Exploring the Drivers of, and Potential Interventions to Reduce, Antimicrobial Resistance in the European Food System Context

by

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This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

STATEMENT OF CONTRIBUTIONS

The four manuscripts presented in this thesis, that have all been prepared for submission, are the work of Melanie Cousins, in collaboration with her co-authors and thesis advisory committee members:

Chapter 2: Mapping out a One Health model in the context of the Swedish food system using a modified scoping review methodology. Prepared for submission to *Emerging Themes in Epidemiology*.

- As lead author, I led the conceptualization of study design, designed the search strategies, and the outline for the database. I conducted the literature search, data collection, data analysis, and drafted the manuscript. I created a database and organized the data found for the existing models. I created a database to organize the data to inform the model, an undergraduate cooperative student Matthew N. Vanderheyden extracted data into the database, under my supervision. Two undergraduate cooperative students (Kim D'Mello and Xenia Man Yuk Kwan) provided input for intercoder reliability. My thesis advisory committee supported with the conceptualization (Dr. Shannon E. Majowicz, Dr. Elena Neiterman, Dr. E. Jane Parmley, and Dr. Amy L. Greer). My co-authors provided feedback on the draft manuscript: Elena Neiterman (University of Waterloo), E. Jane Parmley (University of Guelph), Amy L. Greer (University of Guelph), Irene A. Lambraki (University of Waterloo), Didier Wernli (University of Geneva), Peter Søgaard Jørgensen (Stockholm University), Carolee A. Carson (Public Health Agency of Canada), and Shannon E. Majowicz (University of Waterloo).

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- As lead author, I led the conceptualization of study design and created the codebook. I conducted the coding, data analysis, and drafted the manuscript. Dr. Elena Neiterman provided guidance on methodology and conceptualization. Dr. Irene A. Lambraki and Sara Abdelrahman provided input for inter-coder reliability. The rest of my thesis advisory committee (Dr. Shannon E. Majowicz, Dr. E. Jane Parmley, and Dr. Amy Greer) supported with the conceptualization. My co-authors provided feedback on the draft manuscript: Elena Neiterman (University of Waterloo), E Jane Parmley (University of Guelph), Amy L Greer (University of Guelph), Irene A Lambraki (University of Waterloo), and Shannon E Majowicz (University of Waterloo).

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ABSTRACT

Antimicrobial resistance (AMR) is a growing One Health problem that has become one of the leading causes of death worldwide. AMR emerges from a complex system characterized by multiple interacting factors across the human-animal-environment spectrum, all of which have the potential to be impacted by the effects of climate change. This thesis aimed to explore the drivers of AMR and assess potential interventions to reduce AMR in the Swedish food system context under potential climate change conditions. This thesis had four main objectives, to: 1) identify the quantitative and qualitative data needed to create and parameterize a simulation model of AMR emergence and transmission within the Swedish food system; 2) create and use a simulation model to test the potential ability of selected interventions to reduce AMR in the food system; 3) assess the sustainability of these interventions under climate change;, and 4) outline a systematic approach for creating mixed methods models for complex public health issues.

The structure of the simulation model was based on an expert-derived causal loop diagram (CLD), created by Swedish and European AMR experts during a previously conducted participatory modelling workshop, that contained 91 nodes and 331 relationships deemed important to the development and spread of AMR within the Swedish food system. To determine if there was adequate information to create and parameterize the simulation model of AMR, a scoping review was conducted. This review identified 140 existing models and data from 414 sources to inform 64 of the major nodes within the CLD. The identified models addressed the main parts of the system (e.g., agriculture and farm transmission, antimicrobial use (AMU) and AMR, supply and demand for food); however, there was limited connection between the different areas of the food system. Nodes on the outer edges of the CLD did not have data, nor were they included within the scope of the models identified in the scoping review. Other data gaps included the environmental sector and wildlife.

To further refine and parameterize the simulation model, semi-quantitative statements referring to the state of the nodes and relationships in the CLD were extracted from the transcripts from the prior participatory workshop. Transcript analysis identified 83 nodes, 48 of which were included in the CLD, and 35 were new nodes that emerged during the analysis or were existing nodes that were merged or divided. Based on the data requirements of the models identified via the scoping review, and the data currently available, it was not possible to create a fully quantitative model without including many assumptions. Therefore, the CLD was used as the base structure of a fuzzy cognitive map (FCM) of the Swedish food system, which was refined and parameterized by the data from the scoping review and transcript analysis. The final FCM contained 90 nodes, and 491 relationships. The use of FCM allowed for the evaluation of eight interventions under predicted climate change conditions, however, none of them were able to significantly reduce AMR in the system. Finally, the entire processes was reflected upon, including steps taken, challenges and mitigation strategies, and recommendations for future research in systems approaches for modelling complex systems and public health problems. In conclusion, this thesis identified that it was not feasible to create a purely quantitative model of AMR within the Swedish food system due to data limitations. However, by using data from the literature and experts' tacit knowledge, an FCM of the system provided an innovative way to analyze the complex system, provided invaluable insight into the behaviour of the system, and aided in scenario analysis from a broader systems lens.

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LIST OF ABBREVIATIONS

AM – Antimicrobial

AMR – Antimicrobial resistance

AMU – Antimicrobial use

ARO – Antimicrobial resistant organism

ASF – African swine fever

AV – Activation value

CLD – Causal loop diagram

CRE –- Carbapenem-resistant Enterobacterales

DDD – Defined daily dose

EU – European Union

EEA – European Economic Area

ESBL –- Extended spectrum beta-lactamase

ESD –- Environmental Systems Division

FAO – Food and Agricultural Organization of the United Nations

FCM – Fuzzy cognitive map

FMD – Foot and mouth disease

GMO – Genetically modified organism

ICU – Intensive care unit

ID – In-degree

INAMRSS –- International Network for Antimicrobial Resistance Social Science

IPC – Infection prevention and control

LMIC – Low- and middle-income country

MRSA –- Methicillin-resistant *Staphylococcus aureus*

OD – Out-degree

PR – Public Relations

SDG – Sustainable Development Goals

STEC – Shiga toxin-producing *Escherichia coli*

USA – United States of America

VRE –- Vancomycin-resistant enterococci

VTEC – Verocytotoxin-producing *Escherichia coli*

WHO – World Health Organization

Chapter 1: Introduction

1.1 – Background

Antimicrobial Resistance (AMR) is one of the largest threats to public health across the globe [1,2]. It is estimated that there are 25,000 deaths in Europe and up to 700,000 deaths world-wide due to AMR annually, with this number expected to increase 40% by 2050 [3]. Not only does AMR cause a burden to human and animal health and wellbeing, it is also a burden financially. Europe experiences a loss of 1.5 billion US dollars per year with the increased healthcare costs and loss of productivity connected to multi-resistant bacteria [3]. AMR has also impacted the agricultural sector by causing loss of production due to animal illness with resistant infections and has decreased trade due to a fear of resistance [3].

AMR occurs when microorganisms (e.g., bacteria, parasites, fungi) gain the ability to evade the antimicrobials designed to destroy them [1-3]. A major driver of AMR emergence is the overuse and misuse of antimicrobials [1, 2]. The majority (around 80% in the United States [3]) of the antimicrobials prescribed are used in the agricultural sector with this number continuing to rise globally, making agriculture a larger driver of AMR [3]. In Europe, there was an overall decrease in antibiotic use in food, animals, and humans (community use) between 2010-2014; however, this was not consistent across countries [3]. For example, the largest users of antimicrobials in agriculture are Greece, Romania, and France [3]. The lowest users of antimicrobials in agriculture are the Netherlands, Estonia, Latvia, and Sweden [3]. Sweden has been considered an exemplar country for the implementation of regulations which has led to their low antimicrobial use (AMU) in both humans and agriculture, and their low rates of AMR [3].

Although antimicrobial use is a main driver for AMR, it is only one piece of the complex system of factors that interact to drive AMR [1-5]. AMR can develop in pathogens and commensal organisms in humans, animals, and the environment and be transmitted between them through a multitude of pathways around the world [1-3, 5, 6]. While there are many transmission pathways and factors that work together to drive AMR, there is little evidence regarding the burden or levels of AMR across the entire system of drivers of AMR, the transmission pathways and relationships, and the way each factor impacts other areas of the system. Therefore, coordinated action between all of these sectors is required to address this issue. However, only 25% of countries have a national policy to try and address AMR, and many of these policies fail to address AMR from all angles [3]. Similarly, many interventions and policies that have been put to action have been limited to a single sector or one portion of a sector with little regard to how this may alter the whole system [3, 4, 6].

Systems thinking is a paradigm (an intellectual framework or set of assumptions used when analyzing an issue [7]) that has been gaining interest for use in public health to understand issues like AMR [8]. Systems thinking encourages us to look at an issue from a holistic and "big picture" perspective, focusing on the interconnections and circular relationships between factors that work together to create and perpetuate an issue [9-12]. This perspective then calls for coordinated and transdisciplinary action (a conceptual framework that aims to integrate and mobilize knowledge from multiple disciplines [13]) in order to fully understand and better address complex issues. Systems thinking can utilize many different tools, including qualitative and quantitative methods, to explore and analyze systems from a wide variety of perspectives (e.g., building causal loop diagrams, systems archetypes, simulation modelling) [9-12, 14, 15]. This paradigm could aid in understanding and developing interventions and policies that can address AMR at a systems level by bringing together a variety of people and disciplines that are a part of the wider system. Systems thinking could also help create a common language, foster communication, and facilitate in the research process by committing to a unifying approach to address AMR.

1.2 – Literature review

This literature review provides a brief history of the discipline of systems thinking and an overview of the techniques, reasons for use, and examples of use in public health. It also provides an overview of AMR including how it develops, major drivers, and current knowledge gaps. Finally, mixed methods research is described and how and why it can be used in public health research, and how mixed methods simulation modelling can help better understand public health issues, including AMR.

1.2.1 – Systems thinking

Systems thinking has origins in multiple disciplines which have led to a variety of definitions. The factor that these varying definitions have in common is that systems thinking aims to understand how individual parts are interconnected and learn how these interconnected parts function as a whole to produce a behaviour [9-12]. The term "systems thinking" was coined in 1994 by Barry Richmond who defined systems thinking as "the art and science of making reliable inferences about behavior by developing an increasingly deep understanding of underlying structure" [16]. Therefore, a systems thinker looks at an issue and expands their view to account for interaction upon interaction until they can see the entire big picture [11]. This allows system thinkers to have a greater understanding of the complexity and structure of an issue.

1.2.1.1 – What is a system?

In order to understand systems thinking, first one must understand what is meant by a system. In general, a system is more than just a collection of parts [17]. Systems, as opposed to collections, must have interacting and interrelated parts that together have a purpose [15, 18]. In a system, all parts must be present and arranged in the proper order for the system to work. If you can take, add, or re-arrange parts and nothing changes, this is a collection, not a system [15, 18]. Also, systems can adapt and react to changes through feedback in order to maintain stability [15, 17]. There are two types of systems: mechanical and biological. Mechanical systems are usually "hard-wired" with subsystems interacting in a way to create a specific behaviour or purpose. A car can be considered a mechanical system as it has been created to take you places [9, 15]. Biological or natural systems however are living and evolving with subsystems that can adapt to the environment [9, 15]. For example, it is assumed animals are driven by their basic instincts to survive and mate, however, there is much research showing that animals may also be driven by other purposes, such as social needs or empathy that may result in unexpected or uncharacteristic behaviours (e.g. sharing food with a companion instead of keeping it for yourself) [15]. In biological systems it is harder to understand the behaviour, to identify the purpose or goals, and to predict how changes will impact the system [9, 15]. A biological system can be as simple and small as a single-celled organism or as complex and widespread as the healthcare system [19].

All systems are made up of three parts: elements, interconnections, and a function or purpose [12, 17]. First, elements or nodes are each individual part of the system (e.g., a doctor in a hospital). Elements can be tangible (e.g., a hospital bed) or intangible (e.g., team morale) and can be broken down into sub-elements [17]. The second part of the system are the interconnections or the relationships between the elements [12, 17]. These interconnections represent the flow of information between the elements which holds the system together and determine how it will operate [17]. For example, in a hospital, if we think of a doctor and antimicrobials as two elements in the system, the doctor's antibiotic prescribing rate would be the interconnection. Changing this relationship would greatly change the system. For example, if a doctor would dramatically decrease their prescribing rate, this could lead to an increase in disease in the hospital. This, in turn, would impact many other parts of the system, such as an increased need for quarantine and increased staff to deal with illness. The third and most important part of the system is its function or purpose [12, 17]. This determines the overall behaviour of the system [12, 17]. The term function is usually used for mechanical systems and purpose is used for biological or human systems [17]. Even if all elements and interconnections stay the same, changing the system's purpose would cause a great change in the overall system [17]. For example, if the purpose of a hospital shifted from curing patients' ailments to causing them, the entire system would change.

Beyond looking at the parts of a system (elements and connections), systems can also be looked at in terms of their behaviour. For example, a system can be viewed as an iceberg which consist of three levels: events, patterns, and systemic structures [15]. The simplest part of the system to identify is the events. Events are the visible occurrences that we see daily (e.g., a patient in the hospital gets an infection) [15]. When events are looked at over time and show trends, this makes up the patterns of events (e.g., there is an abnormally high number of people with infections in the hospital wing) [15]. The hardest part of the system to identify but the most important are the systemic structures [15]. Systemic structures are the way in which the parts of the systems are arranged which then generates the observed patterns [15]. This could be tangible or physical organization (e.g., the layout of a hospital) or intangible (e.g., the timing of shift changes) [15]. In order to truly understand a system and enact the greatest change, one must be able to identify the systemic structures as these are responsible for creating the overall behaviour of the system.

1.2.1.2 – History of systems thinking

Systems thinking is relatively new in terms of the way problems are viewed and research is conducted. In the early 1900's, researchers in various disciplines aimed to solve a problem by breaking it down into smaller parts in order to understand it at the most basic level [11, 18]. This is what is referred to as traditional analysis, analysis meaning "to break into constituent parts" [11]. This divided the fields of science and other disciplines into very specific departments based on their specialties with their own set of languages and theories. This led to a deeper but narrower understanding of a problem and little communication or collaboration between fields [18]. Although it is important to understand each individual element, it is also important to understand how the elements fit together (e.g., needing knowledge on each type of tree in a forest but also on how the trees work together to create an ecosystem) [18].

By the 1920's, there was the emergence of general systems theory which aimed to understand more "messy" problems by focusing on the patterns, not just the parts [18]. The goal of this theory was to bring all of the specialties together to look at a common problem from a unified perspective [18]. This allowed for a variety of people and disciplines to understand and gain a clearer picture of the problem and how it works without having to know the specific details of each individual part [18]. This, in turn, made it more accessible and the information could be used by more people [18].

The term systems thinking was not used until the late 1990's by Barry Richmond [16]. His idea of systems thinking is a balance between the specifics of traditional research and the broad view of the relationships of general systems theory. Typically, systems thinkers must be able to see and understand both the big picture of the system and the individual parts [12].

1.2.1.3 – What is systems thinking?

Systems thinking has been described as a paradigm, a language, a theory, or set of tools [10, 14, 15]. In general, systems thinking views the world in terms of feedback and loops as opposed to traditional linear thinking [15]. The linear view looks at simple cause-and-effect relationships in a single linear direction [15]. The feedback perspective, however, looks at the interconnectivity and circular relationships between different parts of the system and recognizes that individual parts of the system affect and are affected by each other [15]. These two perspectives then make sense of the world, and thus make conclusions and decisions in different ways. Linear thinking leads to addressing issues as a series of events that lead to consequences without the ability to answer why or how these are occurring [15]. However, by looking at the interrelationships and understanding how the consequences of an action can feed back into the system, such as in systems thinking, one can better address the issue at deeper and more impactful level [15].

Systems thinking is not limited to a single discipline but is a paradigm that is shared across disciplines [20]. This paradigm is concerned with all the connections between the many components of a system and recognizes the importance of planning for the implications of these relationships when considering how to change the system [21]. This then calls for transdisciplinarity and engagement of stakeholders from the various parts of the system in order to capture all of the factors that make up the system [21].

This is benefitted by committing to a single paradigm which fosters a common language and set of tools [15, 22-25]. Systems thinking can be used across multiple disciplines because it has a unique language [15, 22-25]. Language has the ability to shape the way we think which can alter the way we view the world around us [15]. The language of systems thinking provides a basis for communicating complex issues with multiple relationships and interconnections so that all stakeholders and disciplines can work together to understand the different areas of the system and how they are connected thus enabling transdisciplinarity [15, 22-25].

1.2.1.4 – Systems thinking tools

There are many tools in the systems thinking toolbox that help envision, organize, analyze, and communicate a system. These tools can be broken down by the type and stage at which they are used, which are laid out below in order of implementation.

1.2.1.4.1 – Brainstorming tools

In order to begin to envision a system in its entirety, one must start by brainstorming all of the possible elements involved. This stage should involve a wide variety of stakeholders in many disciplines to brainstorm all types of elements. One structured way to engage in brainstorming is through Double-Q (QQ) Diagrams [15]. This is done by brainstorming all quantitative and qualitative factors with sub- and sub-sub factors branching off of each main factor [15]. These diagrams are useful as they help those involved visualize all elements that make up the system and how they may be grouped together. Once all of the factors have been brainstormed, grouped, and organized it is time to add in the connections and relationships. This is done through dynamic thinking tools.

1.2.1.4.2 – Dynamic thinking tools

Dynamic tools are the next stage in systems thinking in which the connections between elements are discussed and analyzed for patterns and behaviours in order to better understand the system. These connections or interrelationships can be visualized through causal loop diagrams (CLDs) [14,15]. CLDs are a visual representations of the system with the elements connected with lines to represent the interrelationships. The process of building CLDs works best when multiple stakeholders from many disciplines work together, building off each other's knowledge and challenging each other's assumptions and biases [14]. While creating CLDs, conversations about the potential reinforcing (positive feedback) and balancing loops (negative feedback) loops may be present [14]. This gives insight into the feedback systems that may be generating the behaviours seen [14]. Noticing and understanding the feedback loops is enhanced when done in combination with behaviour over time diagrams [15].

Behaviour over time diagrams are simple line graphs that show the trends of variables over time and usually have multiple variables overlaid on the same graph [15]. These graphs can show how variables change over time in relation to each other (e.g., while one variable goes up, the other variable goes down) which can show potential relationships between the two variables (e.g., positive or negative feedback). These two diagrams, especially when used together, are powerful tools for visually displaying the systemic behaviour which provide a starting point to enact change.

After creating CLDs or behaviour over time diagrams, a useful tool to use is systems archetypes. Systems archetypes help to understand the systemic structures and behaviours in order to create the most change in the system [26, 27]. Systems archetypes look at an issue (usually identified by a "symptom" or "problem" event in one of the elements) and help to understand the underlying problem and systemic structures that are working to generate the issue [26, 27]. The archetypes are templates of typical patterns or "common stories" that occur in a multitude of settings. Systems archetypes can be used two ways:

diagnostically and prospectively. When used diagnostically, insight is gained into what systemic structures within a particular context are causing the reoccurring problems. When they are used prospectively, they test how proposed policies or other changes to the systemic structure might act on a system in question [26].

The common systems archetypes include: Limits to Growth (aka Limits to Success), Shifting the Burden, Eroding Goals, Escalation, Success to the Successful, Tragedy of the Commons, Fixes that Fail, Growth and Underinvestment, Accidental Adversaries, and Attractiveness Principle [26, 27]. Once an archetype is identified, high-leverage interventions (as prescribed by the given archetype) can be created to attack the issue at the systemic structure level, thus creating the greatest change to the system [26]. As an example, the *Success to the Successful* archetype is a pattern in which the part of the system that is showing good performance gets rewarded with more resources. This allows the good performance part to flourish and continually improve further above the other part of the system. This further validates pumping resources into the more successful part of the system (see example in Figure 2) [26, 27]. The issue lies in the assumption that the success is based on the part of the systems' inherent skills or capabilities and not based on the initial conditions (amount of resources) [27]. If this archetype fits with the patterns observed in the system under study, then there are specific "fixes" or high-leverage interventions that could help resolve the problem. For this example, these include looking into the reasons for the system to allow for only one successful part, chopping off the unsuccessful part allowing for the first part to take all available resources, or finding a way to allow for collaboration between the two parts instead of competing for resources.

1.2.1.4.3 – Structural thinking tools

The next step in systems thinking are structural thinking tools which act as the bridge between the visual and dynamic diagrams and computer-based models [8, 14, 15, 26]. Graphical functions aim to quantify the effects between variables that are non-linear and hard to measure by graphing these relationships over the full range of values. These graphs are similar to behaviour-over-time graphs, however the variables are graphed against each other instead of over time to see how the two variables interrelate. This then gives us insight into the relationship between these two variable and allows us to make predictions on how one may be impacted by a change in the other.

Structure-behaviour pairs try to link the behaviours found in the behaviour over time diagrams with the underlying system structures within the system [14, 15, 26]. For example, if one factor increases over time as another one increases over time, this would suggest a reinforcing loop or positive feedback [14, 15, 26]. Alternatively, if one factor increases over time and the other decreases over time, this would suggest a balancing loop or negative feedback [14, 15, 26]. The next step would be to identify the structures and interconnections within the system that are producing this behaviour.

1.2.1.4.4 – Computer-based tools

There are two types of computer-based tools: computer models and management flight simulators. Computer models generate mathematical equations to represent each relationship in the system to create a functional simulation or representation of the system [14, 15]. These models can be used to then simulate the system and test out various interventions or changes to the system [14]. Computer simulation models will be discussed in detail in Section 1.2.3.3. Management flight simulators are interactive games based on the computer model. These simulators allow users to make decisions and strategies and see long-term consequences in order to inform future decision making [14, 15]. Computer-based models and simulators are powerful tools that can help understand the system and improve decision making due to the ability to test scenarios and interventions on a wide number of factors simultaneously [8].

1.2.1.5 – When, why, and where systems thinking is used

Systems thinking is used in many areas including business, government, healthcare, weather forecasting and the environment, agriculture, education, and social justice [11, 20, 29, 30]. Systems thinking can be used to address a variety of issues in many different fields but it is especially useful for issues that are: important; complex and multifaceted; chronic or reoccurring; dependent on past events; and those that do not have an obvious solution; have been hard to solve; and have been attempted multiple times and with poor coordinated action [9-11]. Many issues today are complex and involve many stakeholders and actors. These issues have usually had inadequate attempts at solving them and the issue is actually worsened by their actions [11]. This is often a result of poor communication and collaboration, and by individuals who are unable to broaden their scope to look at the big picture, not just their immediate cause [11].

