to withdraw, as their data will be anonymised entirely at this stage. Furthermore, the response data of the withdrawn participants will be included in the analysis and dissemination.

Will the data be required for use in further studies?

The data collected will not be used in future studies beyond the current research.

What happens when the study ends?

The survey responses will be analysed for publication. It is anticipated that the overall results of this study will inform the development of AMS policies and activities to improve antibiotic use and prescribing in hospitals. The survey results will be shared with AMS teams and disseminated within peer-reviewed scientific journals and conferences.

Who has reviewed this study?

This study has been reviewed by:

- The University of Hertfordshire Health, Science, Engineering and Technology Ethics Committee with Delegated Authority.
- NHS Research Ethics Committee.

Whom can I contact if I have any questions?

If you would like more clarification or further information, please contact:

Rasha Abdelsalam Elshenawy, the principal investigator, email: rasha.elshenawy@nhs.net

Work number: 07393530537

Dr Zoe Aslanpour, principal supervisor, email: z.aslanpour@herts.ac.uk

Dr. Nkiruka Umaru, supervisor, email: n.e.umaru@herts.ac.uk

Although we hope it is not the case, if you have any complaints or concerns about any aspect of the way you have been approached or treated during this study, please write to the University's Secretary and Registrar at the following address:

Secretary and Registrar
University of Hertfordshire
College Lane
Hatfield
Herts
AL10 9AB

Thank you very much for reading this information and considering participating in this study.

Appendix 18. Survey for knowledge, attitudes, perceptions of HCPs towards antibiotic prescribing and AMS implementation before and during the COVID-19 pandemic

Welcome to the research study!

You are invited to participate in a survey entitled **"Exploring healthcare professionals' knowledge, attitudes and perceptions towards antibiotic prescribing in Bedfordshire Hospitals NHS Foundation Trust before and during the COVID-19 pandemic"**. This survey study aims to explore the antibiotic prescribing behaviour in Bedfordshire Hospitals NHS Foundation Trust, Luton & Dunstable and Bedford hospitals. Your participation in this survey will help us understand the knowledge, perception and attitude toward antimicrobial prescribing and identify factors that affect Antimicrobial Stewardship (AMS) implementation before and during the COVID-19 pandemic. **This study has received the approval of NHS Research Ethics Committee (REC): Reference number … and the University of Hertfordshire (UH) ethical approval: Reference number …** If you wish to participate, your confidentiality will be maintained. This survey is completely anonymous, and any response will be kept confidential. The inclusion criteria for this survey are doctors, pharmacists, or nurses, who were working before and during the COVID-19 pandemic at Luton and Dunstable hospital and/or Bedford hospital and still working in one or two of these hospitals. This survey contains three domains of a total of 23 questions.

1. Knowledge
2. Attitudes and Perceptions
3. Practice

It will not take more than 20 minutes to complete. **By answering the questions in this survey or responding, you indicate your implied consent to participate in this study.** We are grateful for your input and support. If you have any further

queries, **please contact Rasha Abdelsalam Elshenawy, PhD student at the University of Hertfordshire.**

Email: Rasha.Elshenawy@nhs.net

Questions 1 to 10 will focus on your demographic information:

Q1. What is your age?

- 25-31 years old
- 32-41 years old
- 42-51 years old
- 52-61 years old
- 62-75 years old

Q2: What is your gender?

- Male
- Female
- Prefer not to say

Q3: What is the highest educational degree you have completed?

- Undergraduate degree
- Postgraduate degree
- Other ... (Please specify)

Q4x. What is your professional background?

- Nurse
- Pharmacist
- Doctor
- Other ... (Please specify)

If Nurses

Q8: What is your job title?

- Certified Nursing Assistant (CAN)
- Licensees Practical Nurse (LPN)
- Registered Nurse (RN)

- Advanced Practice Registered Nurse (APRN)
- Chief Nursing Officer
- Other ... (Please specify)

Q9: What is your speciality? Please type your answer in the box below. You can type more than one answer.

If Pharmacists

Q8: What is your job band?

- Band 4
- Band 5
- Band 6
- Band 7
- Band 8a
- Band 8b
- Band 8c
- Band 9

Q9: What is your speciality? Please type your answer in the box below. You can type more than one answer.