In the past, traditional analysis of issues have been focused on breaking down issues into small pieces in order to understand them and the direct causal pathways [17]. However, many issues being researched today are much more complex and traditional analysis will not be able to identify solutions [11]. Systems thinking enables people to view these difficult issues in a different way and uses tools and techniques to help solve these issues because of better understanding. Using systems thinking has allowed teams to generate new ideas and a wider range of novel solutions [10, 11]. Another major benefit and reason to use systems thinking is it forces the team to think about how the decisions made will impact the rest of the system [10]. Past decision making has failed to take into account how potential solutions can have unintended consequences and create new problems or exacerbate the issue in the future. Therefore, when thinking of solutions, by intentionally focusing on these unintended consequences and impacts on the systems, it can help to create solutions that minimize negative outcomes and make more informed decisions [10].

1.2.1.6 – How systems thinking is used in public health research

In the past 5-10 years, there has been growing popularity in systems thinking for use in public health research, such as infectious disease, communicable disease, tobacco control, and obesity [8, 20, 21, 31]. This is partially due to the realization that health is more than just biology. Factors at multiple levels influence health from microscopic elements (e.g., chromosomes), to individual level behaviours, to macro-social and ecological levels [32]. All of these factors interplay to influence health at an individual and global level [32]. This therefore makes public health inherently transdisciplinary. Research in psychology, sociology, biology, chemistry, and ecology are all necessary to look at the various aspects of health issues. It is also important to foster communication between these disciplines, along with the many other important actors (e.g., governments and organizations, businesses, charities, and the greater public) to fully understand the problem [9, 21]. Public health can benefit from systems thinking concepts and tools to create sustainable solutions that can change the underlying systemic structures and create the greatest impact [8, 31].

One of the first initiatives to use systems thinking in public health was the interdisciplinary studies of inequalities in smoking (ISIS) project. This project explicitly applied systems thinking because they wanted to better understand the factors that contribute to tobacco use in order to create the most effective solutions [21]. This initiative brought together existing literature, experts in many fields (e.g., business, the military, systems-dynamics), and experts within tobacco-control to create a tobacco control system [15]. They identified that sharing and flow of information and the linking of diverse experts were essential in creating and understanding the complex system [15].

Systems thinking has also been used to prevent pandemic influenza and other potential global pandemics, combat the obesity epidemic, violence, and other complex public health issues [8, 20, 21, 31]. For example, the Centers for Disease Control and Prevention (CDC) coordinates a global surveillance system to predict and prevent pandemic influenza [20]. This system requires collaboration between public health agencies across the globe along with a multitude of disciplines, fields, scientists, laboratories, and government [20]. Together these actors discover and analyze new influenza strains, develop vaccines, and distribute resources and knowledge to the public in order to prevent an influenza pandemic [20]. The most critical part of ensuring the transdisciplinarity required for looking at systems this large is communication and transfer of knowledge between all actors [20].

Public health uses many systems thinking tools when trying to understand and solve complex issues, especially with computer-based systems modelling. Systems models or simulation models use data that have been collected from multiple sources which represent the entire system in which the issue is embedded [9, 21, 27]. These models can then be used to simulate and predict how the system will change under different policy interventions [9, 21, 30]. This improves decision-making and policy implementation as the model helps show potential unintended consequences or failures in the system before having to intervene physically [9, 21, 30]. This makes decision-making more cost-effective, safe, and impactful leading to effective and safe interventions and policies, which will help prevent illness and save lives [9, 21, 30]. Other tools used in public health include CLDs to understand issues such as neonatal mortality in Uganda, network models to understand advice-seeking behaviours by physicians, and social network modelling to understand the spread of HIV [31]. Overall, systems thinking tools are used in a variety of ways (e.g., brainstorming, dynamic thinking, structural thinking, and computer-based tools) to address many complex public health issues and generate and implement more effective and impactful policies and interventions.

1.2.1.7 – Systems thinking in public health: One Health

One example in which systems thinking has been used in public health is through One Health research and approaches. The World Health Organization defines One Health is defined as "an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes" [32]. Furthermore, the overall aim of One Health is to ensure the health of humans, animals, and the environment and acknowledges the intimate relationship between these three sectors [33]. Many infectious diseases transmit between humans and animals, using the environment as a reservoir or transmission pathway, and therefore all factors are integral to the development and transmission of disease [34-37]. Thus, One Health acknowledges that humans, animals, and the environment are intimately linked, and in order to maintain health across sectors, we must look at the system as a whole. One Health is therefore inherently multidisciplinary and typically engages disciplines such as human medicine, veterinary medicine, agricultural science, public health, environmental science, bioengineering, climatology, wildlife biology, and economics [34]. By including researchers from multiple backgrounds, One Health studies are more holistic, resulting in more integration and sharing of knowledge, and more acknowledgement of the perspectives and potential correlations that occur within and between disciplines [35]. One Health research has been used to address many public health issues including rabies [38], *Campylobacter* [39], *Salmonella* [40], brucellosis [41], food safety and food security [42] and therefore could have applications to address other zoonotic diseases and complex public health issues such as AMR [6].

1.2.2 – Antimicrobial resistance

1.2.2.1 – What is AMR and how does it happen?

AMR is a growing public health concern that has shown to be a complex problem to solve [1, 2]. AMR occurs when organisms (such as fungi, bacteria, viruses, and parasites) develop or acquire genes that reduce the effectiveness of the antimicrobials to the point that they can no longer destroy specific pathogens [1, 2]. More specifically, antimicrobials cause resistance through natural selection [5]. When microbes are exposed to antimicrobials or other resistance-driving chemicals (e.g., heavy metals or biocides), there is selective pressure which can cause microbes to express resistance genes, mutate to protect themselves, or share/acquire resistance genes from other microbes [5]. The antimicrobials can then destroy those microbes that do not have resistance genes, but those who have resistance genes will flourish [6]. This allows for the survival and spread of resistant strains and sharing of resistance genes to other organisms [6].

In addition, when antimicrobials are used when not necessary (e.g., prescribing antimicrobials to patient with a viral infection), it causes microbes in the gut to be exposed to antimicrobials unnecessarily and can causes resistance to develop [4-6]. When pathogens are exposed to antimicrobials at too low of a dose (e.g., sub-therapeutic doses used for prophylaxis) or if full courses of antimicrobials are not taken (e.g., ceasing use when symptoms subside), the antimicrobials will cause selective pressure without destroying pathogens, thus leading to more opportunities for resistance to occur [6].

As pathogens become resistant to antimicrobials, illnesses caused by these pathogens will no longer be able to be managed, which will lead to greater economic and health burden on a global scale [1, 2]. Therefore, it is important to understand what drives AMR in order to combat this problem.

1.2.2.2 – Major drivers of AMR

The misuse and overuse of antimicrobials has been identified as the a major driver of AMR worldwide, however, the overall picture is much more complex [4-6]. Antimicrobials are used in humans, animals, and plants, all of which are connected through direct and indirect pathways [4-6]. Therefore, drivers in one area have the ability to affect the entire system.

Although AMU is said to be the main driver of AMR in humans, the reasoning behind why AMU occurs varies across the globe. In examining Sweden, the total use of antimicrobials in humans decreased by 15% from 2000 to 2015, and continues to decrease [42, 43]. This, however, is not consistent across the rest of Europe, with some countries having extremely high prescription rates and some very low [3]. High prescription rates and inappropriate prescribing of antimicrobials occur often in high-income countries

(HICs) [44]. Some factors found to affect these higher prescription rates in HICs include: physician's age and years of practice; patient expectations; and prescription of antimicrobials for viral infections [45-48].

Alternatively, in low- and middle-income countries (LMICs), one large driver of AMR in humans is lack of infrastructure [44, 49-51]. This includes lack of access to healthcare and appropriate antimicrobials, lack of sanitation and infection control, and lack of education [44, 49-51]. Without proper sanitation and infection control, all pathogens (including resistant pathogens) are more likely to spread between hosts than in a clean and sterile environment. The resistant pathogens can then spread their resistance genes to other surrounding pathogens, which creates more pathogens with resistance. This problem is two-fold. It is: (a) generating widespread infections (some of which are resistant), thus leading to more infections and increasing the need for antimicrobials; and (b) enabling the sharing of resistant genes, thus increasing the amount of AMR in the surrounding environment. This issue is worsened by the lack of access to healthcare [44]. Due to lack of access to hospitals and doctors, infected people are less likely to receive proper care including diagnoses and antimicrobials. Therefore, the infected people will remain infected, allowing them to spread the pathogens to other people [44]. Those who do get access to antimicrobials may not be prescribed the proper antimicrobial (due to lack of resources) or may be prescribed or take incomplete doses (due to lack of affordability) [44]. Prescribing inappropriate antimicrobials can promote AMR as it will expose the microbes and gut microbes to antimicrobials causing selective pressure without destroying any of the harmful pathogens [6]. These issues are further compounded by the lack of education for both those prescribing and receiving antimicrobials on the dangers and drivers of AMR [49-52].

Antimicrobial use has been at the forefront of research and has been the main place to target for interventions to reduce AMR, however, in order to fully understand AMR, we must be able to understand all of the factors that drive AMR. Therefore, it is important to highlight the other pathways in which humans (in both in HICs and LMICs) can contact antimicrobials or resistant pathogens. These include: direct contact with animals; contact with the environment; and through food (both plant and animal products) and water [1, 2, 6, 44, 52, 53].

Antimicrobials are also misused and overused in animals domestically and in agriculture [6, 54-56]. The amount of antimicrobials used in agriculture varies depending on the species of animal and area of the world, but overall greatly outweighs the amount used in humans [3]. Therefore, antimicrobial use in agriculture is a major driver of AMR worldwide [3, 57]. Antimicrobials are used therapeutically (to cure sick animals), sub-therapeutically for prophylaxis (given en masse to prevent disease), and as growth promoters [6, 54-56]. As previously mentioned, sub-therapeutic doses are ideal conditions for selecting for resistance and therefore should be main targets when thinking about AMR [6, 53]. The use of antimicrobials for prophylaxis (usually through feed or water) allowed farmers to house more animals in smaller areas with less risk of infection. Thus allowing farmers to increase production of meat or animal products, which increased profits for farmers and generated more food for the public [6, 53]. This, in addition to the use of antimicrobials for growth promotion, changed the agricultural industry. It allowed for greater production at a faster pace which was necessary to keep up with the growing population and increased consumption of meat [53]. However, this also led to great increases in AMR [53]. Therefore, countries around the world are beginning to place restrictions on the use of antimicrobials sub-therapeutically, with Denmark and Sweden in the forefront [3, 58]. Similar to humans, antimicrobial use is not the only driver of AMR and these other drivers are necessary to consider when addressing the whole system. Animals may also come in contact with antimicrobials and resistant pathogens through contact with humans and the environment [1, 2, 6, 44, 53].

The environment is a key component of the system both in the development of resistant pathogens and transmission of antimicrobials and resistant pathogens. Resistant pathogens and antimicrobials enter the environment through humans, animals, and industrial waste [57]. Humans and animals can shed both antimicrobials in their active form and also resistant pathogens in their urine and feces [57]. Animal waste can enter the environment directly or can be spread via manure or bioaerosols [57]. Human waste, although more heavily treated, is used in agriculture as sludge and waste-water, which can also contain trace antimicrobials and resistant pathogens [57]. Hospitals' and pharmaceutical manufacturers' waste also pumps antimicrobials into the environment [57]. The active antimicrobials along with other resistance-driving chemicals (e.g., biocides and heavy metals) can cause pathogens in the environment to develop resistance genes [57]. Resistant pathogens can also share their genes with pathogens in the environment [57]. Not only is the environment a major transmission route between humans and animals locally, but globally. With the increase of travel and trade, AMR can now be transmitted across the world with ease [44, 59, 60].

1.2.2.3 – Current knowledge gaps

There have been great advances in research, surveillance, interventions, and education surrounding AMR, however there is still a lot that remains unknown about the system. Therefore, it is important to gain a clear, cohesive picture of the system that drives the development and transmission of AMR in order to create effective solutions.

One area that is particularly important in understanding the system is determining the contribution of antimicrobial use in humans and animals to overall resistance [61-64]. Humans and animals can transfer resistant pathogens and antimicrobial residues to each other directly and indirectly, but it is unknown how much resistance in each sector is due to antimicrobial use in the other. For example, in a review of literature on the transmission of resistant *Escherichia coli* (*E. coli*) between animals and humans, only 18% of the studies suggested that humans acquire resistance from food animals, whereas 56% of the studies suggested no directionality [62]. The relationship between human and animal AMR is difficult to determine without an integrated surveillance system and coordination amongst all sectors. However, this remains difficult as each sector has their own set of indicators, surveillance systems, and reporting guidelines [2, 6, 44, 60]. There are also varying levels of perceived importance which dictate where funding should be allocated and where surveillance is most important. The sector with the least perceived importance and therefore least researched is the environment (in terms of development and transmission of resistant pathogens and antimicrobials) [57]. This leads to many interventions and action plans overlooking the environment as an important target [57].

Determining the amount of AMR and the relative contributions of each driver becomes even more challenging when trying to coordinate systems across borders. Many LMICs do not have the infrastructure to implement and conduct such surveillance and research [57]. Therefore, it is impossible to know the relative contributions and levels of AMR in the system as well as the transmission of resistant pathogens and antimicrobials around the globe. It is also important to understand the levels of AMR globally because if there is successful reduction in one area of the world, there could still be AMR imported through travel and trade [53, 57, 65]. In order to determine how AMR may spread globally, it is important to know the amount of travel and trade that occurs, the amount of resistance and antimicrobials that could be transmitted, and regulations at points of entry and exit.

Finally, although antimicrobial use is the a main driver of AMR, there are many other factors that could in principle affect AMR within all sectors, but there are gaps in evidence for their impacts on the development and transmission of resistance. For example, in the agricultural sector, non-antimicrobial factors include: the management system (organic vs conventional); type of feed; housing density; intensity of production; biosecurity regulations; and vaccinations [46]. In humans, things such as hygiene and sanitation and access to proper health care are other factors that can affect AMR. Organisms in the environment are susceptible to other factors such as biocides and heavy metals [6]. Geographical location, weather, and migration are all other factors that can affect AMR [6]. All of these factors can affect pathogen load and transmission and the development and sharing of resistant genes, however, the extent to which they affect AMR is unknown. In order to identify key leverage points and create interventions that account for the entire system, these gaps in knowledge must be better understood. Therefore, we need to understand the underlying system of factors that work together to drive the development of AMR.

1.2.2.4 – AMR as a product of a complex system

There are many drivers and moving parts across sectors and ecological scales that form a complex system that produces AMR. It has been noted that a lack of integration and communication between the multiple actors involved in AMR and a failure to address the entire system may have been factors associated with the lack of success in many past solutions to combat AMR [2].

When interventions and policy are "siloed", with action being taken in only one part of the system, unintended consequences can occur in other parts of the system [3]. For example, if policy was put into place to reduce the amount of antimicrobials prescribed to humans in order to combat AMR in the human sector, this policy may reduce antibiotic use in humans in HICs where overconsumption is of great issue [44]. However, in LMICs where access to antimicrobials is already limited, this would not have much effect and may even exacerbate the issue by limiting resources and access to proper antimicrobials forcing people to use improper antimicrobials for their illnesses or increase infection burden in these countries [44]. Therefore, when creating policy, governments and organizations worldwide need to communicate and coordinate action plans while keeping all countries' needs in mind. Similarly, if policies or interventions were taken in one sector (e.g., reducing antibiotic use in food animals and agriculture), this could negatively impact another sector (e.g., more costs for human consumers) [66]. Therefore, all actors and stakeholders must be able to communicate and coordinate action so that there is consideration for the entire system when creating policy and interventions.

Systems thinking could be extremely beneficial to bring these important actors and stakeholders (e.g., government, organizations, scientist, sociologists) together and look at the big picture of AMR. It would be useful to frame the issue of AMR through a systems thinking lens to make use of the common set of language and tools to foster the transdisciplinarity necessary to understand and combat this issue. It is important for researchers, stakeholders, and policy-makers to look at AMR not only outside of their sector or individual scope, but internationally and globally in order to fully understand this system. With a holistic and 'full picture', governments and organizations can create impactful and coordinated action that accounts for the complexity and multitude of interconnected factors.

1.2.3 – Mixed methods research

1.2.3.1 – What is mixed methods research?

Mixed methods research is the combination of quantitative and qualitative methods in one study [67]. Public health research has been dominated by quantitative research but there has been a recent rise in the appreciation for the ability of mixed methods to gain a deeper understanding of complex public health issues [68, 69]. Mixed methods research has the ability to combine the breadth, generalizability, and measurable evidence of quantitative research and the depth and context-specific nature of qualitative research while making up the other's weaknesses [68, 70-75]. Quantitative and qualitative research methods can be combined in multiple ways to ask novel, multi-faceted questions to gain a more comprehensive understanding and solve complex issues.

In mixed methods research, quantitative and qualitative research can be combined in a variety of ways including: convergent, exploratory, and explanatory methods [68, 70, 72]. Convergent mixed methods research is done by conducting the quantitative and qualitative methods at the same time [68, 70]. This allows the researcher to combine the findings to generate a comprehensive understanding of the issue while validating the findings from both studies [68, 70]. When the issue being researched is new and not well understood, exploratory mixed methods research is useful. First the qualitative research study is conducted to ask more in-depth questions to understand the previously unknown processes behind the phenomenon and follows up with quantitative research to understand the epidemiology of the phenomenon [68, 72]. Explanatory methods, however, begin with the quantitative research to determine the extent of the issue and where it may occur [68, 72]. The qualitative research is then used to gain a deeper understanding and ask the more "why" and "how" questions (Why is this happening? How does it affect the person?) [68, 72].

These three approaches are not an extensive list as there are many ways that quantitative and qualitative research can be combined at various stages of the research to address complex issues such as AMR [75-79]. Mixed methods research has been used to understand the potential drivers for inappropriate prescribing including: why patients may have expectations for prescriptions of antimicrobials [76]; how this may in-turn lead to physicians prescribing antimicrobials to meet this expectation [77]; why inappropriate prescribing occurs and the levels of training prescribers receive [78]; and to evaluate antibiotic stewardship programs to help ensure their success for encouraging appropriate antibiotic prescribing [79]. These studies were able to uncover novel reasons behind many of these phenomena which allowed for a better understanding of these drivers. However, inappropriate antimicrobial prescribing is only one aspect that contributes to AMR and mixed methods could be used to delve deeper into our understanding of many of the other pathways.

1.2.3.2 – Combining mixed methods research with systems thinking

Mixed methods research, by nature, is useful for addressing complex, multi-faceted issues. Mixed methods research has an ability to look at issues from different perspectives, use varying methods, and ask a wider variety of questions. This makes it extremely useful in public health, especially in combination with systems thinking. Many public health issues are the product of complex systems that are multi-disciplinary and multi-faceted. For example, the issue of AMR involves humans, animals, and the environment in local, national, and global settings. Systems thinking can take advantage of both qualitative and quantitative methods and knowledge to understand the complexity of the various factors and connections that make up these systems. When including actors from different backgrounds it is important to account for their different perspectives and expertise. Many disciplines are inherently quantitative (e.g., biology, physics, chemistry) but there are also many disciplines that make use of qualitative methods and data including sociology, psychology, and anthropology [31]. There are also areas within the system for which quantitative data does not exist or are hard to measure. These could be under-represented populations, places where data have not been collected or is hard to collect, areas which are unclear or hard to measure, and relationships or connections that are currently unknown. Therefore, qualitative methods and data can help in the initial brainstorming and development of CLDs to understand how the system may fit together and provide insight into how the interconnections and feedback loops may be working. This can then be complimented with quantitative data and analysis to enhance and solidify the understanding of the system [31], which can then lend itself to more sophisticated methods of analysis, including simulation modelling, to examine the system and predict how the model may behave under different scenarios and changes.

1.2.3.3 – Mixed methods simulation modelling

One way in which mixed methods can be combined with systems thinking is through mixed methods simulation modelling. Like mixed methods research in general, mixed methods simulation modelling (also known as semi-quantitative modelling) combines the strengths of both quantitative and qualitative modelling (described below) [31]. A simulation is a representation of the operations of a real-world process or system over time [80]. This usually involves the creation of a model. A model represents the actual system including its key characteristics or behaviours of each part of the system [65]. Simulation models have been used to explain and predict behaviours of systems in multiple disciplines including physics, engineering, chemistry, economics, sociology, psychology, evolutionary biology, and epidemiology [81, 82].

Quantitative simulation modelling (also known as dynamic mathematical modelling) can create a simplified mathematical representation of a system that can be used to analyze changes in the system and generate predictions or mathematical estimates for future scenarios [62]. This type of modelling, however, requires detailed data on each part of the system to generate an adequate and appropriate model. It uses mathematical equations which require specific values (e.g., levels of pathogen, incidence) and rates of change (e.g., contact rate, pathogenicity, recovery rate) to determine how the system will change at each given time step (e.g., hours, days, weeks.) [67]. Therefore, when trying to generate these models, it is important to balance capturing the full complexity of the system against the amount of data available. In addition, there are many situations in which a variable cannot be accurately quantified without uncertainty or assumptions [83]. For example, in modelling the success of the uptake of a public health promotion on washing your hands to reduce the spread of disease, it is difficult to accurately measure the amount of hand washing or the amount of people who read or watched the promotion material [83, 84]. Therefore, to model these, there is a lot of uncertainty, and assumptions are made to determine values for these variables. This then makes this type of modelling well suited for smaller systems or specific portions of the system in which there are rich data to provide more accurate estimates.

Contrarily, qualitative simulation modelling describes the system by identifying the overall behaviour of the system over time [85]. This type of modelling describes the characteristics of the system in terms of orders of magnitude (e.g., hot, warm, cold) and their changes in direction (e.g., goes from hot or cold). The time-scale is also defined in qualitative terms, meaning that there are no definite time points as seen in quantitative modelling, but that time is “before” or “after” an event [85]. Although qualitative modelling does not require specific numerical data for the characteristics of the system, the major limitation of qualitative simulation modelling is that such models can only describe outcomes and future predictions in terms of changes in behaviour (e.g., there will be a reduction in incidence) and do not provide specific estimates. However, these models are well suited for describing more complex and broad systems for which rich data does not exist.

These two forms of modelling have their strengths and weaknesses, however there are situations which may benefit from using both in combination. For example, when there are insufficient data or variables are too hard to quantify to create a quantitative model, but there are some incomplete numerical data which could be used to provide more specific predictions than qualitative modelling, mixed methods modelling can be of use [86].

Fuzzy logic allows quantitative and qualitative data to be used together by creating a “fuzzy quantity space” in which qualitative data are quantified and/or quantitative data are put into more qualitative terms [85-87]. Quantitative data can go through “fuzzy recoding” where quantitative variables are placed into ordered sets (e.g., high, medium, low). This results in some loss of information but allows for the data to be in the same semi-quantitative space as the qualitative data. Qualitative data, such as common-sense knowledge and descriptions of relationships between parts of the system, can also be put into these ordered sets based on strength (stronger or weaker) and sign (variable goes up or down) information [85-87].

Fuzzy logic has been used as a basis to create the mixed methods simulation (semi-quantitative) modelling technique called fuzzy cognitive mapping [88]. Fuzzy cognitive maps (FCMs) are gaining popularity in modelling complex systems [89] and have been used in many disciplines including complex social [90], strategic [91], and financial systems [92-94]. FCMs are comprised of components (or concepts or nodes) and causal relationships between components, which together form a neural network of components [88, 95, 96]. Using participatory approaches, FCMs are created based on stakeholder input to define the structure of the model (such as when creating cognitive maps) by defining the components and the interconnections. Then, using linguistic terms, participants define the current states (called activation values) of the components, and the strength and directions of the correlations for the relationships (called weights) [96]. Fuzzy cognitive mapping uses fuzzy logic [70-72, 97] to convert the linguistic terms into numerical categories using degrees of truth, which extends binary logic to multi-values logic and rule-based approximate reasoning [97, 98]. The activation values of the components take on a value between [0,1], and the weights of the relationships can take on a value between [-1,1], with negative values representing an inverse relationship between the two components [97]. The use of fuzzy logic thus allows for the incorporation of various forms of data from a wide variety of sources. FCMs can then be used to simulate how a system will behave over time. Using updating rules and transformation functions, the activation value of each component is re-calculated at each discrete time-step which is dependent on the combination the weights of the relationships that influence each component [99]. Finally, these models can be used for scenario analysis by altering activation values and weights of relationships to reflect various scenarios such as testing policy, interventions, or other future conditions (e.g., climate change) [97].

Many systems in public health, like the system that generates AMR, are complex with many moving parts and relationships that have not or cannot be measured numerically. Although there have been many advancements in surveillance and research that have value for informing models such as these, there is still a lot that is unknown in terms of the multitude of relationships between the various parts of the system and the levels of AMR in each. Thus far only small, and very specific parts, of the system have been modelled in the context of AMR (e.g., within a chicken coop or within a hospital) as there are detailed and complete data [100]. In a systematic review of population-level models on AMR, most modelling has been done with a focus on human transmission (89% of the studies found), with significantly less on animals (7%), most of which focused on agriculture, with the least studied involving plants (2%) [100]. Of these studies, only a small proportion (2%) looked at the human-animal interface and only one study involved transmission between a host and the environment [100]. The number of studies which involve modelling the transmission of AMR is increasing, however, there is a lot of research that needs to be done in order to create these models. This is especially important when trying to tackle the wide-spread complex issue of AMR as it is impossible to collect data on microscopic, local, national, and global levels. Therefore, understanding AMR could benefit from the combination of the detailed data that have been collected, the associations or relationships that have been explored, and the knowledge of stakeholders and researchers on the relationships and pathways in order to create a mixed methods simulation model of the system that promotes the development and transmission of AMR.

1.2.4 – Summary of literature review

Overall, systems thinking and mixed methods have the ability to enhance public health research, policy, and interventions by allowing research to create a more holistic and comprehensive understanding of the complexities that are public health issues. In combination, they give researchers the ability to create a powerful set of methods and tools to look at complex health issues from multiple perspectives, which is necessary to be able to combat these issues at the underlying systemic structures. Using mixed methods within the systems thinking paradigm will generate more knowledge from a wider perspective which should help uncover relationships and connections that may be missing or not well understood. Understanding the underlying system is essential in assessing how interventions will impact the broader system and identify potential unintended consequences.

1.3 – Study Rationale and Objectives

AMR is the product of a complex system of drivers that are interlinked and span multiple hosts which are connected by the environments they share. Current research to address AMR often fail to address this complexity, and many knowledge gaps about important areas of the underlying system still exist, especially in the environmental sector and on the social-ecological drivers of AMU and AMR. Therefore, interventions and policy are still often created and assessed in a sector-specific manner and may not account for potential unintended consequences in the broader system. The methodologies and tools found in systems thinking and mixed methods, which have been researched and used in many different contexts, allow for the integration of data from multiple sources and could help to organize the complexity of the system that drives AMR into a useable format.

To this end, in 2019, research was initiated with experts in Europe, with special attention to Sweden, which aimed to capture the underlying structure of the systems of drivers of AMR [65] and to use the structure to qualitatively model, via a participatory scenario planning approach, how two selected interventions (increased infection, prevention, and control measures; and taxation of AMs at point of sale) might work to reduce AMR in the future under a changing climate [101]. I served as a research assistant throughout this research and aided in participant recruitment, data collection (as a notetaker during the workshops), and the data analysis (in the extraction of data from the transcripts, creation of the causal loop diagram, and provided input in the intercoder reliability). However, given my more traditional quantitative modelling background [102-104], I saw an opportunity to use quantitative modelling techniques to complement the qualitative research that had been conducted. The structure of the drivers, as outlined by the experts, provided a solid basis for a more quantitative dynamic model that, data permitting, could be used to create a One Health and integrated model of the development of transmission of AMR within a Swedish food system context. This model could then be used for scenario analysis to assess if interventions identified by the experts as particularly influential, would be impactful at reducing AMR within the system, and if they would be sustainable under potential climate change conditions.

Therefore, the overall aim of this thesis was to explore the drivers of AMR and assess potential interventions to reduce AMR in the Swedish food system context, including under potential climate change conditions, with modelling that captures the complex system of underlying drivers and integrates various types of existing knowledge, including both quantitative and qualitative data. The specific objectives of this thesis were to:

1. identify the quantitative and qualitative data needed to create and parameterize a simulation model of AMR emergence and transmission within the Swedish food system (Chapter 2 and Chapter 3);
2. create and use a simulation model to test the potential ability of selected interventions to reduce AMR in the food system (Chapter 4);
3. assess the sustainability of these interventions under climate change (Chapter 4);
4. outline a systematic approach for creating mixed methods models for complex public health issues (Chapter 5).

These objectives were addressed via research described in four manuscripts prepared for peer- reviewed publication.

Chapter 2

Mapping out a One Health model in the context of the Swedish food system using a modified scoping review methodology

Manuscript as prepared for Emerging Themes in Epidemiology.
Referencing and formatting appears as per journal standards.

2.1 – Abstract

Background: Antimicrobial resistance (AMR) causes worsening health, environmental, and financial burden. Modeling complex issues such as AMR can help clarify the behaviour of the system and assess the impacts of interventions. However, inadequate multisectoral collaboration and data availability make it difficult to effectively address AMR. While models exist for specific contexts (e.g., on-farm, in hospital), how well such models cover the broader One Health system is unknown. Our study aimed to identify models of AMR across the One Health system with a focus on the Swedish food system (objective 1), as well as data to parameterize the models (objective 2), to ultimately inform future development of a comprehensive model of possible AMR emergence and transmission across the entire system.

Methods: Using a previously developed causal loop diagram of factors identified as important in the emergence and transmission of AMR in the Swedish food system, an extensive literature scan was performed to identify models and data from peer-reviewed and grey literature sources. Articles were searched using Google, Google Scholar, and Pubmed, screened for relevance, and the models and data were extracted and categorized in an Excel database. Visual representations of the models and data were overlayed on the existing causal loop diagram to illustrate coverage.

Results: A total of 126 articles were identified, describing 106 simulation models in various parts of the One Health system; 54 were AMR specific. Four articles described models with an economic component (e.g., cost-effectiveness of interventions, cost-analysis of disease outbreaks). Most models were limited to one sector (n=60, 57%) and were compartmental (n=73, 69%); half were deterministic (n=53, 50%). Few multi-level, multi-sector models, and models of AMR within the animal and environmental sectors, were identified**.** A total of 414 articles were identified that contained data to parameterize the models. There were major data gaps for factors related to the environment, wildlife, and broad, ill-defined, or abstract ideas (e.g., human experience and knowledge).

Conclusions: There were no models that addressed the entire system and few that addressed the issue of AMR beyond one context or sector. Existing models have the potential to be integrated into a more holistic mixed methods model, provided that data gaps can be addressed.

2.2 – Background

Antimicrobial Resistance (AMR) is one of the largest threats to public health across the globe [1,2], causing an estimated 25,000 deaths in Europe and up to 700,000 deaths world-wide annually, with this number expected to increase 40% by 2050 [3]. Beyond the burden to human health and wellbeing, AMR also negatively impacts animal health and is a financial burden. Europe loses 1.5 billion US dollars annually from increased healthcare costs and loss of productivity connected to multi-resistant bacteria [3]. AMR also impacts the agricultural sector via production losses from animals with resistant infections, and decreased trade due to a fear of resistance [3].

Antimicrobial use (AMU) is known to drive resistance, but other factors impact how and where antimicrobials (AM) are used, and can affect spread and transmission of resistant bacteria [1-5]. AMR can develop in micro-organisms in humans, animals, and the environment and be transmitted between these sectors through a multitude of pathways [1-3, 5, 6]. While it is known that resistant bacteria can spread through many transmission pathways, how these pathways intersect to impact AMR is less known. This makes it difficult to build a model that captures the entire system of drivers of AMR based on current empirical data and mathematical modelling techniques.

To date, many models of disease transmission and AMR exist, but most are oriented towards specific contexts within sectors (e.g., on-farm transmission in a small cattle herd, or transmission in an intensive care unit (ICU) at a hospital). Few have attempted to merge existing models to better account for the inter-connections between the sectors, despite AMR being a One Health issue at the intersection of humans, animals, and the environments they share [6]. Therefore, to build a model of AMR that covers a broad and more complex system of drivers across the One Health spectrum, it is useful to identify what types of models currently exist for different sectors or sub-systems and how they could be combined to cover the broader system. It is then necessary to identify data to parameterize such a complex model. We chose to do this for the Swedish food system, as an exemplar case study.

Systematic and scoping reviews have been conducted in the field of AMR, however, they have been limited in their scope. For example, systematic reviews have been conducted to find population-level mathematical models of AMR within human populations [7], at the microbial or within-host level [8], and have summarized within-host and population-level models in humans [9]. A more recent scoping review (conducted in 2019) aimed to identify dynamic models of AMR [10]; however, the results were still mainly human-focused. This review aims to be more comprehensive and capture models that extend beyond field-specific models, to identify models that represent the broader system and have the potential to be adapted for the AMR context.

Scoping reviews are not an essential first step in the model building processes, however, due to the vast number of factors to be parameterized, a modified scoping review methodology can provide a framework to gather and organize the data for use in modelling. With a shift towards more inclusive and integrated models, conducting scoping reviews for parameters has risen in popularity as a primary step [11, 12], and may become the norm in One Health modelling due to the increased number of factors and connections to be included. This review aimed to gather data that could be used to parameterize a broad

One Health model (which we defined as a model that include factors from the human, animal, and the environmental sectors that interact to create and perpetuate an issue) of AMR developed during participatory modelling workshops [13]. The qualitative model created through participatory modelling included many factors that were unlikely to have quantitative data available. Therefore, we aimed to find a wider variety of data, both quantitative and qualitative, from a broad set of sources (grey and published literature) to be able to expand the scope of current AMR models and incorporate a wider array of factors from the broader system.

The objectives of this study were to identify: (1) the different types of existing models across various parts of the broader One Health system, and (2) the data sources and evidence that could be used to model the different parts of the Swedish food system (further referred to as "the system").

2.3 – Methods

To set a broad scope for what to consider as part of a One Health model of AMR in the Swedish food system, we used an existing causal loop diagram ("diagram") from two participatory modelling workshops that were held in Stockholm, Sweden in September 2019 in which participants mapped the wider system of drivers of AMR in the Swedish food system (refer to the workshop carried out by Lambraki et al. for the methods and full results) [13]. The resulting diagram contained 91 nodes and 331 relationships and represents the structure of a hypothetical One Health model of AMR in a European (specifically Swedish) food system context. Using this diagram to bound the scope and define the search terms, we conducted a scoping review using a modified Arksey & O'Malley [14] framework, to address our two objectives. The search took place from September 1st to December 31st, 2020.

2.3.1 – Objective 1: Existing Models

A literature search of peer-reviewed publications was performed in Google Scholar and PubMed to identify different types models, including: 1) mathematical models pertaining to the transmission of micro-organisms between humans, animals, and their environment; 2) mathematical models of AMR transmission or emergence; 3) models of AM decay and residue build up in waste, waste-water, and other settings; 4) economic models of agriculture and the food system, and; 5) economic models of health systems. Models were not limited to a specific geographical context, however the search was conducted in English.

A snowball search approach was used, starting with broad, high-level search terms that aligned with major domains of the diagram (e.g., "*model* AND *antimicrobial resistance* AND *humans/animals/One Health*" or "*model* AND c*onsumer demand* AND *food*"). Models of *E. coli* were also explicitly searched because *E. coli* is heavily represented in the existing AMR surveillance data for animals and humans [15, 16]. In instances where specific sections of the diagram were not well described, search terms were refined and the search was narrowed to capture more specific nodes or parts of the system (e.g., for the models of AMR and resistant *E. coli* were further refined to the healthcare or agricultural systems using search strings such as: "*infectious disease model* AND *antimicrobial resistance/resistant E. coli* AND *hospital/on-farm/abattoir*", or economic models for specific food commodities were searched using a search string such as: "*economic/supply-demand/consumer demand model* AND *chicken/beef/fish*"). This approach allowed for a narrowing of the search criteria to ensure key models were captured in the search, that would be of use for our specific purpose. A full list of search criteria is given in Appendix A, Table A1. We found that the first 100 results generally yielded the best fit given our search criteria, therefore, we focused on the first 100 results for each search. Broad search terms and few exclusion criteria were deliberately used to capture a wide range of models from a variety of sectors. Citations about models that were strictly statistical in nature (e.g., linear and logistic regression) were excluded. This was because we wanted to obtain models that simulated the transmission or emergence of AMR or simulated other parts of the system (economics) and not models that provided estimates of association between nodes (e.g., AMU increases the risk of AMR using relative risk or odds ratios).

The lead author (MC) screened the titles and abstracts for inclusion based on the criteria above, and then reviewed the full text and excluded any sources that were not identified as simulation models (e.g., statistical models). For the sources that were included, the following information was extracted and organized into a database created in Microsoft Excel version 16.60: type and process of model (e.g., agent-based model, network model, compartmental model), the sector(s) it represented (e.g., food-producing animals, humans, crops, environment), the micro-organism and/or the antimicrobial involved (e.g., fluoroquinolone-resistant *E. coli*), and other model characteristics (see Tables 2.1, 2.2, and 2.3, full database [17]). We categorized models to the environment sector if they represented all that is external to a host [18]. That includes any area in which a person, animal, or plant is living or operating [19], which was dependent on the setting of the model and the population of interest (e.g., the bed, the light switch, or the keyboard in a hospital, or a river or surrounding landscape).

The identified models were visually situated within the diagram (Figure 2.1) to help identify gaps in system coverage, as well as depict the amount of overlap between sectors captured by existing models. For example, to highlight if there models of human health, on-farm, or the environment, as well as models that cross sectors such as zoonotic transmission, food transmission, models including environmental reservoirs, or One Health models.

2.3.2 – Objective 2: Existing Data Sources and Evidence

A second literature search of peer-reviewed publications and grey literature was performed in Google Scholar, PubMed, and Google, to find and compile data to populate the model outlined above using multiple types of data (quantitative and qualitative) from a variety of data sources from 1995-present; we prioritised sources 2000 to present and those that were Sweden-focused. While our interest was to identify data from 2000 to present, we used 1995 as a cut off to account for potential gaps in data collection (e.g., data collected every five years which causes a gap from 1997-2002). Furthermore, if no Sweden-specific data existed, northern Europe was used as a proxy, and if nothing was specific to northern Europe, then all of Europe or a European average was included. The search was not limited by language; all non-English publications were translated with Google Translate.

Search criteria were created based on the 91 nodes identified on the diagram [13]. A search was created for each node, and some were refined further if found necessary during the search. For example, for the node "on-farm production", a separate search was done for on-farm production of animal-based foods (e.g., chicken, beef, dairy), fruits (e.g., apples), vegetables (e.g., potatoes), and other important crops (e.g., wheat, rice). Examples of search criteria include: "*Antimicrobial resistance* AND *human* AND *Sweden*", "*Imports* AND *chicken* AND *Sweden*", "*Profits* AND *Pharmaceuticals* AND *Sweden*". Some searches were narrowed using specific examples given by the participants within the workshop that led to the diagram [13] when the nodes were too broad to perform an adequate search. For example, for the node "New and emerging food", specific products that are in development or becoming of interest to the European population were searched, such as: insects, genetically modified foods, three-dimensionally printed foods, and lab-based meat. There were nodes for which it was more difficult to create an adequate search strategy. These nodes were those that were abstract (e.g., diverse experiences and opinions) or broad (e.g., AMU in countries other than of Sweden). The aim was to find search strategies that were specific enough to retrieve relevant information, while still capturing a broad range of data and sources. A full list of the search strategies used can be found in Appendix A, Table A2. As with objective 1, the searches for the 91 nodes each returned over 750 results, and therefore we reviewed titles from the first 100 results, for each search string, from each database. Citations that were excluded were: 1) those that did not contain information relevant to the list of nodes from the diagram, and 2) those published before 1995.

Due to the number of separate searches performed (at least one per node), the scoping review was time and resource intensive. Therefore, per recommendations by Arksey & O'Malley [14], a three month cut-off date was used (December 31st, 2020), and a separate list of articles that were scanned in by title and abstract was created (see Appendix B). These articles did not undergo the proceeding steps of full review for inclusion and data extraction.

MC reviewed the full text for titles and abstracts that were screened in and excluded any sources that did not contain data relevant to the nodes of interest. MC then extracted the data. Due to the variety of sources and types of reported data, an inter-coder reliability check was done with three members of our team (MC, KD, XMYK) to ensure the same data were being extracted from the articles. MC selected three articles that represented the spectrum of the articles identified for data extraction (2 peer-reviewed and 1 grey literature that were quantitative, qualitative, and mixed method) and a full article review was performed. MC, KD, and XMYK compared and discussed results to refine what needed to be extracted, or what was being missed.

For the sources that were included, the following information was extracted (MC) for each node and organized into an excel database (MNV & MC): the data or parameter extracted (e.g., 1,000,000 prescriptions/year), the year the data were collected, the type of data (e.g., pharmaceutical sales, quantitative), the type of source (e.g., peer-reviewed or grey literature), the country or countries for which the data were available, and the date and country of publication (see Table 2.4, full database [17]). The country of publication was identified by either the affiliation of the first author on a peer-reviewed publication, the country in which the author of an article (magazine, newspaper, blog) was located, or the country of the main headquarters of an organization, magazine, newspaper, or webpage.

The amount of data and an associated level for the node was then initially assigned by MC's personal judgment, and then verified by the research team through discussion, with disagreements being resolved through consensus. The level of the node refers to the position of that node in Sweden on a scale of the amount, quantity, extent, or quality compared to a referent (e.g., Sweden versus other countries within or outside of Europe, Sweden currently versus historically). For example, there is "high" AMU in agriculture in Sweden in 2020 compared to 2010 or there is "low" AMR in Sweden compared to other countries in Europe. The following levels were assigned: very high, high, medium, low, very low, or none. A node was able to be assigned a level based on the decision criteria found in Figure 2.2, as follows.

First, a node had to have enough data to create an accurate judgement of the state of the node. Then it had to satisfy the following two criteria: 1) a good comparator to be able to judge the node against (e.g., historical data or data from another country), and 2) the node could be accurately described by a single level. For example, the node "Consumer choice, demand, and behaviour" could theoretically be split into many different nodes that represent how consumers feel about different commodities (e.g., consumers in Sweden have "high" demand for organic and animal-welfare friendly foods, but "low" demand for genetically modified foods). Although our search identified that this node could be split into multiple nodes, including demand for: animal welfare-friendly products, consumption of meat and other animal-based food vs other (non-food producing animal) food, antimicrobials, new and emerging food, organic vs conventional food (production system), and local vs imported food, doing so was beyond the scope of our study but the data were captured in the database for future use [17].

The amount of data to inform each node was also assigned a categorical level (very little, a little, some, a lot, and most), which was based on the number of sources and data points (e.g., many sources or many years of data collected), and the amount of quantitative and qualitative data that existed for a given node (refer to decision tree in Figure 2.3).

A visual representation of the existing data was overlayed on the diagram of AMR in the Swedish food system. This included a representation of major data gaps, the amount of data that exists, and the associated level of the nodes.

Although searches were conducted based on the nodes, data pertaining to the relationships between the nodes was also found and extracted into the database [17]. New relationships that were identified via the literature search were mapped on top of the original diagram (Appendix C, Figure C1), and the sources that had data pertaining to the existing relationships were also visually mapped (Figure 2.4).

2.4 – Results

2.4.1 – Objective 1: Existing Models

We identified a total of 140 relevant peer-reviewed articles (Table 2.5, full database [17]) that provided good coverage of the One Health system (Figure 2.1). Most articles were published after 2000 (Figure 2.5). Although articles were not limited by geographical context, most (79/140, 56%) were either non-context specific or were models that included countries from all over the world (e.g., international travel, global food demand [17]), four of which were situated in multiple countries of Europe. Many articles in which a country was defined were from high income countries (58/140, 41%), as defined by World Bank (e.g., United States of America (USA), Sweden, Denmark) [20], and only 10 articles (7%) represented models from low- and middle-income countries. Our search yielded 14 articles that described economic models, however upon further analysis we found that these models were not useable for our purpose as they represented statistical models (e.g., econometric, time series) that reflect the associations between nodes and were not simulation models. These excluded models are described in Appendix A,

Table A3 (details about each model can be found in the database [17]) and are of interest for future research.