If Doctors

Q8: What is your job title?

- Foundation year 1 (F1) and equivalent
- Foundation year 2 (F2) and equivalent
- Specialty registrar (StR) at ST/CT1-2 and equivalent
- Specialty registrar (StR) at CT/ST3 and above
- Consultant and equivalent
- Other ... (Please specify)

Q9: What is your speciality? Please type your answer in the box below. You can type more than one answer.

Q10: How many years of experience do you have in your profession?

- less than five years
- Six years to less than ten years
- 11 years to less than 15 years
- 16 years to less than 20 years
- 21 years to less than 25 years
- 26 years to less than 30 years
- 31 years or more

Question 11 is related to your **knowledge** about antibiotics during the pandemic.

Q11. To your knowledge, during the COVID-19 pandemic, how much did you agree with the following statements?

Item	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
There were bacterial infections resistant to all available antibiotics.	☐	☐	☐	☐	☐

The empty antibiotics pipeline, a 'miracle solution' to AMR, is unlikely to be found soon.	☐	☐	☐	☐	☐
I understand the basics of microbiology and clinical therapeutics.	☐	☐	☐	☐	☐
I am aware of the appropriate selection of antimicrobials in my daily clinical practice.	☐	☐	☐	☐	☐
I am aware of the optimal antimicrobial use dosage, route and duration of administration.	☐	☐	☐	☐	☐
I keep updated on the scale of AMR within trust during the COVID-19 pandemic.	☐	☐	☐	☐	☐
Antibiotic Resistance (AMR) is a worldwide public health problem that affects clinical practice.	☐	☐	☐	☐	☐
Actions in combating AMR within the trust will affect society and future generations.	☐	☐	☐	☐	☐
Antimicrobial Stewardship (AMS) implementation can maintain the rational use of antibiotics.	☐	☐	☐	☐	☐
Failure of AMS may result in a pre-antibiotic era.	☐	☐	☐	☐	☐
AMS implementation was affected by other factors, such as veterinary prescribing or international trends on AMR.	☐	☐	☐	☐	☐
Regardless of the AMS strategy followed, the implementation of AMS improves patients' outcomes.	☐	☐	☐	☐	☐

The use of intravenous antibiotic therapy was better than oral alternatives during the COVID-19 pandemic.	☐	☐	☐	☐	☐
Antibiotics for a duration shorter than that indicated contributes to antibiotic resistance.	☐	☐	☐	☐	☐
The blood culture test was requested at admission before first prescribing any antibiotics for patients.	☐	☐	☐	☐	☐
AMS implementation was affected by other factors such as veterinary prescribing or international trends on AMR.	☐	☐	☐	☐	☐
Regardless of the AMS strategy followed, the implementation of AMS improves patients' outcomes.	☐	☐	☐	☐	☐
Watchful waiting and delayed antibiotic prescriptions were helpful in AMS implementation.	☐	☐	☐	☐	☐

Question 12 focus on your **perceptions & attitudes** toward AMS implementation during the COVID-19 pandemic and communications

Q12. How much did you agree with the following statements about antibiotic prescribing during the COVID-19 pandemic?

Item	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Senior leadership in the trust prioritised AMR as a challenge to be overcome.	☐	☐	☐	☐	☐

I have had a clear understanding of the changing in antimicrobial guidelines during the pandemic.	☐	☐	☐	☐	☐
Antibiotic prescribing was affected by the change in the clinical situation of the COVID-19 infected patients.	☐	☐	☐	☐	☐
The challenge of the time pressure affected antibiotic decision-making.	☐	☐	☐	☐	☐
During the COVID-19 pandemic, clinical judgment had priority over antimicrobial guidelines.	☐	☐	☐	☐	☐
The use of use broad-spectrum antibiotics is more attractive with multidrug-resistant organisms (MDROs).	☐	☐	☐	☐	☐
Patients continued antibiotic therapy during the COVID-19 pandemic even in the presence of negative microbiology.	☐	☐	☐	☐	☐

Q13. How did you find each of the following **AMS interventions** to improve antibiotic prescribing during the COVID-19 pandemic?