There were a total of 126 articles that described models focused on disease transmission and/or AMR emergence and transmission, 102 of which were models of a single system, 4 were models of a single system that included an economic component (e.g., cost-effectiveness of an intervention or cost-analysis of a disease outbreak), and 20 were review articles. Table 2.3 summarizes the microbes and AMs that were modelled and the different sectors or transmission pathways they encompass. Overall, less than half of these models addressed two or more sectors (46/106, 43%). Many articles were focused on humans (42/106, 40%), and many of those that occurred at the human-animal interface were concerned with human illness as the main outcome and considered animal exposure as a risk factor. Models that considered the environment as part of the transmission pathway looked at either the immediate surroundings of the host (contaminated pens, hospital equipment, and production equipment; 23/106, 22%) or the natural environment (water sources, soil, plants; 8/106, 8%). The environment as a target area for modelling was very limited (3/106, 3%), and was mostly framed in terms of causing human illness or as a reservoir for pathogens. Models of crop agriculture were also very limited (5/106, 5%).

Resistant bacteria, specifically *E. coli* (targeted in the search strategy) and methicillin-resistant *Staphylococcus aureus* (MRSA), were the most commonly modelled compared to other resistant microbes, (Table 2.3). Five models focussed on an AM instead of a target microbe (Table 2.3), specifically on the decay of antimicrobials in different settings (one in the gut of a host, and four in water systems) and the build-up of residues in these settings. One model also described the antimicrobial's effect on the development of AMR in a pathogen. Five models did not have a specified host (Table 2.3), and were mainly concerned with transmission of resistance genes and the development of resistance in a population of micro-organisms after exposure to an antimicrobial.

Transmission model characteristics related to the type of pathogen (susceptible or resistant) and AM being modelled are shown in Table 2.1 and 2.2. The majority (42/106; 40%) were human-focused and were either at a population level (e.g., transfers of patients between hospitals and community members) or at a microscopic or micro-organism level (e.g., within-host models of gene transfer and AMR emergence), with very few including both mechanisms into a multi-level model (Table 2.2). There were very few animal-focussed models of AMR. Alternatively, models of susceptible microbes (or those that did not state the resistance status) were mainly animal centred and focussed on within-farm or between-farm transmission (Table 2.2).

Finally, most of the models described were compartmental (n=73/106, 69%) and deterministic (53/106, 50%), and used data from the peer-reviewed literature as inputs for model parameter values

(53/106, 50%). This was especially true within the AMR-focused models (Table 2.2). The use of theoretical models was also widespread (34/106, 32%), especially within the AMR models. Theoretical models are models that provide a general structure and are solved mathematically but are not informed by empirical data. These models are occasionally tested with parameters from the literature or with wide ranges for parameters to capture many possible values. Models rarely included all indications of rigour (sensitivity analysis, validation, and calibration [21-23]) but over half of the models (56/106, 53%) included at least one of these features.

2.4.2 – Objective 2: Existing Data Sources and Evidence

A total of 414 sources were read in their entirety that addressed 64 of the 91 nodes identified as important drivers in the Swedish food system for the emergence and transmission of AMR (see full database [17]). Despite the thorough review, there were 28 nodes for which no literature was found. These nodes included: AMU in wildlife; AMU in countries other than Sweden; antimicrobial resistant organisms (AROs) in plant agriculture; cost per unit set by quota; disposal of AMs (e.g., unused, unmetabolized); diverse experiences, education, and training; existing farm infrastructure; existing healthcare infrastructure; exposure to AROs through imported products; good farm practices; host microbiome; level of resistance in countries other than Sweden; national budgets money, and funding; non-AM infection prevention and control in plant agriculture, by the public, and in other social institutional settings; producer profitability; research, development, and innovation; resistance at the abattoir/processor; restocking with animals/eggs at higher risk of infection; retail availability of meat/eggs in domestic market; science and academia; time to market weight; treatment post-procedure; what is being farmed; and the wider environment microbiome (e.g., water, soil).

The data came from both peer-reviewed (149/414, 40%) and grey literature (228/414, 60%). Full details on the types of sources identified in the grey literature are depicted in Figure 2.6. These sources came from multiple countries (Figure 2.7) with Sweden being the predominant country of origin since it was prioritized in the search (117/414, 28%). The sources were mainly published after 2017 (205/414, 50%; Figure 2.8). Many databases reported surveillance data and national and regional statistics or indicators which were particularly useful, including: Food and Agriculture Organization of the United Nations (FAO), Worldbank, Eurostat, Migration Data Portal, Our World in Data. Similarly, other useful statistical webpages depicted or combined information found in common databases: Statista, Knoema, TrendEconomy, and Indexmundi.

There was a combination of qualitative and quantitative data reported, the majority being quantitative in nature (4445/5432 data points, 82%). However, qualitative data were found to be the main source of data to parameterize some nodes, due to either a lack of available quantitative data (e.g., development of alternatives to AM), or due to the nature of the node being described (e.g., animal welfare/low stress, consumer demand and behaviour). The data described in Table 2.4 was used as a basis to determine the amount and quality of the data for each node (depicted in Figure 2.4 by the amount of shading of the nodes; most, a lot, some, a little, very little) and a personal judgment was used to assign a level to each node (depicted in Figure 2.4 by the colour of the nodes; very high, high, medium, low, very low). Ten of the nodes had very limited sources (1 source) and data (1-15 data points) to inform the node and were assigned the category "very little" for amount and quality of data. Six of the nodes had a "most" for the amount of data. These nodes had 16 to 30 sources and 234 to 413 data points per node, with an average of 94% (88-97%) being quantitative data points.

The literature search was targeted towards the nodes, however as a result of reading and analyzing the extracted literature, there was valuable information identified pertaining to the relationships (arrows) in the diagram. There were a total of 325 relationships found in the literature, 86 were already in the diagram (Figure 2.4), and 239 were newly identified as a result of the data extraction (see Appendix C, Figure C1).

Two new nodes, mentioned as a part of the newly identified relationships, were also added to the diagram: "Access to healthcare (doctors, hospitals, veterinarians, etc.)" and "Number of abattoirs".

2.5 – Discussion

The primary purpose of this modified scoping review was to map out the existing data landscape, specifically models and data related to AMR that exist across a wider One Health system, specifically the Swedish food system context. We found a wide variety of dynamic models that described many of the transmission pathways within the system. These models however were segregated and had limited connection across sectors. We also found quantitative and qualitative data to help understand the current and past states of many of the nodes representing the system. The data was highly variable in terms of quantity, source, and type but overall helped extend our understanding of the system and have the potential to be incorporated into future models of AMR.

Scoping reviews are useful tools for summarizing and disseminating existing literature in a useable and concise format for use by other researchers, policy makers, and other stakeholders who do not have the time and resources to perform such a task [24]. In addition to supporting the building of a future comprehensive One Health model of AMR related to the Swedish food system, this review can assist other modellers by providing a comprehensive list of existing models of AMR in various sectors, where data exist within those sectors, and how to gain access to these data. It also provides insight into the areas in which more empirical data is needed before comprehensive quantitative models can be created. For example, we found that more data are needed about AMR in the environmental sector (e.g., levels of resistance within the soil and waterways), in wildlife populations (e.g., the level of resistance in birds, rodents, and other wild animals that have intimate contact with food-producing animals and humans and the relative contribution these pathways have to transmission), in crop agriculture, and for nodes referring to economics, resources, and practices on farm and in healthcare (e.g., healthcare and farm infrastructure, good farm practices, feed quality and feed efficiency). Furthermore, because most models were only created to encompass a single sector, we also found that more research is needed into modelling methods that can be used to connect existing models from the various sectors.

We found 106 existing models that together provided good coverage of the main parts of the One Health system (human, animal, environment), especially for specific human populations (e.g., within hospital) and agriculture (e.g., on-farm transmission). However, the models had limited connection between the sectors, and did not cover nodes less directly related to human health and agriculture (e.g., development of new AMs, research and development, what is being farmed), which has been identified as a major gap in models of AMR in previous reviews [25,26]. Because many microbes and resistant organisms easily spread between humans, animals, and the environment (e.g., resistant *E. coli* can be shed by animals into the environment and contaminate the watershed which can then infect humans and vice versa [1,2,16]), and because AMU in one of these sectors has the ability to select for resistance in the other sectors (e.g., humans excrete antimicrobial residues in their faeces which can then make their way to the environment through wastewater and select for resistance in pathogens in the environment [1,2]), cross-sector connections are important to capture in models if we want to model the complex One Health dynamics of AMR. Furthermore, the identified models typically took a humanistic perspective, looking at how animals, crops, or the environment can lead to resistance in humans, however the opposite is also true. Therefore, looking at this issue from a more One Health perspective, including how humans influence the system and drive AMR in animals and the environment, within models is another important step into a more cohesive modelling approach.

Here, most smaller scale models, such as those in a single hospital or farm included the environment as a source of transmission (e.g., shedding feces, contaminated spaces and workers in hospital). In contrast, larger community models of AMR were simplified to just human-human or animal-animal transmission. Therefore, it is becoming increasingly clear that models need to account for these different transmission pathways to fully understand and address the complex issue of AMR. Compartmental models provide a good foundation, and are typically the starting point for modelling new systems [27]. Therefore, by creating a set of interlinked compartmental models from multiple areas of the system, we could create a more comprehensive model of the system. However, models of this level of complexity are difficult to create due to lack of data and knowledge about some of the associations or dynamics, which can lead to larger uncertainty in results and difficulty in interpreting results.

Economic modelling is becoming more important in making policy change in many fields, including: health interventions such as obesity [28, 29], the use of medicine and other healthcare technologies [30, 31], hospital interventions for disease control [32, 33], and AMR [34], as well as other fields such as energy [35], agriculture [36], and climate change [37]. It has been deemed necessary to identify solutions that can have the most impact with the least amount of associated costs [38-40]. Cost is important to consider when dealing with agricultural and food production as there are many levels at which the costs can be applied [41, 42]. For example, if the ultimate goal is for impacts at the human population level (e.g., reducing AMR) but it is not economical for producers to implement the intervention (e.g., reducing AMU, changing farming practices, or updating farm infrastructure), then it is not going to be adopted as easily as an intervention that allows producers to still make a profit [5, 6, 41, 43]. Economics are also important because consumer demand is a strong driver of food availability, cost, and ultimately AMR [12, 13]. To provide enough food for the growing population, at a price that consumers can afford, agricultural practices have adapted to high intensity farming which drives the need for AMs to combat inevitable diseases [13]. Including economic analysis when modelling the impacts of interventions can be useful to help weigh high initial costs against longer-term pay-offs to determine the overall cost-effectiveness of the intervention. Therefore, engaging economists and economic modelers to help create more cross-over models (models that include economics and AMR dynamics) may be an important next step when it comes to testing interventions that can inform policies that address controlling AMR at an international scale.

The AMR-specific models identified were mainly quantitative, deterministic, compartmental models, which aligns with past reviews of the literature [25, 26] and was expected since AMR is a developing field, and these models are usually the starting point for understanding processes and the first models built when addressing an issue [27]. These compartmental models also lend themselves well to be expanded into integrated or multi-level models (e.g., within-host and population level [27]). Agent-based, or individual-based models allow researchers to add more heterogeneity to the population and include additional population level attributes (e.g., different levels of contact, spatial elements, individual behaviours [27, 45, 46]). These models are extremely useful but require more data about the populations and the pathogens they model and therefore can be more difficult to parameterize [25, 45, 46]. Expanding a compartmental model is a good starting point to incorporate more complexity and capture the wider system, but still the data must exist in order to parameterize the model without the need for multiple assumptions and uncertainty. In fact, many of the models were theoretical models, which are models that outline the structure and transmission pathways but do not use data to inform them. Previous reviews highlighted that although these theoretical models are useful to understand the overall transmission, without data to inform them, their ability to be used to accurately model a system or to assess interventions is limited [25, 26]. Although quantitative models dominate the simulation modelling world, the inclusion of qualitative data would greatly expand the information that could be used in modelling and a further search for qualitative or mixed methods simulation models could help bridge the gap.

Overall, we found the evidence landscape was challenging to navigate. The data existed across many formats and sources, and it required a lot of searching, deciphering jargon, and sifting through multiple databases, government webpages, and other literature. After the data was found, it was hard to compare between populations and contexts, with many different metrics being used and reported. In some cases, the data were patchy and incomplete, or were not publicly available. Therefore, to create a simulation model including all 91 nodes identified by the experts from the participatory modelling workshops [13], a separate scoping review may need to be conducted for each specific research question (node), especially those for which data were not readily available. This could take upwards of 273 person-months (given a cut-off of 3 months per node), which would require significant time and resources.

From our scoping review, we found that some of the nodes were informed by quantitative data, and this data captured many years and was specific to the Swedish context. However, the way in which the data were either collected or reported was not useful for quantitative modelling purposes. For example, some data were only reported monthly or yearly (as opposed to daily or weekly which is required for many quantitative models), were not representative of the entire country, or did not capture the entire context (e.g., surveillance data but only for specific hospitals or farms) and could not be generalized to a population level. The types of quantitative data we found could, however, be reduced to qualitative categories to represent the state of the node within a semi-quantitative model. For example, Sweden's AMU in 2015 was 4.72 defined daily dose (DDD) per 100,000 population, the AMU in France was 13.1 DDD per 100,000 population, and the AMU in Turkey was 18.1 DDD per 100,000 population [47]. These values could be turned into categories with Turkeys AMU at the high end, Sweden at the low end, and France falling in the middle (medium). We also found that some nodes were mainly represented in qualitative terms. These nodes are still important to the system (as identified by the workshop participants [13]) and therefore finding a way to incorporate this valuable data is necessary to capture the nuances of the One Health system. This provides further evidence of the need for qualitative or mixed methods simulation modelling when trying to model a system of this complexity and breadth.

2.5.1 – Limitations

This literature scan aimed to identify a breadth of models that fit our context and outcome of interest (One Health model of AMR in a high-income food system), not to identify every possible model of AMR and zoonotic transmission. Therefore, it is likely that some models were missed that could provide additional insight into the system. However, many models were identified that provide wide coverage of the system and a good foundation for creating a One Health AMR model.

When performing the scoping review, the search for models were not limited by geographical context. However, the majority of the models identified were from a high-income context. Although this is not an issue for our specific goal of creating a model in Sweden, a high-income country, this limits the generalizability of this review to modelling low- and middle-income contexts and a specific search would be necessary to find these models.

The scoping review of the existing evidence landscape was thorough, and searches for data to inform all 91 nodes were attempted by refining of the search strings. However, it was more difficult to create searches that captured some nodes in their entirety or were narrow enough to capture some of the more detailed or niche aspects of the nodes. For example, the node "Consumption of other (non-meat/egg) foods", is extremely broad and could include fruits, vegetable, and grains, but also things such as pop, snack foods, and alcohol. Therefore, while executing a scoping review of a large and complex system requires significant time and resources, it is an extremely important first step in the research and model building process. Through conducting this literature scan it became evident that this area of research requires greater attention. This could include a more comprehensive scoping review of the system by a large inter-disciplinary team to identify all potential data sources that could be used to inform a model. However, this literature search provides a preliminary review of the existing models and data in the realm of AMR and highlights that despite the availability of information, it is not cohesive, accessible, or easy to find and compile. This is also true for the relationships (arrows) in the diagram. There were 331 relationships in the diagram as identified by the workshop participants [13], with 239 new relationships identified through the scoping review. To quantify (or semi-quantify) these relationships, a more in-depth search would need to be performed targeting each of these relationships individually.

Similarly, there were a subset of nodes that were broad and abstract in nature (e.g., diverse experience, knowledge, and training) and although these nodes are important to AMR dynamics, they are too challenging to describe on a national and population level. For example, an individual's cultural and educational background along with their past experiences can greatly shape how they view different aspects of the system, such as: what they eat [13,48], how they access the healthcare system [13,49], their trust in doctors and medicine [13,50]. This can then shape their exposures and risk of AMR. However, it is impossible to put this into a compartmental model and capture these differences amongst the population at a national level to determine as a collective how AMR may emerge and spread through the country. There are certain aspects that are important and would be interesting to address when modelling but some nodes may be too complex or abstract, and some relationships may exist that quantitative modelling cannot capture. Therefore, further engagement with experts would be required to better define these nodes, for example, by discussing how best to create more defined and quantifiable nodes (e.g., population averages for level of education, dietary preferences, or knowledge of AMR [51]). This highlights that there needs to be intimate and ongoing relationships between researchers and participants to further refine the system. However, more sophisticated modelling techniques (e.g., individual level models that incorporated decision making based on past experiences) or other approaches beyond quantitative simulation modelling (e.g., scenario planning [52]) could also help address the issue of incorporating individual level characteristics, and future research should include interdisciplinarity and One Health approaches.

Finally, this scoping review was conducted as a pragmatic way of collecting data to outline and parameterize a large-scale model of AMR across a One Health system. Therefore, validating the quality of evidence to support the data or validity of the sources was not a primary aim of this review and not inherently part of the scoping review process. However, most sources were from peer-reviewed, government, or major newspaper sources, and therefore, we have confidence in the data that were collected can be representative of the situation within a high-income country such as Sweden.

2.6 – Conclusion and recommendations for future research

This scoping review identified many models that addressed different aspects of the Swedish food system, however, they were disparate and primarily quantitative, and have not been integrated into models that represent the One Health aspects of this issue. Furthermore, there are many data gaps that exist for multiple nodes, making it difficult to model the entire system using empirical data, with some nodes being too broad or abstract to include in a population or national level model, though they were deemed important to the overall system. Therefore, given the existing models found from this literature search along with the data requirements for the models and the data availability, it is not possible to create a fully quantitative model of the drivers of AMR in the Swedish food system context without including overtly simplifying assumptions. This study shows that there is a base of knowledge that exists in the literature, however much work is needed to determine how to put the different pieces together to create a comprehensive model and understanding of the food system that drives AMR emergence and transmission within the Swedish context.

One way in which we could use the plethora of valuable data we found through our review, including both the quantitative and qualitative data, is through the creation of a mixed methods or semi-quantitative compartmental model of the 64 nodes for which there was data. In the interim, the data gaps found through this review can be used to advocate for further evidence that could inform an empirically driven quantitative model of the broader One Health system that drives AMR in a high-income context. To accomplish this, there is a need for more interdisciplinarity and cross-sector collaboration to help bring different perspectives, expertise, and knowledge of existing or novel models or where and how data are being collected and utilized, thus fostering communication and sharing of information to gain a more holistic and One Health view of the system of AMR.

2.7 – Tables

Table 2.1: Distribution of the 106 articles referring to models of disease transmission (n=102) and models of disease transmission with an economic component (n=4) according to model processes, type of transmission, and type of model system (sensitive microbes, AMR microbes and AMs, and AMs).

Model process	Type of transmission	Total	Sensitive microbes	Resistant microbes	AM* only
Community	person-person, person-environment	10	8	2	-
Hospital/healthcare facility	person-person, person-environment	11	2	9	-
Community-healthcare facility	person-person, person-environment	13	-	13	-
On-farm transmission	animal-animal, animal-environment	18	17	1	-
Between/introduction to farm transmission	animal-animal	10	9	1	-
Farm-to-slaughter	animal-animal	2	1	1	-
Crop agriculture	plant-environment	3	-	3	-
Processing plant/Slaughter house	animal-person, plant-person, cross-contamination	4	4	-	-
Zoonotic transmission	animal-person	5	4	1	-
Veterinary clinic	animal-person	1	-	1	-
Foodborne	animal-person, plant-person	5	2	3	-
Waterborne	environment-person	2	2	-	-
One health model	human-animal-environment	1	-	1	-
Pathogen level	with-in host, AMR emergence	14	-	14	-
Pharmacokinetic model	AM levels and decay	2	-	1	1
Hydrological model	AM residue and genetic element levels and decay	5	-	1	4
TOTAL		**106**	**49**	**52**	**5**

*AM – Antimicrobial

Table 2.2: Distribution of the 106 articles referring to models of disease transmission of a single system (n=102) and models of disease transmission with an economic component (n=4) according to study characteristics including the main population of interest, model type and specific model features, and the type of model system (sensitive microbes, antimicrobial resistant (AMR*) microbes and antimicrobials (AMs†), and AMs†).

	Total	Sensitive microbes	Resistant microbes	AM* only
Main population of interest				
Human	28	9	19	-
Companion animal	-	-	-	-
Cattle	7	4	2	1
Pigs	3	1	2	-
Poultry	3	1	2	-
Sheep	1	1	-	-
Fish/Aquaculture	-	-	-	-
Crops	2	-	2	-
Wildlife	-	-	-	-
Unspecified host (bacterial level)	5	-	5	-
Environment	3	-	1	2
2 populations	43	28	13	2
>3 populations	11	5	6	-
Model class				
Compartmental	73	31	39	3
Agent-based	9	3	6	-
Network	8	5	3	-
Risk analysis	11	9	2	-
Combination/multiple	3	1	2	-
Other	2	-	-	2
Model type				
Deterministic	53	21	27	5
Stochastic	43	23	20	-
Both	6	1	5	-
Hybrid (e.g., semi-stochastic)	4	3	1	-
Specific Model features†				
Mult-strain/co-infections (e.g., competition and gene transfer)	30	2	28	1
AMR emergence from AMU	23	-	23	1
Spatial (e.g., patch models, position or GPS data)	17	15	2	-
Multi-level model (e.g., within host and population transmission)	8	4	4	-
Vector-borne	11	3	8	-

	Total	Sensitive microbes	Resistant microbes	AM* only
(e.g., healthcare workers)				
Seasonal factors	5	4	-	1
Super-shedders/shedding rate	9	8	1	-
Pathogen survival	11	6	5	-
Vertical and pseudo-vertical transmission	3	2	1	-
Importation/Migration	36	22	14	-
AM effect on gut microbiome	6	-	6	-
AM residue levels and decay	7	-	2	5
Cost-benefit/cost analysis	4	3	1	-
Participatory modelling	1	-	1	-
Model parameters				
Referenced data	53	28	23	2
Primary data	12	4	8	-
Both	7	2	2	3
Reference/Theoretical model	34	16	18	-
Publicly available dataset				
Yes	7	1	4	2
No	99	48	48	3
Type of data				
Quantitative	103	47	51	5
Qualitative	-	-	-	-
Mixed methods	3	2	1	-
Model rigor				
Calibration	52	26	23	3
Validation	56	30	21	5
Sensitivity analysis	56	24	31	1

*AM – Antimicrobial

† The subsection "Specific model features" provides details about specific components that were addressed within the models, in which a model could address multiple components or none of the components, therefore this subsection does not equate to the total number of models analyzed (n=106).

Table 2.3: Distribution of the 106 articles referring to models of disease transmission of a single system (n=102) and models of disease transmission with an economic component (n=4) according to microbe and/or antimicrobial class and sector/population involved.

	Total	Unspecified host/ Microbe	Human	Animal	Crops	Environment	Human-Animal	Human-Environment	Animal-Environment	Crop-Human	Human-Animal-Crops-Environment (any 3)
Sensitive microbe											
African swine fever (ASF)	1	-	-	1	-	-	-	-	-	-	-
Campylobacter	1	-	-	1	-	-	-	-	-	-	-
Vibrio cholerae	1	-	-	-	-	-	-	1	-	-	-
Clostridium difficile	1	-	1	-	-	-	-	-	-	-	-
Shiga-toxin producing *Escherichia coli*[*†]	18	-	-	3	1	-	-	-	13	1	-
Foot and Mouth Disease (FMD)	2	-	-	1	-	-	1	-	-	-	-
Influenza	6	-	3	-	-	-	3	-	-	-	-
Listeria monocytogenes	1	-	-	-	-	-	-	-	-	-	1
Neisseria gonorrhoea	2	-	2	-	-	-	-	-	-	-	-
Salmonella	3	-	-	1	-	-	-	-	2	-	-
Not defined (multiple)	13	-	3	6	-	-	2	1	-	-	1
TOTAL	**49**	**-**	**9**	**13**	**1**	**-**	**4**	**2**	**15**	**1**	**2**
						-					
Antimicrobial only											
Chlortetracycline	1	-	-	1	-	-	-	-	-	-	-
Fluoroquinolones	1	-	-	-	-	1	-	-	-	-	-
Tetracycline	2	-	-	-	-	1	-	-	1	-	-
Unspecified (multiple)	1	-	-	-	-	-	-	1	-	-	-
TOTAL	**5**	**-**	**-**	**1**	**-**	**2**	**-**	**1**	**1**	**-**	**-**
AMR (Microbe/AM)											
CRE (Carbapenem-resistant Enterobacteriaceae)	1	-	1	-	-	-	-	-	-	-	-
Chlorotetrecycline resistant *E. coli*[*]	1	-	-	1	-	-	-	-	-	-	-
ESBL (extended-spectrum-β-lactamase)-producing ST131 *E. coli*[*]	1	-	1	-	-	-	-	-	-	-	-

	Total	Unspecified host/ Microbe	Human	Animal	Crops	Environment	Human-Animal	Human-Environment	Animal-Environment	Crop-Human	Human-Animal-Crops-Environment (any 3)
ESBL (extended-spectrum-β-lactamase) and AmpC (AmpC-β-lactamase)-producing *E. coli**	1	-	-	1	-	-	-	-	-	-	-
Fluoroquinolone-resistant *Campylobacte*r	1	-	-	-	-	-	1	-	-	-	-
Tetracycline-resistant *E. coli**	1	1	-	-	-	-	-	-	-	-	-
MRSA (methicillin-resistant *Staphylococcus aureus*)	10	-	6	1	-	-	-	3	-	-	-
VRE (Vancomycin-resistant enterococci)	1	-	-	-	-	-	1	1	-	-	-
Resistant *Klebsiella pneumoniae*	1	-	1	-	-	-	-	-	-	-	-
Resistant *Campylobacte*r	1	-	-	-	-	-	1	-	-	-	-
Resistant *E. coli**	12	1	3	2	-	-	-	2	1	-	1
Resistance in commensal bacteria	4	1	3	-	-	-	-	-	-	-	-
Resistance in foodborne pathogens	1	-	-	-	-	-	-	-	1	-	-
Resistant bacteria (general)	10	1	3	1	-	1	1	2	-	-	1
Resistant fungi (general)	2	-	-	-	2	-	-	-	-	-	-
Resistant parasites (general)	1	-	-	-	1	-	-	1	-	-	-
Not defined (multiple)	3	1	1	-	-	-	-	1	-	-	-
TOTAL	**52**	**5**	**19**	**6**	**3**	**1**	**4**	**10**	**2**	**-**	**2**
					-						
TOTAL	**106**	**5**	**28**	**20**	**4**	**3**	**10**	**13**	**18**	**1**	**4**

**E. coli* - *Escherichia coli*

†Shiga toxin-producing *E. coli* includes: Shiga toxin-producing *E. coli* (STEC), Verocytotoxin-producing *E. coli* (VTEC)

Table 2.4: Distribution of the 414 sources of data relating to the nodes (n=64) according to the study characteristics including the number of sources, number of data points, type of data, and regions and years covered within the data.

Node	Number of Sources	Number of data points	Qualitative data	Quantitative data	Region(s) covered	Year(s) covered
(Terrestrial) On-farm AM* use	3	31	1	30	Denmark, Sweden, EU/EEA and Switzerland	2000-2018
Access to AMs* outside of the system	5	32	16	16	Global, EU, Europe, Northern Europe, Southern Europe, Eastern Europe, Sweden, Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, North Macedonia, Republic of Moldova, Russian Federation, Serbia, Tajikistan, Turkey, Ukraine, Uzbekistan, Kosovo, USA	2002-2019
AM* use in companion animals	5	20	6	14	Europe, EU/EEA and Switzerland, Sweden, Italy	2000-2017
AM* use in plant agriculture	5	18	7	11	Global, EU, Sweden, The Netherlands, USA	2007-2017
Amount of imported product	16	234	8	226	Global, Europe, Sweden, Norway, Thailand	1990-2019
Amount of product in the domestic market	3	31	3	28	Sweden	2000-2018
Animal density	3	7	2	5	Sweden	1980-2005
Animal welfare/stress	8	58	46	12	Sweden	2001-2020
Aquaculture AM use	2	4	1	3	Global, EU/EEA and Switzerland, Sweden, Norway	2008-2017
AROs† in companion animals	7	54	5	50	Europe, Austria, Belgium, Denmark, France, Germany, Greece, Italy, the Netherlands, Portugal, Serbia, Spain, Sweden, Switzerland, United Kingdom	2005-2018
AROs† in food products	5	35	2	33	Sweden, Switzerland, UK	2004-2018
AROs† in food-producing animals	9	84	6	78	EU, Belgium, Denmark, Spain, Sweden, Switzerland, The Netherlands, UK	2007-2019
AROs† in humans	4	7	1	6	Sweden	2014-2018
AROs† in imported food products	1	1	0	1	Sweden	2004
AROs† in wildlife	1	3	0	3	Sweden	2009-2019
Chronic, non-communicable diseases	3	14	0	14	EU, Poland, Sweden	1986-2017

Node	Number of Sources	Number of data points	Qualitative data	Quantitative data	Region(s) covered	Year(s) covered
Companion animal illness	5	22	3	19	Europe, Austria, Belgium, Denmark, France, Germany, Greece, Italy, the Netherlands, Portugal, Serbia, Spain, Sweden, Switzerland, United Kingdom	1999-2020
Consumer choice, demand, and behaviour	57	365	289	76	Global, Europe, EU, North America, Nordic countries, Austria, Belgium, China, Denmark, England, Finland, France, Germany, India, Italy, Leitchenstein, Spain, Sweden, Switzerland, Thailand, The Netherlands, UK, USA	1960-2020
Consumption of other (non-meat/egg) foods	20	312	11	301	Europe, Finland, France, Iceland, Norway, Russia, Spain, Sweden, UK	1960-2018
Corporate profits from AM*	12	61	12	49	Global, Europe, EU/EEA and Switzerland, US	1980-2018
Death (Human)	16	60	6	54	Global, Europe, EU, Poland, Sweden	1990-2019
Development of alternatives to AM*	14	97	82	15	Global, Europe, EU, Australia, Brazil, Canada, Denmark, Japan, Singapore, The Netherlands, UK, USA	1997-2020
Development of new AMs*	35	175	84	91	Global, Europe, EU, Canada, England, India, Scotland, UK, USA	1911-2020
Diagnostics	8	30	18	12	Global, Europe, Africa, Australia, Canada, Norway, Sweden, UK, USA	2003-2018
Digital health	20	77	18	59	Global, Europe, EU/EEA and Switzerland, Austria, Belgium, Denmark, Finland, Estonia, Ireland, Sweden, Denmark, Portugal, Spain, Germany, UK, France, Italy, Russia, Poland, Switzerland, The Netherlands, UK, USA	2002-2023
Disease in plant agriculture (crops, horticulture)	2	9	0	9	Sweden	2006-2011
Domestic and international trade	12	184	18	166	Global, EU, Sweden	1990-2019
Feed efficiency	1	1	0	1	Global	2019
Feed quality	1	1	1	0	Sweden	2020
Food and water security (personal, national)	4	27	0	27	Global, EU, Sweden	2000-2019
Food-producing animal illness	11	44	1	43	Denmark, Norway, Sweden, UK	1998-2020

Node	Number of Sources	Number of data points	Qualitative data	Quantitative data	Region(s) covered	Year(s) covered
Healthcare costs	12	53	2	51	Global, Europe, EU, Canada, China, Germany, Malaysia, Norway, Sweden, Switzerland, Serbia, Thailand, USA	2000-2050
Healthcare resources	16	314	8	306	Global, Europe, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden, United Kingdom	1999-2019
Human AM* use	17	51	3	48	Global, Europe, Southern Europe, Northern Europe, Eastern Europe, Central Europe, Austria, Belgium, Denmark, England, Finland, France, Germany, Greece, Italy, The Netherlands, Portugal, Spain, Sweden, United Kingdom	1994-2020
Human illness	15	106	3	103	Global, High-Income countries, Europe, Nordic region, Albania, Bosnia, Bulgaria, Croatia, Czech Republic, Hungary, North Macedonia, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia, Denmark, Finland, Iceland, Norway, Sweden, Greenland, Poland, Spain, The Netherlands, UK	1970-2018
Human vaccination	8	41	5	36	Europe, EU, EU/EEA, Canada, Italy, Sweden	2000-2019
Market price per production unit	5	187	1	186	EU, Sweden	1980-2018
Meat/egg consumption	30	296	20	276	Global, Europe, EU, Denmark, Finland, France, Germany, Norway, Italy, Poland, Russia, Spain, Sweden, UK, USA	1960-2020
Movement of animals	15	95	16	79	Europe, EU, Sweden	1999-2020
Movement of people	10	127	18	109	Europe, EU, Austria, France, Germany, Italy, Sweden, Poland, Hungary	2000-2018

Node	Number of Sources	Number of data points	Qualitative data	Quantitative data	Region(s) covered	Year(s) covered
New and emerging foods	36	335	60	275	Global, Asia, Africa, Europe, North America, Australia, Belgium, Brazil, Canada, Czech Republic, The Netherlands, France, United Kingdom, Denmark, Sweden, Norway, England, Italy, Poland, Portugal, Slovakia, Spain, Switzerland, United States, UK	1965-2020
Non-AM* disease prevention and infection control in health and social care settings	16	140	26	114	Global, EU, Northern Europe, Austria, Belgium, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden, United Kingdom,	2002-2020
Non-AM* infection control in food-producing animal agriculture	1	1	1	0	EU	2016
Number of units set by quota	1	3	0	3	Sweden	2002
Nutritional quality of diet	2	8	3	5	Sweden	2002-2020
On-farm production level	17	341	15	326	Denmark, Norway, Sweden	1984-2020
Pharmaceutical market, sales, and PR‡	6	63	7	56	Global, Europe, EU, Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, North Macedonia, Republic of Moldova, Russian Federation, Serbia, Tajikistan, Turkey, Ukraine, Uzbekistan, Kosovo, Canada, France, Ireland, Sweden, UK	1995-2018
Population vulnerabilities	12	156	22	134	Global, OECD countries, Europe, EU, Nordic countries, Austria, Bosnia, Belgium, Romania, Bulgaria, Croatia, Czech Republic, Denmark, England, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Norway, Poland, Portugal, Romania, Russia, Scotland, Slovania, Spain, Sweden The Netherlands, United States, Wales, Switzerland	1992-2019
Prescribing, diagnosing, treatment practices (appropriateness)	35	186	34	152	Global, Europe, EU**, Austria, Belgium, Canada, Croatia, Denmark, England, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Lativia, Lithuania, Norway, The Netherlands, Spain, Sweden, United Kingdom, USA	1995-2019
Production costs	1	3	0	3	Sweden	2018

Node	Number of Sources	Number of data points	Qualitative data	Quantitative data	Region(s) covered	Year(s) covered
Production systems	28	413	48	365	Global, Europe, EU, Austria, Bosnia, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Latvia, Lithuania, Italy, Malta, Macedonia, Norway, Romania, Russia, Spain, Sweden, Switzerland, Thailand, UK, USA	1991-2030
Psychological health	8	60	0	60	Europe, EU, Belgium, Bulgaria, Czechia, Cyprus, Finland, France, Germany, Iceland, Italy, Lithuania, Luxemburg, Netherlands, Norway, Portugal, Romania, Spain, Sweden, Switzerland, The Netherlands, Turkey	2000-2018
Resistance in the wider environment	1	1	1	0	Global	2018
Retail cost of food	16	245	16	229	Europe, EU, Austria, Czech Republic, Belgium, Bulgaria, Denmark, Finland, France, Hungary, Iceland, Ireland, Lithuatia, Luxemburg, Monico, Norway, Poland, Romania, Sweden, Switzerland	1999-2020
Retailer demand for product	8	9	7	2	Europe, Sweden	2005-2019
Treatment of waste and waste-water	2	12	2	10	Global, EU, Bangladesh, Ghana, India	2000-2018
Understanding and awareness	2	11	1	10	Global, EU, Sweden, United states	2010
Unregulated meat sales	1	1	0	1	Sweden	2002
Use for prevention in humans	3	46	0	46	EU/EEA, Sweden	2002-2012
Use for preventive purposes	1	2	0	2	Italy	2000-2007
Use for treatment	1	1	0	1	Denmark	1995-2008
Use for treatment in humans	1	15	0	0	Sweden	2003-2010
Viability of domestic meat production	3	10	5	5	Europe, Sweden	2002-2019

*AM: Antimicrobial

**EU/EEA: European Union/ European Economic Area

†ARO: Antimicrobial resistant organism

‡PR: Public relations

Table 2.5: Breakdown of the types of models found in the sources identified in the literature (n=140).

	Number of articles
Disease transmission models	**122**
Single model or system	102
Review articles	20
Economic models	**14**
Single model or system	10
Review articles	4
Combination models	**4**
Single model or system	4
Review articles	0
Total	**140**

2.8 – Figures

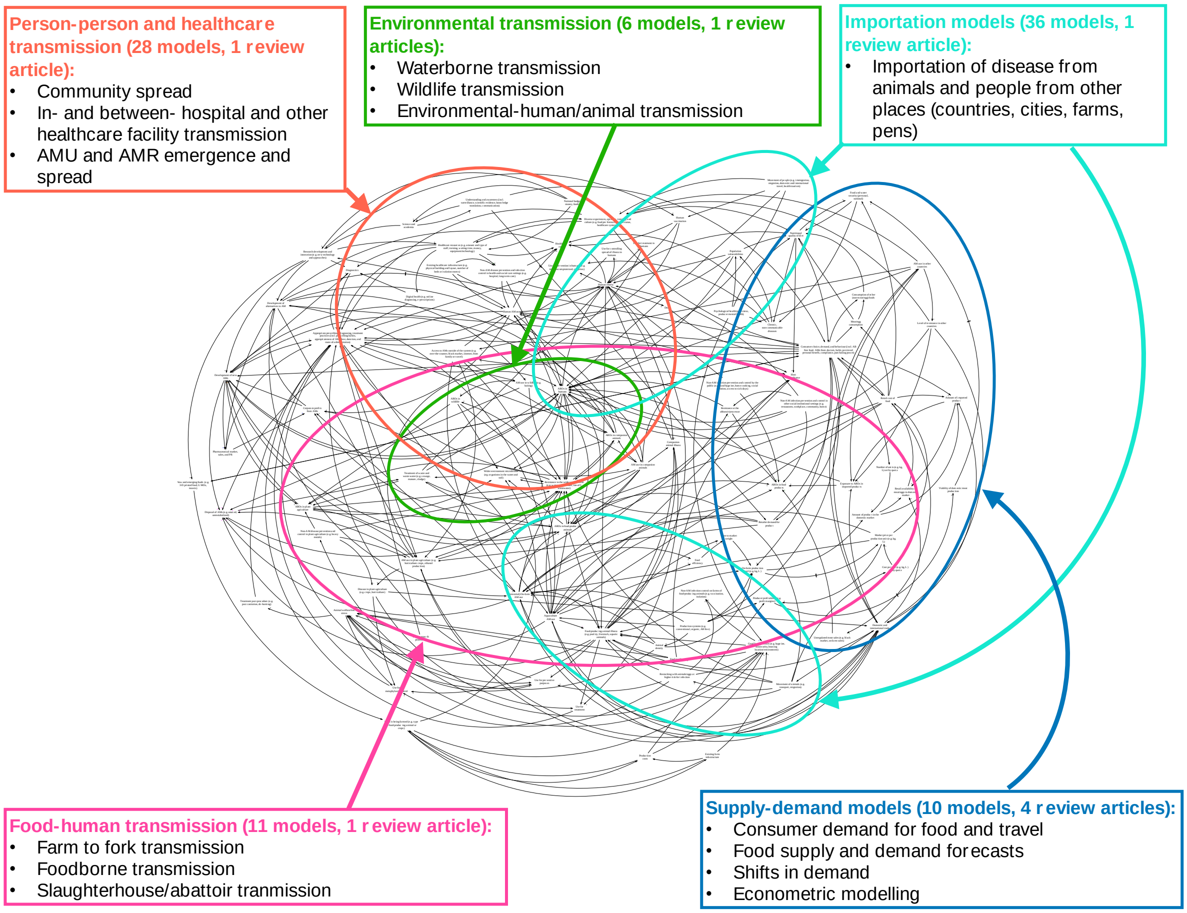

Figure 2.1: The diagram of AMR adapted from Lambraki et al., [13] with the types of models found from the literature search categorized into broad themes overlayed to depict model coverage of the system. Note: this figure is zoomable in the PDF version of this thesis to legible font size.

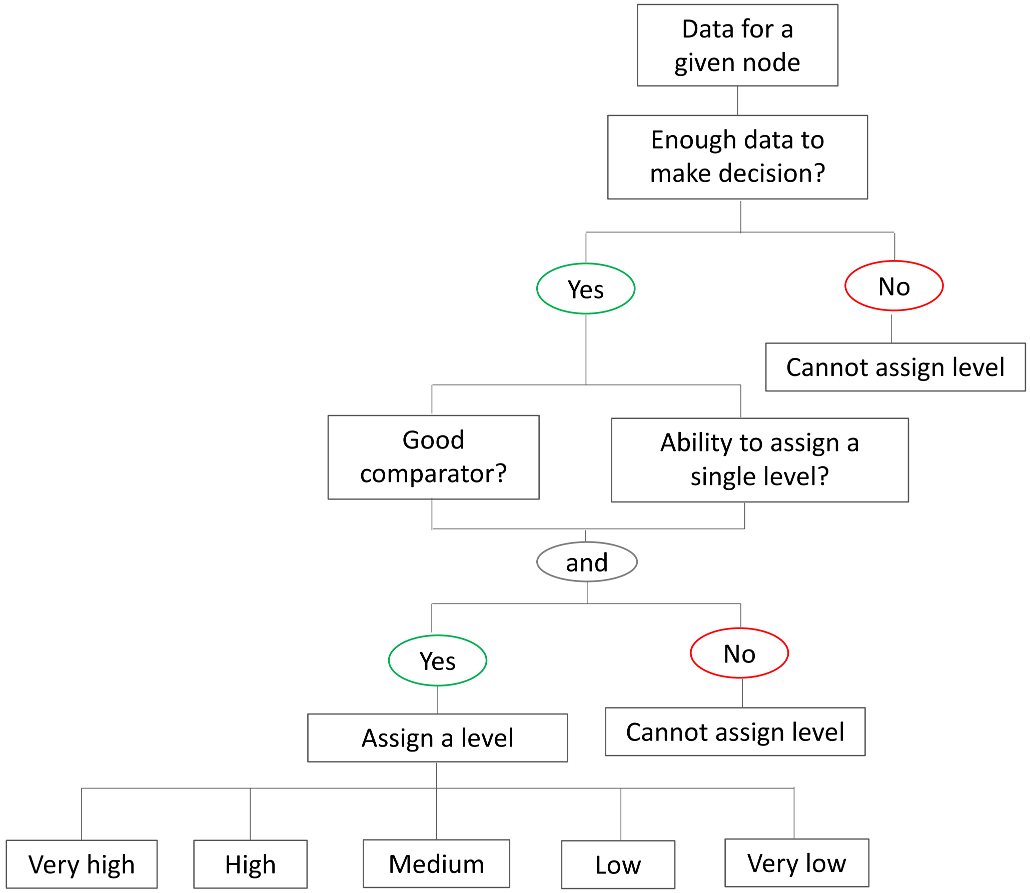

Figure 2.2: How each of the 64 nodes were categorized into ordinal levels (very high, high, medium, low, very low).given the quantitative and qualitative data found from the scoping review to inform the model the different parts of the Swedish food system.

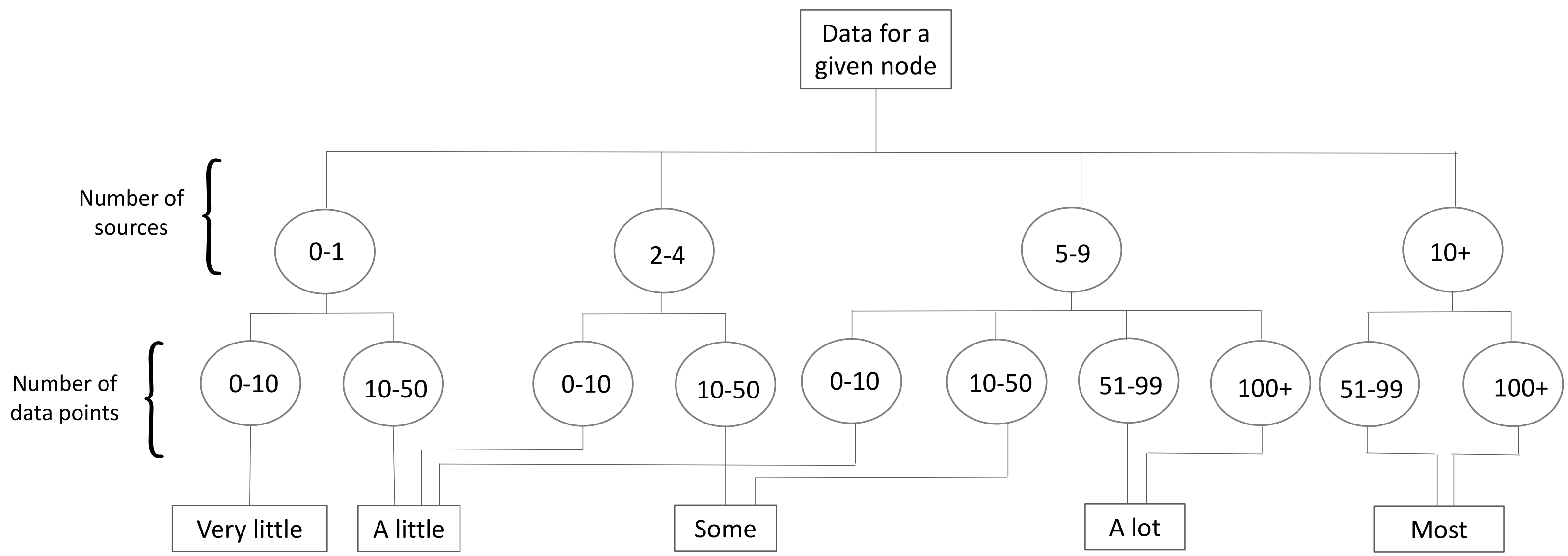

Figure 2.3: How each of the 64 nodes were categorized into ordinal levels that describe the amount of data (very little, a little, some, a lot, most).given the number of source and amount of the data found from the scoping review to inform the model the different parts of the Swedish food system.