Item	Not helpful	Slightly helpful	Somewhat helpful	Very helpful	Extremely helpful
Educational sessions and training regarding optimal use of antimicrobials	☐	☐	☐	☐	☐
The AMS champion role within the trust were helpful	☐	☐	☐	☐	☐

Close communication with the clinical microbiologist and AMS team supported the antibiotic decision making	☐	☐	☐	☐	☐
Antibiotic guidelines were updated in my trust during the pandemic.	☐	☐	☐	☐	☐

Q14. Which of these **AMS strategies has an impact on antibiotic prescribing** during the COVID-19 pandemic?

Item	Negative	Positive	No impact	Not applicable
AMS ward rounds	☐	☐	☐	☐
Multidisciplinary team meetings (MDTMs)	☐	☐	☐	☐
Reviewing antibiotic prescribing	☐	☐	☐	☐
Prospective audit and feedback	☐	☐	☐	☐
Public Health England (PHE) “Start Smart - then Focus” AMS toolkit	☐	☐	☐	☐
Point prevalence surveys (PPS) for regular surveillance of antimicrobial use	☐	☐	☐	☐
Antibiotic Review Kit (ARK) intervention	☐	☐	☐	☐
Prescribing indicators/targets reporting, such as Commissioning for Quality and Innovation (CQUIN)	☐	☐	☐	☐
AMS education and training	☐	☐	☐	☐

The switch from intravenous to oral antibiotic therapy	☐	☐	☐	☐
Quality improvement (QI) interventions	☐	☐	☐	☐
Technology-based interventions that ease AMS communication, such as Zoom, MS Teams or Skype for informal meetings.	☐	☐	☐	☐

Q15. During the COVID-19, how were the antibiotic use key messages communicated internally within the Trust? (Tick all that apply)?

- No specific cascade of messages on antibiotic use
- Internal Communication via Trust Intranet
- Emails to staff
- Specific guidelines
- Grand rounds
- Online learning, e.g., internal webinars
- Virtual meetings/teleconference
- Antibiotic App
- Other ... (Please specify).

Q16. In your opinion, how much impact would you say COVID-19 has had on your routine AMS activities?

- Very negative impact
- Some negative impact
- Neither negative nor positive
- Positive impact
- Very positive impact

Q17. What has been the most **helpful/positive impact of COVID-19 on AMS** activity? Please specify?

Q18. What has been the most **negative impact of COVID-19 on AMS** activity? Please specify?

Questions 19 - 23 focus on your **AMS practices** to update your knowledge towards AMS implementation during the COVID-19 pandemic

Q19. The existence of the **AMS practices** in your trust during the COVID-19 pandemic:

Item	Not applicable	Slightly applicable	Moderately applicable	Significantly applicable	Extremely applicable
The management plan was amended when the situation changed, without fear of blame or penalty.	☐	☐	☐	☐	☐
Increase compliance with local antimicrobial guidelines via clinical audit.	☐	☐	☐	☐	☐
Receive timely feedback on the scale of antimicrobial resistance at the trust level.	☐	☐	☐	☐	☐
Concerned about overuse/misuse of antimicrobials and antimicrobial resistance.	☐	☐	☐	☐	☐
I was informed of the resistance pattern or antibiogram in my trust.	☐	☐	☐	☐	☐

Review the use of intravenous antibiotics after receiving the culture results.	☐	☐	☐	☐	☐

Q20. How often did you find the **AMS activities** in your hospital during the COVID-19 pandemic?

Item	Never	Once or twice a month	Once or twice a week	More than twice a week	Every day
Routine antibiotic ward round and reviews	☐	☐	☐	☐	☐
I got feedback on my antibiotic prescribing	☐	☐	☐	☐	☐
Reviewing microbiological evidence at the appropriate time point and discontinuing therapy as required	☐	☐	☐	☐	☐
Consider antimicrobial resistance when selecting an antibiotic	☐	☐	☐	☐	☐
Access the local hospital antimicrobial guidelines during the COVID-19 pandemic	☐	☐	☐	☐	☐
Reduce unnecessary intravenous antibiotics and consider alternative oral therapies were appropriate during the COVID-19 pandemic	☐	☐	☐	☐	☐

Q21. Which of these AMS training was/were significant to you during the COVID-19 pandemic?