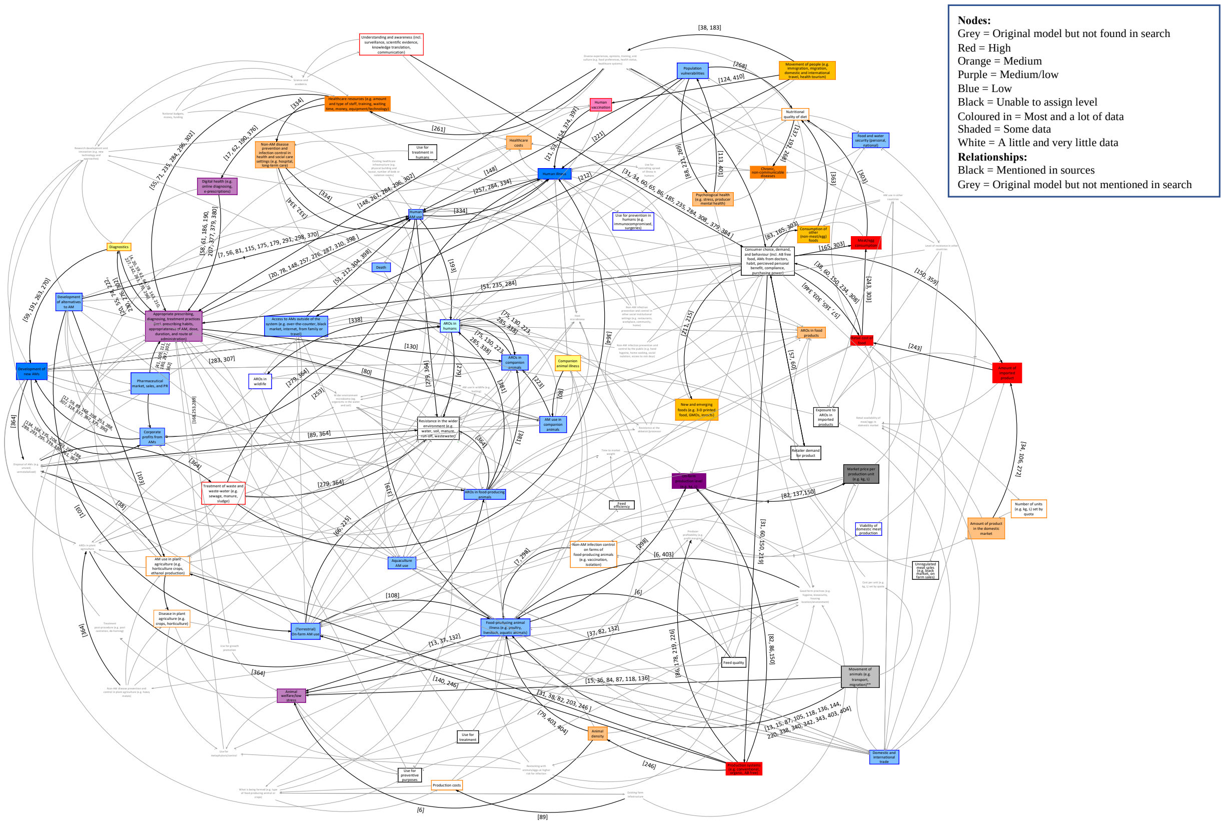

Figure 2.4: The diagram of AMR adapted from Lambraki et al. [13] to show the data sources and evidence found from the scoping review: nodes colour represents the assigned level for the given node, the darkness of the shading represents the amount of data for the given node, and the relationships that were mentioned in the sources are coloured in black with numbered references (found in database;[17]) provided in brackets. Note: this figure is zoomable in the PDF version of this thesis to legible font size.

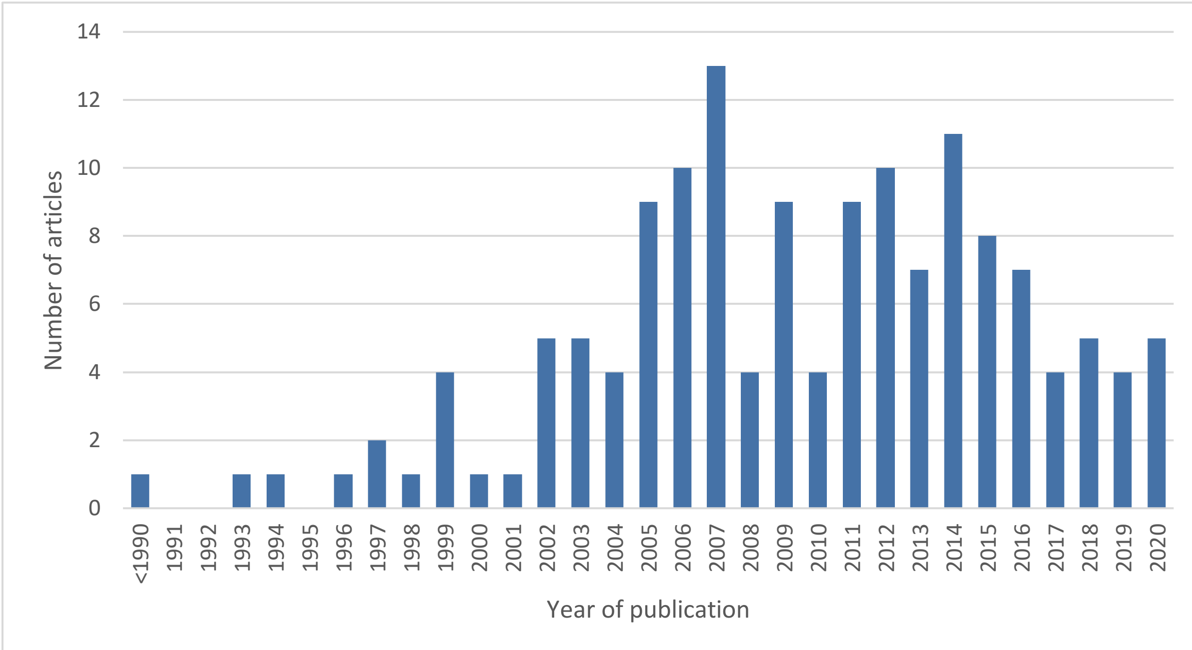

Figure 2.5: A description of the publication year of the sources (n=140) from the scoping review for the different types of existing models across various parts of the broader One Health system.

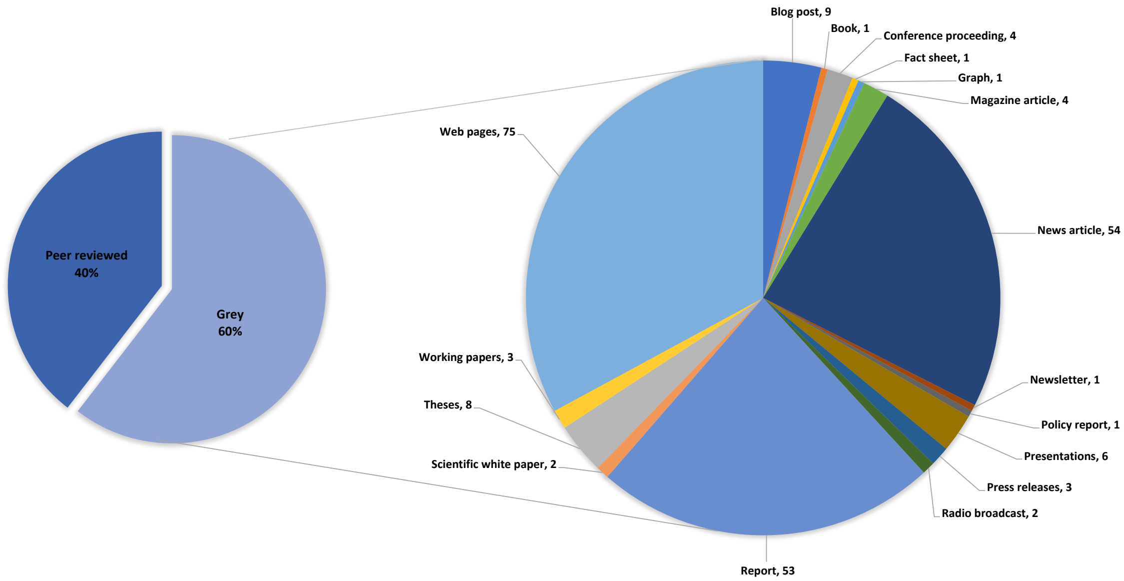

Figure 2.6: A description of the types of sources (n=414) found from the scoping review for the data sources and evidence that could be used to model the different parts of the Swedish food system.

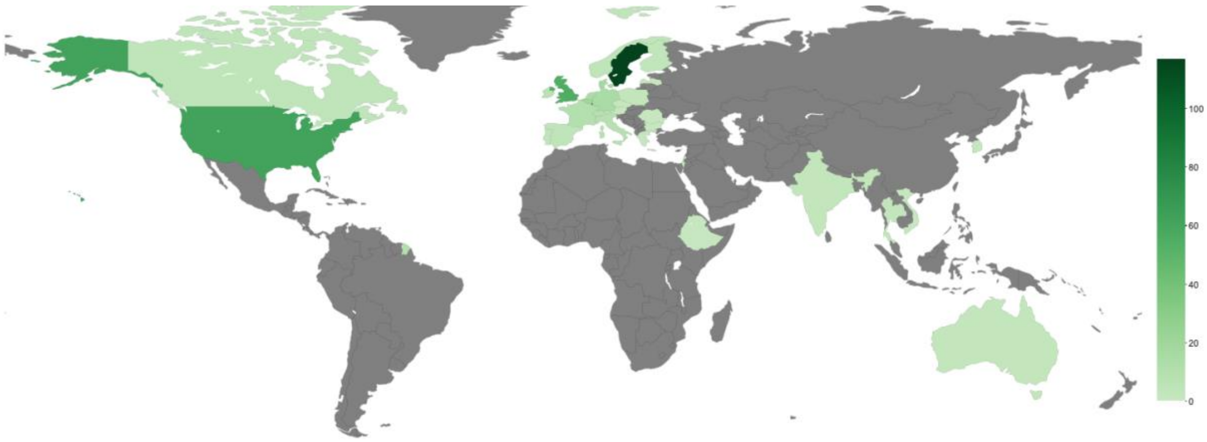

Figure 2.7: A visual depiction of the number of sources per country of origin (n=414) from the scoping review for the data sources and evidence that could be used to model the different parts of the Swedish food system.

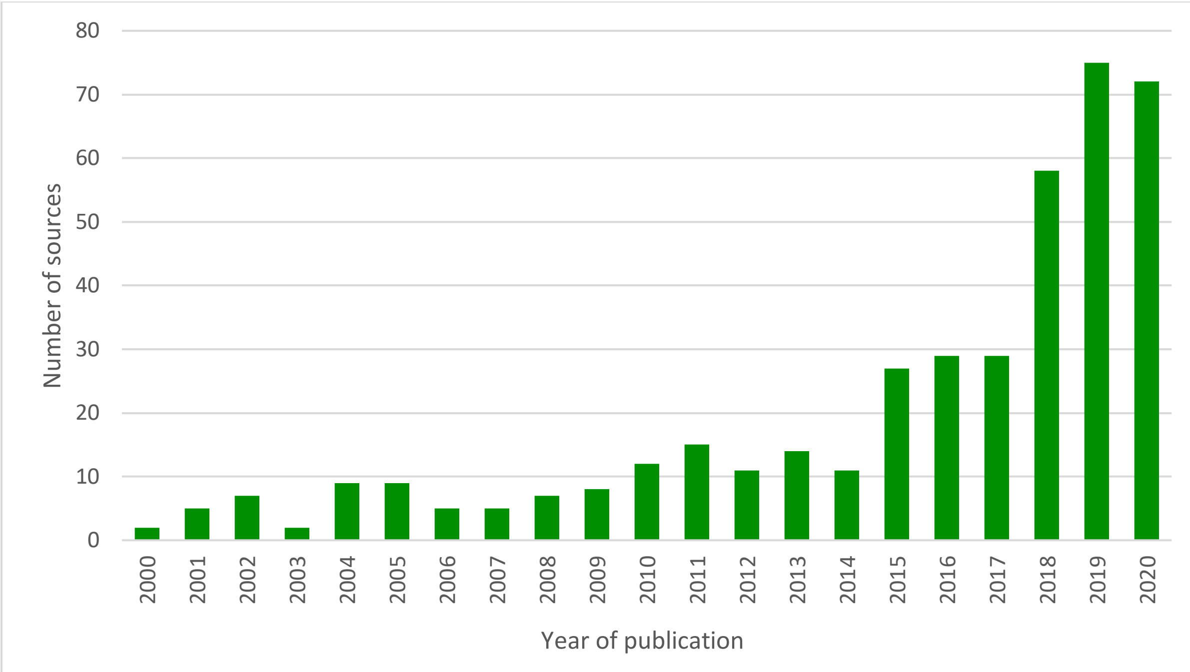

Figure 2.8: A description of the publication year of the sources (n=414) from the scoping review for the data sources and evidence that could be used to model the different parts of the Swedish food system.

Chapter 3

Using expert knowledge and experience to parameterize a simulation model of antimicrobial resistance emergence and transmission in a Swedish food system context

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3.1 – Abstract

Background: Antimicrobial Resistance (AMR) is a global One Health problem that has caused great health and economic consequences. Models intended to simulate the biology of AMR and its drivers exist in many contexts but there is a lack of integration of models across sectors and many data gaps. In order to build a model of the entire complex system, expert knowledge of direct and indirect drivers of AMR is required to fill current gaps in quantitative data. Therefore, the objective of this study was to compile quantifiable data from statements made by a group of experts to help parameterize a simulation model of AMR emergence and transmission in a Swedish food system context.

Methods: This study builds upon previous work that developed a causal loop diagram of AMR using input from two workshops conducted in 2019 in Sweden with experts within the European food system context. A secondary analysis of transcripts derived from the two workshops, coded in NVIVO 12, was done to identify which of the main drivers can be parameterized in a simulation model of AMR based on available data.

Main findings: Participants spoke about AMR by combining their personal experiences with professional expertise within their fields. For example, one expert mentioned that "*we are very rarely applying a lot of the preventative measures we know we could"*, which could imply that preventative measures are important to combat AMR but are currently underutilized. The analysis of participants' statements provided semi-quantitative data that can help inform a simulation of AMR emergence and transmission based on a causal loop diagram of AMR in a Swedish food system context.

Conclusion: Using transcripts of a workshop including participants with diverse expertise across the system that drives AMR, we can gain invaluable insight into the past, current, and potential future states of the major drivers of AMR, particularly where quantitative data are lacking.

3.2 – Introduction

Antimicrobial resistance (AMR) is a global, One Health problem that has the potential to cause up to 10 million human deaths globally per year by 2050 (1-3) and has had other devastating impacts on the health and well-being of humans, animals, and the environment (1-3). The major driver of AMR has been commonly reported to be the overuse and misuse of antimicrobials (AMs) in humans and animals, mainly in agricultural settings (1-3). However, the overall picture is not so clear. There are many drivers of AMR that relate to why and how we use AMs, which stem from cultural, social, and economic conditions (1-7). Due to AMR's complexity, and the intricate social and economic dynamics that underpin much of the system of drivers of AMR, AMR has yet to be discussed and dealt with at a broad scale (5-7). Many interventions to combat AMR are siloed to single sectors and, if implemented, may have unintended consequences in the broader system, may not be adopted into policy, or those adopted may be met with non-compliance (3, 7). For example, many policies and regulations that try and limit antimicrobial use (AMU) have failed to account for the underlying reasons for use (e.g., overcrowding and lack of biosecurity on farms) and therefore are not willingly adopted by those they are intended to regulate (e.g., producers continue to overuse AMs; 7-9), or may lead to unintended consequences (e.g., purchasing of AMs on the black market, or the loss of animal lives and production). Therefore, to better address the issue of AMR, it is necessary to understand this problem from a systems view and engage stakeholders in exploring the why and how of the issue to be able to identify drivers of AMR and how they may influence each other.

One way to better understand how a system works is through quantitative, qualitative, or mixed methods simulation of said system (10-17). A simulation is a representation of the operations of a real-world process or system over time (17). This usually involves the creation of a model. A model represents the key components of a system including its main characteristics or behaviours (17). Simulation models have been used to explain and predict the emergence and transmission of AMR, however these models are rarely integrated across sectors and usually focus on small populations in specific settings (Chapter 2). Creating complex and integrated models that capture the diverse One Health aspects of AMR requires a large amount of data. In a previously conducted scoping review (Chapter 2), we wanted to determine if it would be possible to create a simulation model of AMR within a broad One Health system, based on a previously described participant-derived causal loop diagram (CLD; a visual representation of all of the key variables (called factors or nodes) and all of their interconnections (called relationships) within the system; 18) of the emergence and transmission of AMR within a European food system context (7). For this research, we used the Food and Agriculture Organization of the United Nations (FAO) definition of a food system, which includes the entire range of actors and interlinked activities within the broad context (economic, societal, and natural environments; 19). This definition therefore encompasses the sub-systems (farming system, waste management system, etc.) and other key systems (e.g., trade system, health system) with which they interact (19).

The scoping review found that the published literature and empirical data (i.e., explicit knowledge) are limited in many sectors (Chapter 2). However, other types of knowledge exist, such as professional knowledge, experiences, and opinions (tacit knowledge) that could provide important insights about a sector’s context, novel research in their field, and emerging trends that could help to better understand existing knowledge gaps. This knowledge can also help to better contextualize existing factors and relationships across the broader system. Therefore, by engaging experts in AMR (e.g., human medicine, veterinarians) and experts in broader areas of the food system (e.g., animal welfare, consumer advocacy), it is possible to tap into their tacit knowledge and experience to fill data gaps.

Therefore, the goal of this study was to extract data that can be used to populate a simulation model of AMR emergence and transmission in the Swedish food system, by identifying relevant parameters for the model from expert participant discussions of drivers of AMR. Specifically, we were interested in the content of statements made by experts in terms of the objective indicators they reported (e.g., the current state of the main factors and the strength and direction of relationships between drivers), and the evidence they used to support their statements (e.g., tacit knowledge or explicit knowledge).

3.3 – Methods

This paper expands on a previously published study by Lambraki et al., which identified AMR drivers and their interconnections in a European food system context, through two participatory modelling workshops (7). Full details of the workshop methods and outputs are provided in Lambraki et al. (7), but here we provide a brief overview of the workshop setup, the participants involved, and the major outcomes of the workshops relevant to the secondary analysis we conducted for this study (7).

3.3.1 – The workshops and participants

Two model-building workshops, each lasting about 6.5 hours, took place on September 19th and 20th, 2019 at the Stockholm Resilience Centre in Stockholm, Sweden. The two days were identical in structure and intended outcomes, however, they differed by the types of participants involved. The first day consisted largely of "AMR experts" who had expertise in AMR within various areas of the overall food system (e.g., public health advocacy, nursing, food safety, aquaculture, agricultural economics, food trade law, and veterinary medicine and epidemiology). These experts were engaged first to give a better understanding of the state of AMR within Europe broadly. The second day was mainly made up of participants who were considered "non-traditional experts", who were individuals with expertise within the broader food system, but are not traditionally engaged in discussions of AMR (e.g., consumer advocacy, pharmacy, animal welfare, pharmaceutical law, pharmaceutical marketing, human medicine, peace and leadership, urban agricultural innovations, nutrition and dietetics, and sustainability). In total, 17 participants took part in the study, 7 in the first and 10 in the second workshop. The participants engaged were mainly from Sweden and therefore while providing insights into the European food system, the resulting CLD took on a European Union and more specifically Sweden focus.

Using open-ended questions and group discussion, the participants and the facilitators physically mapped out the major drivers of AMR (called nodes) and sought to identify how these drivers were connected (called relationships) using a CLD of AMR, originally made for the Canadian context (20), that they tailored to reflect the European context. Participants were asked to describe the nodes in measurable terms (i.e., something that can increase or decrease) versus more subjective descriptions. To begin, participants were asked where they felt their expertise "fit" into the CLD and if there were any aspects missing or that needed to be changed or removed from the CLD, to reflect the European context. The final causal loop diagram is available online (7; See supplementary file, Figure S7). The study was approved by a University of Waterloo research committee (ORE # 40519) and consent to participate and be audio recoded was obtained from all study participants.

3.3.2 – Data analysis and approach

For this study, the transcripts of the above workshops were coded in NVIVO 12 using the same codebook from the previous study (7), as well as allowing for open coding to identify new, missed, or refined themes. The codebook was originally created for the purpose of identifying major drivers of AMR and relationships between the drivers (7). For this study additional codes were added to identify the level of the nodes (high, medium, low, none, unknown, or varies throughout Europe). The level of the node refers to position of that node in Sweden on a scale of the amount, quantity, extent, or quality compared to a referent (e.g., Sweden versus other countries within or outside of Europe, Sweden currently versus historically). For example, there is lower AMU in agriculture in Sweden now compared to 10 years ago (21), there are low levels of human AMR in Sweden compared to low- and middle-income countries (22), and there is zero use of antimicrobials for growth promotion compared to the United States of America (USA) where it is fairly commonplace (23). Codes were also used to identify the strength (strong, weak, not mentioned) and direction (positive, negative, not mentioned) of the correlation of relationships between the nodes.

In their accounts, participants referred to a variety of sources of data; this was of particular interest because it helped to identify the areas where scientific evidence exists or is absent. The tacit knowledge and practical experiences shared by the experts helped to inform our model, by filling the gaps in the published evidence and validating evidence from the literature with the data generated from the participants' accounts. Some of these accounts were explicitly stated, in which the experts stated that data exists or does not exist, referred to the specific government, scientific reports, or studies for which the data they are referring to, or described an experience from their work (e.g., "*when I was a nurse..*", "*at our company we*…", "*in my professional opinion*…" are all examples of accounts related to professional experience or opinion). Other times the source of the data was implicit and was revealed through the language they used (e.g., "*it is well known that…*" implies general knowledge). Therefore, additional codes were added to capture the source of the data related to AMR: general knowledge; personal opinion and experience; professional opinion or experience; and scientific evidence. General knowledge was used for knowledge that the general public or the "lay person" would know from encounters through their daily lives as opposed to knowledge on a specific subject that would result from training or exposure to a specific area. Scientific evidence was further broken into three levels based on perceived quality or amount of data that exists for a given node: low – no data exists (e.g., surveillance or research has yet to be done), medium – poor, inconsistent data, proxy data used; high – good data, experimental studies, published literature or surveillance reports. To ensure the coding was consistent, intercoder reliability (24) was assessed between three independent researchers on 10% of the nodes (n=12) and relationships (n=20). There was 61% consistency between the coders, which reflects the subjective nature of the coding, most of which was due to different interpretation of the code definitions. The definition of the categories of the codes were refined for better understanding, and any resulting differences were discussed until resolved.

Framework analysis (25-27) was used to organize the codes into a matrix showing the intersection between the node of interest, the level associated with that node (Table 3.1), and the source of data to support the claim (Table 3.2). The framework matrix was generated in NVIVO 12 and then exported to Excel to be organized and refined. A separate matrix was created for each workshop, in which the first transcript was coded and put into a matrix and was refined through discussion with the qualitative expert on the research team (EN) until consensus was reached. The second transcript then went through the same steps. After both workshops were coded and organized into a matrix, the matrices were combined to create one matrix to represent a collective view of the participants regarding the Swedish food system context. The framework matrix was compared to data from the scoping review that was performed to identify mathematical models and quantitative and qualitative data to parameterize a model of AMR emergence and transmission in a Swedish food system context for validation (Chapter 2).

During the analysis, it became apparent that a framework matrix could not fit the data due to the complexity and number of interconnections (relationships) between the nodes that were identified from the transcripts. Therefore, a concept map was created to visually represent these connections with colour and weight of the lines depicting the strength of the relationships and the type of evidence used (explicit or tacit knowledge) respectively, and symbols (+/-) depicting the direction of the correlation of the relationships. Concept maps (28-30) are useful in the visual representation of complex data and help to organize and reduce many themes and concepts into one clear diagram. The concept map was designed using miMind version 3.13 (Figure 3.1).

Nodes were grouped under larger headings based on the coding scheme and this was depicted through large bubbles representing the broader concept (e.g., AMR) and smaller bubbles inside representing the more specific aspects of the concept (e.g., AMR in humans, AMR in food-producing animals). Relationships could be between the broad concepts or the specific nodes depending on the level of detail provided by the participant. The nodes (which were visually represented as a box) were then colour coded and shaded to reflect the level (colour) and the source of the data (darkness of the shading) which was informed by the framework matrix. When two or more claims were made pertaining to the same node or relationship and one referenced how the level may vary in Europe versus the other claim referencing Sweden, the level that was specific to Sweden was chosen for visual representation. Similarly, when two or more statements were made about a node or relationship using different sources of evidence, the following hierarchy was used to determine which was used to visually represent the evidence: scientific evidence > professional > personal > general knowledge. In instances where participants had conflicting views in relation to the level of the nodes or the strength or directions of relationships, the opinion of the majority of participants was used on the concept map, and both views were noted in the framework matrix.

The combined concept map created from the two workshops was compared to the existing CLD (7; See supplementary file, figure S7) to ensure that the nodes and relationships identified in this analysis appeared and matched those in the CLD, which was previously validated with workshop participants through member checking (7,31,32). Nodes and relationships that were not found in the original CLD (nodes: n=35, relationships: n=74) were noted for further discussion with the broader research team for inclusion in the final model.

3.4 – Findings

3.4.1 – Framework matrix of nodes

There was a total of 83 nodes included in the framework matrix: 48 nodes were nodes found within the original CLD (n=40) or its overarching factors (n=8) (7), and 35 were new nodes that were created and added to the framework matrix from this analysis. These 35 nodes emerged from: 1) new nuances that came to light during this analysis of the data from the workshops, or 2) nodes broken down into sub categories or merged into broader categories (e.g., AMR as a broad category; AMR in humans, food-producing animals). The latter was important because sometimes the broad category was referenced instead of the specific node. For example, one conversation that took place mentioned infection prevention and control measures in broad terms, "*we are very rarely applying a lot of the preventative* *measures we know we could."* This excerpt was part of a discussion on how we as a society are not doing enough in terms of prevention measures. However, some participants referred to a specific sector. For example, one participant mentioned that "*these countries in some of the hospitals, they don't have any infection control nurses or any infection control staff at all.*" This claim was directly related to infection prevention and control measures within the healthcare system (specifically in hospitals).

There was a broad range of topics covered in the two workshops that spanned many sectors (humans, animals, the environment) and scales (sub-national, national, international). Excerpts from the combined framework matrix are depicted in Table 3.1 and 3.2 (full framework matrix; 33), which shows the variety of topics (nodes) covered, tabulated against the associated level of the node (Table 3.1) and the source of the data that was either explicitly stated or was implied through the participant's wording (Table 3.2).

Although transcripts were coded using "high", "medium", and "low" codes, statements were only made in language that referenced "high" or "low" but not in the "medium" category and thus it was dropped from the finalized framework matrix. A total of 27 nodes were categorized as "high", 23 as "low", 23 as "unknown", 8 as "none", and 16 nodes were said to "vary across Europe".

Strong language was used to refer to "high" levels, such as in the case of one participant who said that Sweden "*...is a huge import of chicken meat, beef, even pork from South America, Brazil, which are produced under completely different conditions concerning the environment, concerning the use of antimicrobials...*" This language implied a high or even very high level of importation by Sweden and that this participant was concerned about imports that may condone some unfavourable agricultural practices and exposure to AMs, AMR, and other harms in other countries.

Alternatively, strong language was also used to refer to "low" levels, such as when one participant said *"....actually during 2019 WHO [World Health Organization] has tried to boil down all the resistance is to all bacteria into one score, to simplify it, and then Sweden comes out on top, India comes out in the bottom*". In this case, the participant was referring to Sweden as having low levels of AMR in general compared to other countries.

There were a few instances (8 out of the 83 nodes) where Europe (specifically Sweden) was mentioned to have "zero" or "none" for a given category. For example, quota for meat, dairy, and eggs was identified to not be an important part of the agricultural system in Sweden (it is an "*absolutely free market"*). Also, AMU for growth promotion and (soon to be) for prevention of disease is banned in the European Union (EU), post-harvest interventions for disease control (e.g., chloride washes) are not common practice, nor is insurance for producers who may lose crops or animals to disease, and finally selling insects for human consumption is illegal (see framework matrix for quotations pertaining to these nodes; 33).

In terms of the evidence used by participants, the majority of statements (52 of 83 nodes) were coded as professional experience and opinion (tacit knowledge) based on observations in the participant's professional background. For example, one participant in the second workshop mentioned:

> *… I had the privilege to come back to intensive care. Since I have worked with that twenty years and then I have worked as a, in my own company and now since June, I jump in some days and work inside, and I can see what have happened in intensive care, and I think it is, it is generally in Sweden because before, people, people, nurses and doctors used their craft, the hand craft. They.., they exam[ine]… patients much more. Today it's, the reference is the computer system. You take a long [inaudible] report. You read and then you have the reference about, you know, this patient, and then we got into it, and see, oh, it is not as it was written, or I was reading in there.*

This quotation suggested that there has been a change in healthcare practice in Sweden and its potential impact on healthcare professionals' ability to diagnose patients. Based on personal recollection, this opinion was categorized as tacit knowledge.

There were eight claims that were categorized as referencing participants' personal knowledge. For example, one participant mentioned:

> *I am wondering, I don't know the data about Sweden, but I have this guesstimate based on someone that knows, or you can find out, like what is, how are people feeling in Sweden, like, in terms of the stress level, depression, psychological wellbeing, because I know my own experience as a young kid and older kid back in the day, I was incredibly stressed, focused on like producing stuff and not getting well, and then I didn't care what I ate and I know a lot of other young people who are not necessarily feeling super well and I heard now in day care, there they have these, you don't go to day care as a three, four year old just to learn and develop, but you also are evaluated. So I am wondering how are the systems that we live in affecting like long term preventions perspective. Our stress levels, and how is that affecting us.*

This participant provided examples from their personal experience to generalize about the state of psychological health and stress levels in Sweden and how it relates to the current culture and pressure to perform.

There were four statements coded in the category of general knowledge. One example was from the second workshop in which one participant mentioned, *"…we have no wars in Sweden for two hundred years, at least for two hundred years*" In this case, the participant was stating that Sweden has been in a state of peace for many years (thus the node Peace and Affluence was categorized as "high"). This was considered general knowledge within this context because within Europe, an average citizen would most likely be aware of this fact.

The last category of evidence are those statements that refer to the scientific evidence (or lack of evidence) for a given node, of which there were 33. Some participants specifically referred to there being no data or that the existing data are of very poor quality, which was coded as "scientific evidence – low" (7 out of the 33 scientific evidence nodes).These types of statements were usually used to highlight the lack of data and the need for better data in these areas as illustrated in this representative example:

Participant: I mean antimicrobial use sounds easy.

Laughter.

Participant: We can measure that. I mean that is exactly the point is you know our measurements on these things, the accuracy still remains …

Facilitator: Is that a research thing as well how you actually measure, or is it a willingness.

Participant: It is not only research. It is not only willingness, you know, there are many details that we don't understand about how many antibiotics are used, you know. We can get sales figures. But, split packs and things like this, this gets chucked away and doesn't get chucked away.

Participant: I mean we are not even measuring it.

Participant: We don't actually have precise figures on use. Most of the figures used are based on sales from pharmaceutical companies, or from prescription figures from definitely surgeons, or doctors and so on and they are very broad aggregate figures. How many of those are actually used, we really don't know. We just assume that the sales figures are a good proxy, but yea it is true, And we don't really know how much actually go into the environment through residue or waste that go on like this, and you know.

This conversation showed that the way in which we currently measure AMU in agriculture (specifically aquaculture) is not an adequate or reliable measure and that there are many reasons for this.

The claims that referenced scientific or experimental data or data that were referred to as more accurate ("scientific evidence – high") occurred for 13 of the 83 nodes. An example of a claim backed up by good scientific evidence from the second workshop is shown in Table 3.2. This quotation referenced a study that was performed, the name of the study, and the results from that study to back up their claim that Swedes are "rule-followers" and tend to adhere to regulations and legislations in general.

3.4.2 – Map of drivers and relationships

Overall, there were 189 relationships mentioned, and a direction for the correlation of the relationship was usually easy to decipher from the example using our background knowledge of the AMR system (131/189 directions deciphered). However, the strength of the relationship was less commonly reported or able to be deciphered from the language used during discussions (32/189 strengths deciphered). In this case, the "unknown" category commonly represented a claim that did not contain language that would indicate the strength of relationship (see purple lines in Figure 3.1). For example, one participant in the first workshop mentioned "*this [research and development] will lead to better gathering of data, sharing of data, which will in turn lead to better prioritization of policies and also allow us more budget around the whole system and within the system for each species and I think it is all this systematic approach and it will take a lot of time."* This quotation mentioned a lot of relationships that are important to understand how the research and data drive each other, and how that leads to policy and opens up budgets for further research. This participant gave insight into the direction of these relationships through the language they used (x will lead to better y is indicative of a positive relationship). However, they did not use language to indicate the strength of the relationships (e.g., x will lead to a lot/a little better y). This quotation was coded as professional opinion as they referred to budgeting as "us" and therefore positioned themselves professionally within the context.

Overall, most relationships were mentioned without an indication of the strength of the relationship (n= 157/189), 28 indicated a strong relationships, and very few were considered weak relationships (n=4). Two of the weak relationship claims were made in comparison to their strong counterpart. This was seen when comparing the relationship between AMU in terrestrial food-producing animals and the risk of AMR in humans which had a strong relationship, compared to the use of antimicrobials in aquaculture, which was said to pose less risk (or a weak relationship) of AMR development in humans. The other was in reference to the use of expensive diagnostics over cheap broad spectrum AMs. Diagnostics therefore had a strong relationship with cost of healthcare resources by the government and AMs had a weak relationship. The other weak relationship claims made by participants were categorized based on the language used in the claims that indicated the relationship did not really exist or was not overly important in the European context. For example, for the Sweden context, one participant mentioned that "*we don't see increased deaths in untreated [inaudible] for example, or we don't see that children mortality is going up even though we have reduced the antibiotic use enormously. So, we are following that, but that is the easy part to see antibiotic total use.*" This indicated that there was a weak association between AMU and deaths in humans in Sweden, whereas this may not be the case in other countries (e.g., low- and middle-income countries where untreated infections may more often lead to death). The last weak relationship was between domestic and international trade regulations and on-farm AMU and this was a weak relationship because participants said that "*there is a code of practice, but I don't know if it has an effect, but we tried at least in Sweden to re-establish, to practice that.*" They argued that even though there are clear guidelines and recommendations, these things are not being followed by many other countries and this can impact Sweden through trade and travel.

There were many instances in which personal (n=80/189) and professional opinion and experience (n=95/189) were used to back up claims of relationships between nodes. However, scientific evidence was used to support data to inform only 24 of the relationships, of which only 5 indicated the strength (all categorized as strong) of the relationships. For example, when discussing how consumers can have a large influence on the government, one participant mentioned:

> *Some of those triggers can be for example, the, the making the transparency, increasing transparency, making data by the book [available] to general members of the society, and so that they are aware of what a situation is, … I am guessing about what is happening in the Netherlands with the* ESD *[Environmental Systems Division] …. That is what triggered the decision of the Minister to say, 'okay, now we will implement targets [for] use and I want to see this done by a year two or year three, and I want 75% reduction in the use of antimicrobial In farm production.' … That was all driven by newspapers showing [the] data.*

This participant provided a specific example of how an increase in data transparency and making data more available to the general public (e.g., through news and media) has led to a change in consumer demand for products (e.g., a reduction of AMs used for food agriculture) which in turn led to large change in government decisions (implementation of targets for agricultural AMU to reduce by 75%) and cause great changes in the country (reduction in AMU). This participant's claim gave insight into the strength and direction of the relationship and used a scientifically based measure to back up their statement. Only five of the relationships were supported by statements which we categorized as general knowledge.

Interestingly, sometimes the statements made by one participant in reference to the strength and/or direction were followed by another participant who provided additional evidence from their own personal experience or professional knowledge (or vice versa) to collectively create an evidence-based statement for the relationship. In one example, the conversation began with discussion on how investing in good farm practices and infrastructure can lead to a reduction in animal disease and involves short term costs with long term benefits. One participant mentioned *"…you would improve your farming practices, and therefore in the short term there would be a large investment, but in the long-term as you are reducing your disease burden…"* which indicated the direction of this relationship (negative correlation between farming practices and disease burden). Another participant then added the evidence to back it up by saying that "*the studies that are complete…. In the Netherlands and in Denmark, are on exactly that*". Later in the conversation a participant mentioned that it is "*fairly obvious around the good farming practices, and anything that we can do to improve the way we raise the food producing animals and keep them being in healthier conditions*", which provided an insight into the strength of the relationship using language such as "*fairly obvious*". Overall, through the conversation between the participants, we were able to decipher that this was a strong, negative relationship, and that there was scientific evidence, in addition to personal and professional knowledge to back up this statement.

3.5 – Discussion

Overall, the participants spoke about the issue of AMR by combining their personal backgrounds and experiences with professional expertise and knowledge from within their field and related fields. Through these conversations and sharing of expert knowledge, the participants were able to create a complex and interlinking map of the drivers of AMR and provided valuable semi-quantitative statements about the nodes and relationships that can help inform a simulation of AMR emergence and transmission in a complex system.

3.5.1 – Key findings

It was noticed that most participants' comments were coded with the level "high" and "low", but not "medium". Similarly, "strong" relationship claims were much more apparent than "weak" relationships. This makes sense in terms of the way people tend to remember things. It is human nature to better remember the extremes rather than the average (34, 35). This could explain why participants mainly focused on strong relationships, as these would be the ones that stand out in their minds. One would first think of those relationships that have large impacts or are known to be major drivers than those weaker relationships that may be less important. Participants may even feel that these weaker relationships are not worth mentioning as they are so far removed. However, it is important to include all of these relationships even if deemed small or insignificant because they could become a large driver if another part of the system were to be changed or removed (e.g., purchasing of AMs on the black market is very limited in Sweden currently but could become more apparent if AMU is extremely limited through regulations).

We noticed that many statements referring to both the nodes and relationships were made based on tacit knowledge (e.g., personal and professional knowledge and experience). As this was a secondary analysis, and was not defined *a priori* as a major objective of the workshops, we did not probe the participants for the sources of their knowledge or the basis for their claims. The data collected were based on organic conversation. Thus the nodes or relationships categorized as opinion or professional evidence may also have scientific evidence to support them that was not mentioned in the context of the workshop, and which should be verified with further expert engagement.

Finally, although Sweden is one of the leaders of the AMR movement and they have some of the lowest levels of AMR and AMU compared to many other countries (Chapter 2; 36, 37), it is also possible that the participants were framing their claims to place Sweden in a better light, either consciously or unconsciously, to highlight their achievements to our Canadian research team and to those participants from outside of Sweden or other Nordic countries. Participants spoke very highly of Sweden in terms of their levels of factors such as regulations, disease, AMU, and resistance, and usually did so by comparing these to other countries (e.g., comparing the USA's overuse of AMU for growth promotion or chlorine washes in their meat industry to the more preventative biosecurity practices in Sweden). However, this could be partially due to illusory superiority, in which a person can overestimate their own qualities and abilities in comparison to others (38). Therefore, future studies should cross-check the statements of the participants against available data (if it exists) to be able to confirm the claims of the participants.

3.5.2 – Limitations

This workshop took place in a specific setting (Stockholm Resilience Centre, Sweden), at a specific time (Fall of 2019), with distinct participants from a variety of backgrounds related to AMR and the broader food system, and therefore cannot be generalized beyond the scope of this study. For example, if this workshop were to be done during or after the COVID-19 pandemic, the findings may have been quite different. The pandemic could have out-competed AMR for importance and diminished the importance of certain nodes or relationships or changed the experts' views on certain aspects of the system. Participants could have related more examples to the pandemic, and levels or amounts of factors and relationships between these factors may have changed (e.g., trust in science or leaders, socioeconomic status of the population, rates of illness, or amount of AMU). Therefore, these findings are context specific and are limited to this time and place, but were valid at the time of creation. Further studies in multiple different contexts (both in high income country and low- and middle-income country contexts) can further expand our knowledge within each context and allow for comparisons between contexts to assess the generalizability of these findings (39).

One limitation that has been associated with qualitative research is that the interpretation of the participants words, the coding, and the analysis and presentation of findings are subject to the researchers' own personal biases and intended outcomes (40). However, through discussion with others, inter-coder reliability and refinement of the analysis (40), as well as through triangulation (41) with other sources of data, the potential biases associated with personal interpretation have been minimized to the best of our ability.

This study was also undertaken with a specific goal in mind (identify semi-quantitative data pertaining to the nodes and relationships). Therefore, there was a pre-conceived goal that may have limited the scope of what was identified in this analysis. However, using the stricter approaches found in framework analysis (25-27) permitted the identification and organization of the findings for use in future studies (e.g., model building) and streamlined the approach for use in mixed methods research more broadly.

The final limitation within this study was that since this was a secondary analysis, we did not prompt the participants to discuss the nodes and relationships in terms of semi-quantitative indicators. We did not explicitly ask for participants to describe the strength or directions for the relationships they mentioned, or even asked for the relative importance for the drivers. We also did not explicitly ask the participants to provide the type of evidence being used to inform the claims being made. Therefore, some nodes and relationships that were categorized as tacit knowledge could have actually been from a scientific source that the participant did not explicitly cite when making the statement. However, without prompt, the participants provided great insight into many of the nodes and some relationships, but future studies could explicitly use participant input to provide quantitative estimates for the nodes and relationships through the use of participatory modelling approaches such as fuzzy cognitive mapping (42).

3.5.3 – Implications

Despite these limitations, this research has highlighted the importance of using qualitative research to better understand complex One Health issues. Through the engagement of multiple participants from a variety of backgrounds, it was possible to provide estimates to begin to quantify a broad One Health model of the system of drivers of AMR in a Swedish food system context. This is of importance (especially with AMR) where there are so many drivers at play with complex nuances, such as socio-economic and cultural factors, that can drive human behaviour in unpredictable ways and may be difficult to quantify and model with current quantitative epidemiological methods. Therefore, from a disease modelling perspective, the engagement of experts to outline the structure of the model and to provide estimates into the current states of the nodes and the strength and direction of the correlations captured by the relationships is an important (and potentially) essential first step in the modelling of complex systems. Current quantitative dynamic models of AMR are limited in scope, both in terms of the populations capture but also in terms of the factors that are included (Chapter 2; 43, 44). These models typically include populations from one sector (e.g., humans or animals), in small settings (e.g., in a single hospital or farm), and only include basic factors such as AMU, hygiene practices, and transmission factors such as contact and transmission rates (Chapter 2; 43, 44). One major reason for the limited scope is due to data limitations and lack of understanding of the quantitative relationships between sectors (43, 44). However, through the use of qualitative methods, as done in this study, we can expand the factors that may be included in these models.