- I was unable to take any AMS training
- I took AMS training on my own time
- I learnt on the job

- I received formal training, which my hospital mandated.

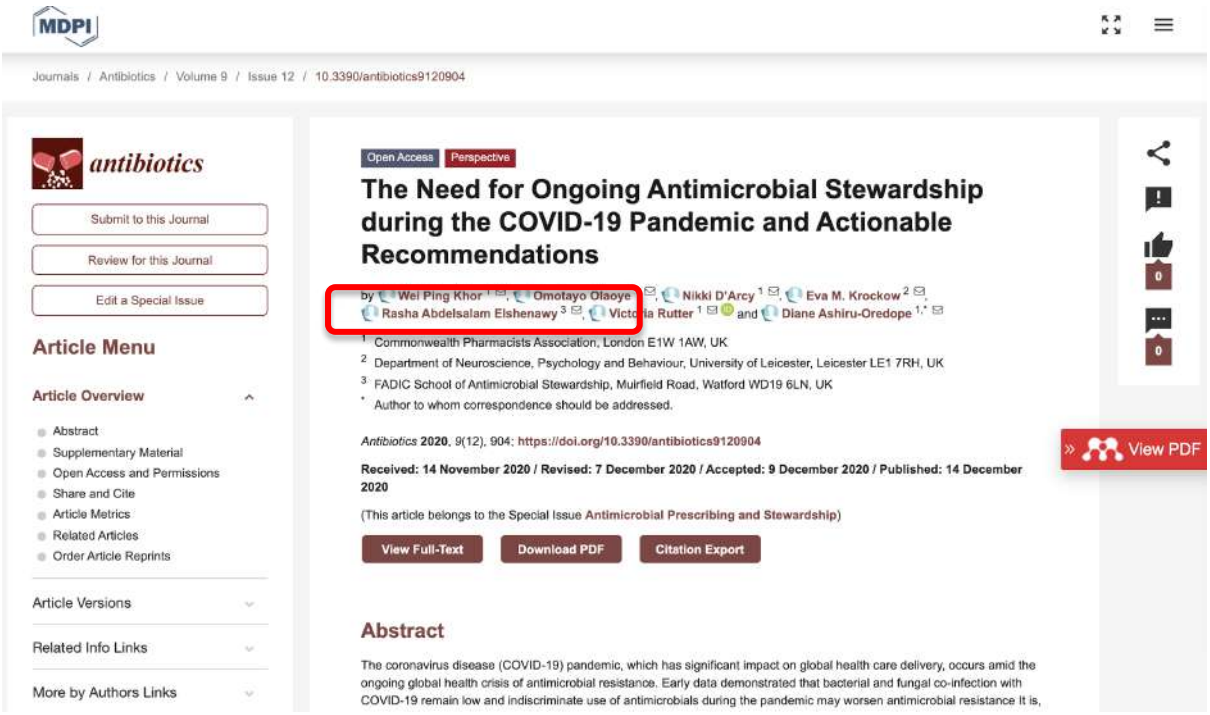
Q22. Which AMS training resources had you taken during the COVID (Tick all that apply)?

- Accredited Course
- Webinars
- Discussion forum
- WhatsApp group
- Other ... (Please specify).

Q23. What key learning points from AMS implementation during the COVID-19 pandemic would you like to share?

Appendix 19: The Need for Ongoing Antimicrobial Stewardship during the COVID-19 Pandemic and Actionable Recommendations

https://www.mdpi.com/2079-6382/9/12/904



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The Need for Ongoing Antimicrobial Stewardship during the COVID-19 Pandemic and Actionable Recommendations

by Wei Ping Khor [1], Omotayo Olaoye [2], Nikki D'Arcy [1], Eva M. Krockow [2], Rasha Abdelsalam Elshenawy [3], Victoria Rutter [1] and Diane Ashiru-Oredope [1,*]

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(This article belongs to the Special Issue Antimicrobial Prescribing and Stewardship)

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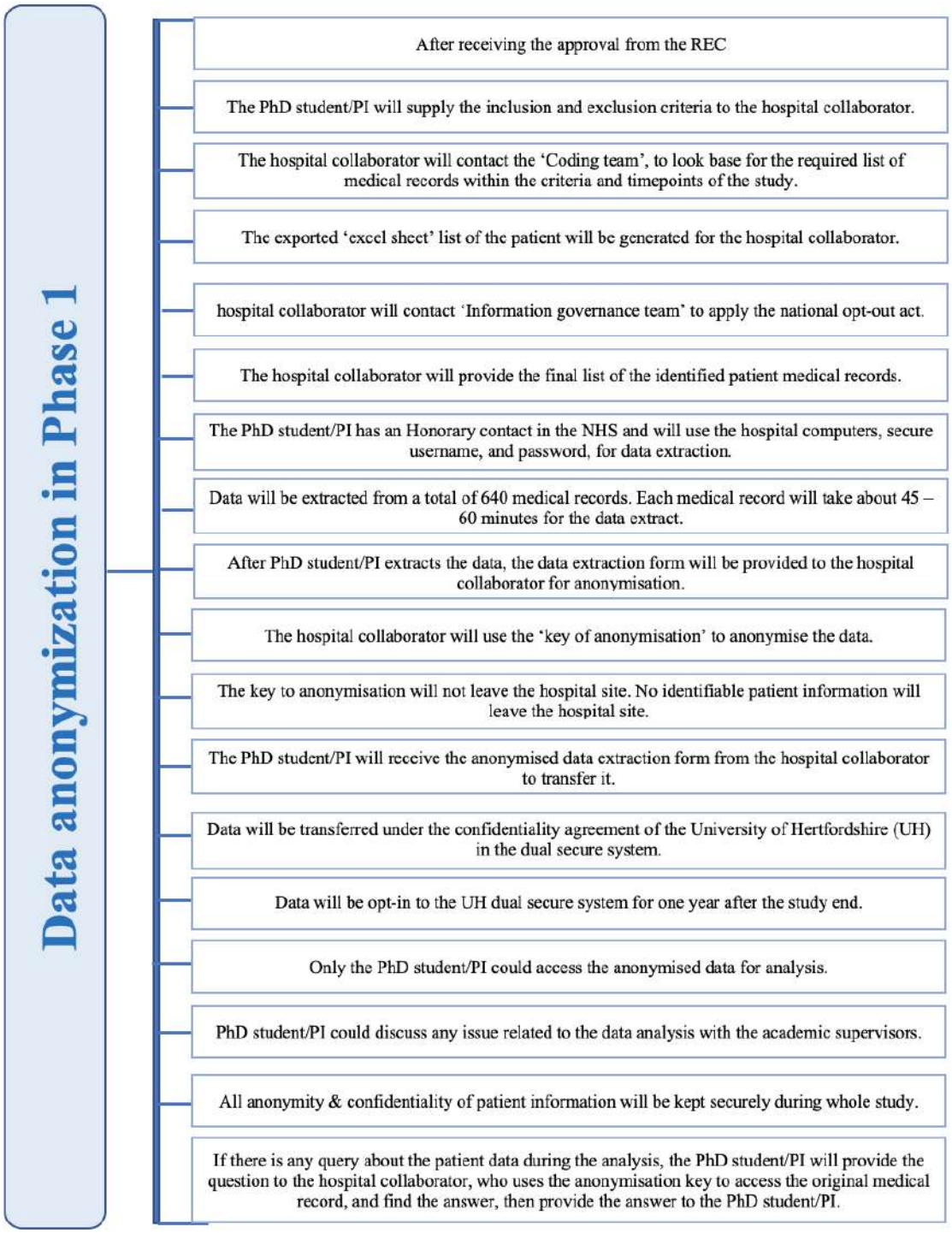
Abstract

The coronavirus disease (COVID-19) pandemic, which has significant impact on global health care delivery, occurs amid the ongoing global health crisis of antimicrobial resistance. Early data demonstrated that bacterial and fungal co-infection with COVID-19 remain low and indiscriminate use of antimicrobials during the pandemic may worsen antimicrobial resistance It is,

Appendix 20: Data Anonymisation Detailed Flow Chart