Participatory modelling approaches have been used to identify and potentially map out the major socio-ecological drivers of AMR in Europe (7), South-East Asia (45), New Zealand (46), and Tanzania (47), but these studies did not aim to estimate values for the various components of the system. Many studies have used qualitative methods to try to better understand the motivations that drive AMU in humans (48, 49), companion animals (50), and agriculture (51-55), and the drivers of prescribers in these settings (52, 56, 57) in both high-income (e.g., Denmark, United Kingdom) and low- and middle-income settings (e.g., Bangladesh, Thailand, and many African countries). These studies typically engage farmers, prescribers, or the general public in focus group or interview settings to discuss the knowledge and opinions on ARM, healthcare seeking behaviour, prescribing practices, and the barriers or drivers around AMU (7, 45-57). These studies have helped to enrich the understanding of many drivers of AMU and AMR in these contexts which can help to inform the structure of the system (e.g., identify nodes and relationships). However, some studies have started to "quantify" these factors and relationships using expert knowledge and input from the general public (58,59). First, in a study in Switzerland, experts and consumers were engaged to discuss the relative importance of the multiple pathways in which humans can be exposed to AMR, including: pets, farm animals, food, travel, the environment, and hospitals (58). Similarly, in the United Kingdom, experts related to the companion animal veterinary field (including policy, academia, and leaders in professional bodies) ranked the veterinary behaviours which contribute to AMR in companion animal veterinary practice (59). These studies not only describe factors that may drive AMR but also provide estimates (rankings) of the relative importance of the factors which could provide a basis to begin to quantify these factors and relationships. Therefore, future qualitative studies to understand the drivers of AMR could include a component to help quantify the parts of the system.

Semi-quantitative modelling approaches, such as fuzzy cognitive mapping (42), could be used to model the drivers of AMR within the complex system. Fuzzy cognitive mapping is a participatory modelling approach which engages experts to not only define the structure of the system of drivers but to provide estimates for the current states of the nodes and weights (strengths and directions) for the associations captured in the relationships (42). Fuzzy cognitive mapping has been used to address other public hath issues such as diabetes (60) and cervical cancer (61) in Aboriginal communities in Canada. This method could be applied to address AMR, and could be expanded to not only include expert knowledge but also current empirical data. For example, the previously described CLD created through expert engagement created a basis could provide the structure for a model of AMR within the Swedish food system context (7), data from the literature and other published sources (Chapter 2) and the data found through the semi-quantitative statements made by participants (this study) could be used to parameterize a model of the system. These methods in tandem could expand the available knowledge to inform the model. For example, participants' tacit knowledge can be used in place of explicit knowledge (e.g., quantitative data), or tacit knowledge could be used to back-up or support the limited data that does exist. Participants' knowledge can also be used to highlight what may be the most important factors, and therefore necessary to remain in the model, which relationships may have the most influence on the system, and which connections may be less important to the overall model structure. Thus, when creating a simulation model of a large and complex system (e.g., for AMR), it is clear that input and communication between experts provides invaluable information to better understand the system.

3.6 – Conclusion

Using the transcripts of a workshop that included traditional and non-traditional experts in AMR provided valuable insight into the major drivers and interconnections related to AMR from both tacit and explicit knowledge. This study helped us better understand the Swedish food system context and the past, current, and potential future states of the factors that may be driving AMR in this system. This study highlighted how the use of qualitative methods may allow us to better understand the issue of AMR and can be used to help parameterize models, especially in such a complex system. Finally, although these results are limited to this specific context and not necessarily generalizable, this study provided a strong base for the future creation of a participant lead, mixed methods simulation model of the emergence and transmission of AMR within this context.

3.7 – Tables

Table 3.1: Sample combined framework matrix with quotations showing how workshop participants explained the level at which four different drivers of AMR in the Swedish food system context exist, stratified by expert type (1: traditional AMR experts, workshop day 1; 2: other experts in upstream drivers of AMR, workshop day 2).

	Access to AMs outside the system	**Agreements, regulations, and standards: compliance and enforcement**	**Non-AM disease prevention**	**Antimicrobial Resistance**
Level – High		*I just want to add, just a small thing about the legislation, and it was a project some years ago called Eco Welfare, where they looked at different countries, and how they implemented the legislation and so on, and Sweden were, we are relying a lot on the legislation, and we are really, we are following the legislation* (2)		
Level – Low				*Oh that is what I started with all my lectures in every country where I go. I go to a lot of countries and tell them about Sweden, and Sweden is one of the extreme positive examples of the world. We started long ago. We started like in the early nineties. On the vet side even in the eighties, and not only because of that, but probably partly because of that, we had today an extremely good situation when it comes to resistance, and you can compare it for different bacteria, resistance to different antibiotics, and there is someone now, actually during 2019 who has tried to boil down all the resistance is to all bacteria into one score, to simplify it, and then Sweden comes out on top, India comes out in the bottom* (2) *Yea, I remember now what one thing I should add here. If you look at resistance, we are in a good situation* (2)
Level – none			*We very rarely applying a lot of the preventative measures we know we could, regardless whether that is changing our role, our behaviours, strong vaccination and stuff like that, and vaccination in one place. I actually believe that relates to, to*	

	Access to AMs outside the system	Agreements, regulations, and standards: compliance and enforcement	Non-AM disease prevention	Antimicrobial Resistance
			like foreign practices and stuff like that (2)	
Level – unknown	*And of course not everyone is buying antibiotics to begin with but people pass them along the family to friends, and some people get them abroad when travelling because it's easier than in the country that they live in. So it's the whole mobility aspect as well* (1) *Of course, we don't take into account black market operations or internet sales and stuff like that which are tricky* (1)			
Level – varies				*I mean so and that, there are other such maps mapping the situation globally and in Europe, and it is obvious that we are living in a country with extremely privileged situations when it comes to resistant, resistance. Together with, I should say, the other Nordic countries and the Netherlands, which is the good example to show that it is not only a north, south effect of Europe because generally Greece, Italy, Spain, fares a lot worse than we do and the Nordic countries up there is other colours, if you put them on maps for example, which would have come from other ECDC, the European communities and centre, and but then Netherlands, they are, I mean they are there in the middle of Europe anyway and they still have the same problem as we do, and what is common for them and us, it is much antibiotic policy.* (2)

Table 3.2: Sample combined framework matrix with quotations showing the source of the data workshop participants were assumed to have been used when describing five different drivers of AMR in the Swedish food system context, stratified by expert type (1: traditional AMR experts, workshop day 1; 2: other experts in upstream drivers of AMR, workshop day 2).

	Access to AMs outside the system	**Appropriate prescribing, diagnosing, treatment: Prescription necessary for AMs**	**Burden of illness: Human illness**	**Resistance : Resistance in wider environment**	**Science and academia**
Scientific Evidence/Data – Good, experimental, accurate		*P: Just on the regulatory side we talked about a few minutes ago here in the EU, I understand all antibiotics for humans and animals are by a prescription by a medical doctor, veterinary doctor or veterinary surgeon. So it's the professional vets and professional doctors who have to give a prescription for use.* *P: Even though in Europe it is a little bit different because everything leads to a prescription.* *F: Yea.* *P: Maybe that in a way, but in other parts of the world where there are no prescriptions and the farmer makes the decision, it is ….* *P: Yea, yea. Absolutely, the vets…There are key… bottleneck effect on…* (1)			
Scientific Evidence/Data – poor, inconsistent, proxy			*It also falls on the human side of course, but just as well as when we talk to microbiologists about our surveillance systems for antimicrobial systems, and if some microbiologists as soon as they*		

	Access to AMs outside the system	Appropriate prescribing, diagnosing, treatment: Prescription necessary for AMs	Burden of illness: Human illness	Resistance : Resistance in wider environment	Science and academia
			realize that the samples may not be taken the same way in each hospital or the cut off, for when you take a blood sample it is not the same. The immediately say, it cannot be used. You cannot compare this data. And every time we have to say, well this is the best data we have. Let's try to make the best out of it. Let's try to conclude as much as we can putting the disclaimers that this may not be fully comparable, but it is the best we have, and then as P1 said a couple of times already, sometimes we need to take action, even though we don't have an absolute guarantee that when we do this, the effect will be that, and then otherwise we die before we have taken any action. Right. (1)		
Scientific Evidence/Data – no data exists or is very poor quality/quantity				*I mean you know we know actually nothing about really what is going on in the natural environment, largely because much of that research is just not been funded. You know, funded, we are starting to get some more funding in the UK for that kind of thing, but you know even now it is very difficult to get funding for antimicrobial research in agriculture, because it is perceived to be a much lower risk than terrestrial livestock species. Right and then it is another step down for the environment, but it is slowly changing.* (1)	
Professional experience/knowledge	*And of course not everyone is buying antibiotics to begin with but people pass them along the*	*P: I think…one question is also for instance in Sweden and I think also Europe nowadays recently,*			

	Access to AMs outside the system	Appropriate prescribing, diagnosing, treatment: Prescription necessary for AMs	Burden of illness: Human illness	Resistance : Resistance in wider environment	Science and academia
	family to friends, and some people get them abroad when travelling because it's easier than in the country that they live in. So it's the whole mobility aspect as well. (1) *Of course, we don't take into account black market operations or internet sales and stuff like that which are tricky* (1)	*you cannot buy and just going into a store, but I know in many other countries you can buy antibiotics yourself.* *R: Yea.* *P: You do not even have to have a prescription. So, I think that is a very, very important.* (2)			
Personal experience/knowledge			*So we are less prone to suffer from such infections I think than… than malnourished in African, I mean if you take, you take that as a great example, and we are also more prone to go to the doctor immediately in these cases, which is a problematic thing, we are really healthier.* (2)		*I am just talking about this. I mean there is another very important actor that I missed and that is science and…and academia, because I mean I don't know. Maybe you know more about that, but from my point of view, I think that we have the expertise and the knowledge, science-based knowledge is very high in Sweden, so that is also something that is very good.* (2)
General Knowledge		*It is an evolving process in Europe you might say. I mean there're, countries like Southern Europe, Greece, Italy, Spain, they have it on paper, but it is not implemented, and Greece I think has taken exception law regulation a number of times, but still you can go down there and buy it, so it is still to come. So it is a matter of implementing.* (1)			

3.8 – Figures

LEGEND:

Relationships (lines):

Direction of relationship:

- + = positive relationship
- - = negative relationship

Strength of relationship (colour):

- green = strong
- blue = weak
- purple = unknown

Amount/quality of evidence (weight):

- thick/solid = scientific evidence
- thin/solid = professional knowledge
- thin/dashed = personal opinion and experience

Nodes (bubbles):

Level/amount (outline colour)

- red = high
- yellow = low
- orange = high/low
- black = none
- pink = varies in Europe
- purple = unknown

Amount/quality of evidence (shading):

- solid colour = scientific evidence
- shaded = professional knowledge
- no shading (white) = personal opinion and experience

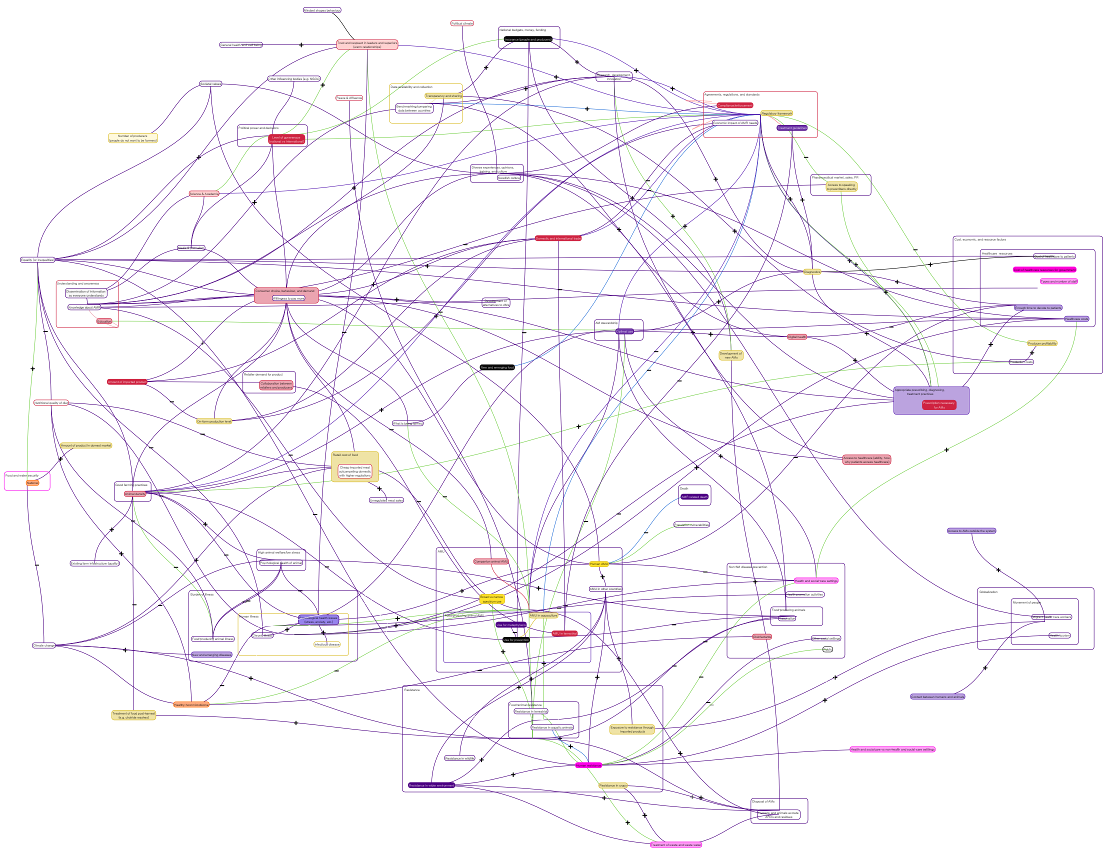

Figure 3.1: Combined concept map from the two workshops in which participants described the drivers of antimicrobial resistance in a Swedish food system context. The map consists of nodes (bubbles) and relationships (arrows) referenced by the participants in which the colour of the nodes represents the level at which the drivers of antimicrobial resistance exist, the amount of shading of the nodes represents the source of the data, the colour of the arrows represents the strength of the correlation of the relationship, the weight of the arrow represents the source of the data, and the direction is represented by +/- when available. Note: this figure is zoomable in the PDF version of this thesis to legible font size.

Chapter 4

A One Health and fuzzy cognitive map-based approach to assess interventions to reduce antimicrobial resistance in a Swedish food system context under potential climate change conditions

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4.1 – Abstract

Introduction: Antimicrobial resistance (AMR) is a growing One Health problem that is impacted by climate change. Interventions to reduce AMR have not been assessed with a systems-wide lens. Fuzzy cognitive mapping is a semi-quantitative modelling technique that could be used to address AMR holistically and assess how interventions impact the entire system. The objectives of this study were to: 1) create a fuzzy cognitive map (FCM) of the Swedish food system based on a previously defined expert-derived causal loop diagram of the system; 2) use a FCM to test the potential ability of interventions to reduce AMR in the Swedish food system; and 3) assess the sustainability of these interventions under potential climate change conditions.

Methods: The FCM was based on a visual model created through a series of previously conducted participatory modelling workshops with experts within the broad system that drives AMR in a Swedish food system context. Data from a scoping review and extracts from the modelling workshop were used to inform activation values and weights of the relationships in the FCM. Scenario analysis was done to assess the sustainability of eight interventions under potential climate change conditions by altering the activation values and weights of the relationships in the FCM and performing an inference process. Network metrics and model features were calculated and described.

Results: The FCM consisted of 90 components and 491 causal relationships. Due to the system's characteristics (e.g., complexity score, density, and hierarchical index), the system was found to be more easily manipulated by outside management strategies with a lower possibility of unintended consequences, but less far reaching impacts. None of the 18 scenarios evaluated, which assessed interventions under predicted climate change conditions, were able to reduce AMR within the system.

Conclusions: Overall, fuzzy cognitive mapping provides an innovative way to analyze complex public health problems including examining the potential impact of interventions using a broader systems lens.

4.2 – Introduction

Antimicrobial resistance (AMR) is a One Health problem (1-6) that is the leading infectious health issue in the European Union (EU) and European Economic Area (EEA), costing 33,000 lives and 1.3 billion Euros each year in the healthcare system alone (7). AMR has and will continue to cause great economic and health burdens in humans, animals, and the environment (4-6). AMR emerges from a complex system characterized by multiple interacting factors across the human-animal-environment interface (4-6, 8-10). Antimicrobial use (AMU) in human medicine and food production has been at the forefront of research and the focus of targeted action to reduce AMR (4-6), however there are a multitude of factors that affect why and how we use antimicrobials, including socioeconomic factors (e.g., poverty, access to nutritious food and clean water), society and social pressures (e.g., quick fix to get back to work), and economic factors (e.g., decreased losses in food production; 4-6, 8-16). Furthermore, resistant microorganisms can easily spread between humans, animals, and their shared environments, which is being exacerbated by globalization due to increased movement of people and animals around the world and increased demand for imported goods (8-16). Past attempts to combat AMR have been unsuccessful as they have failed to account for the entire system and lack integration and communication between the multiple actors involved in the complex system that drives AMR (5, 6, 11).

Furthermore, climate change is predicted to exacerbate the problem of AMR, however the impacts across the One Health system are unclear (17-20). Within Sweden, temperatures are predicted to increase (especially in the northern part of the country) with increased precipitation events and unpredictable weather patterns (21). Increased temperatures and unfavourable weather are predicted to cause heat stress in food-producing animals, which can have negative health and reproductive outcomes, thus reducing food production (22-27). Humans are also predicted to experience increased illness, both with non-communicable (e.g., asthma, cardiovascular disease) and infectious diseases (28, 29). With warming temperatures, new diseases are expected to emerge and thrive in regions that were previously unhabitable, especially vector-borne diseases (20, 28-30). Plants will be able to be grown further north as the climate warms, thus increasing crop production, however these plants will also be subject to more disease due to the warming climate (31). Floods and other unpredictable weather effects may cause habitat loss and devastating impacts in other countries across the world, leading to mass migration and immigration into more protected areas such as Sweden (23, 32-34). Through this loss of food production and increased presence of and vulnerability to illness, all exacerbated by loss of habitat and increased migration, there is expected to be great need for effective antimicrobials in the future. Therefore, it is important to understand how climate change will shape the AMR system as a whole, especially how it may impact AMU and AMR, and to be able to identify sustainable interventions that can help mitigate these impacts in the future.

Simulation modelling (35) is a powerful technique that can be used to explore how a system may be affected by different scenarios (e.g., climate change) and test interventions to determine their ability to modify the model outcomes. AMR has been modelled within many specific areas of the broad system, however, the entire system has yet to be modelled (Chapter 2). Therefore, interventions to reduce AMR have also not been assessed with a systems-wide lens. This can be potentially dangerous. By only assessing the direct impacts of interventions, we can miss potential unforeseen and undesirable (or desirable) effects elsewhere in the system. However, modelling complex issues is difficult due to data limitations and a lack of information on the inner-workings of the system (e.g., associations and relationship between different factors; 36). A previously conducted scoping review of models pertaining to AMR and data to parameterize a One Health model in the Swedish food system context, concluded that modelling this system in a purely quantitative manner would require many assumptions due to the type, quality, and amount of the data that are currently available (Chapter 2).

Fuzzy cognitive mapping is a semi-quantitative modelling technique that could be used to address AMR from a system-wide and One Health lens (37). First introduced by Kosko in 1986 (37), fuzzy cognitive maps (FCMs) have shown great promise in modelling complex dynamic systems in ecology (38-40), engineering (41), economics (42-46), energy efficiency (47-49) waste and wastewater management (50), sociology (51,52), and health and health system (53-56). These models use expert knowledge and perceptions to construct representations of the causal relationships between the main components that describe a system (52). FCMs are made up of concepts (or components or nodes), connected by weighted causal relationships, both of which are defined in linguistic terms (e.g., strong vs weak, high vs low; 37, 52, 57). FCMs are especially useful for decision making when data are incomplete or non-specific, and the interactions between components are not well defined or accurately assessed (58).

This study expands upon a previously conducted participatory modelling workshop held in Sweden with experts from within the European food system (11). The food system was broadly defined as the entire range of actors and interlinked activities across different contexts (economic, societal, and natural environments; 59). During this workshop, experts discussed the major drivers of AMR and the inter-relationships between these drivers, which were visually represented as a causal loop diagram (CLD) consisting of 91 nodes (drivers) and 331 relationships (11). The CLD therefore represents the structure of the broad One Health system of drivers that impact the development and transmission of AMR within the European food system, more specifically the Swedish food system context. Therefore, the objectives of this study were to: 1) create a FCM of the Swedish food system based on the previously defined expert-derived CLD of the system; 2) use a FCM to test the potential ability of interventions to reduce AMR in the Swedish food system; and 3) assess the sustainability of these interventions under potential climate change conditions.

4.3 – Methods

This study is based on a series of previously conducted workshops in which experts from within the broad One Health system in Europe: 1) mapped out the drivers of AMR including the major factors and interrelationships (11), and 2) discussed the success of two interventions to combat AMR (taxation of antimicrobials (AMs) at point of sale, and increased infection prevention and control measures) under potential climate change conditions (60). The structure of this FCM was based on the CLD that was created during a set of participatory workshops with experts from various sectors within the Swedish food system (11). The data collected during the prior research (Chapter 2 and Chapter 3) helped refine the structure of the FCM and generate the initial state (called activation values; AV) and the strength and directions (called weights) of the relationships between the components.

4.3.1 – Fuzzy cognitive maps (FCMs)

FCMs (37) are semi-quantitative dynamic models that combine elements of fuzzy logic, neural networks, and cognitive mapping (37, 52, 57). These models are made up of concepts (or components) and causal relationships between the components, which together form a neural network of components (52, 57). Each component has an AV that is assigned a value from [0,1]. Each relationship has a weight which reflects the degree of causality between the components and is assigned a value between [-1,1], with negative values indicating an inverse relationship (57). FCM uses fuzzy logic (61) to convert quantitative data (e.g., surveillance data) and qualitative data (e.g., linguistic terms) into a common format so that both quantitative and qualitative data can be used to inform the AVs of the concepts and the weights of the relationships. This process therefore allows for the use of a wide range of data and expert knowledge and opinions (52, 57, 58). Once the structure of the FCM is defined, FCMs can be used to simulate how the system will change over time. This is done through what is referred to as an inference process (57). At each discrete time step (iteration), the AV of each concept is re-evaluated using the updating rule and the transformation function, and are informed by the combination of all the relationships connected to each concept (62). The software FCM Expert (57) uses the standard McCulloch-Pitts model to calculate the AV of each concept at each time step (63). The inference process (model simulation) can result in three different behaviours: 1) equilibrium being reached; 2) the FCM reaches a cyclical state; or 3) total chaotic behaviour (62) which are determined graphically. FCM software (e.g., FCM Expert (57), and Mental Modeler (40)) can be used to explore the system dynamics, explore pattern recognition, and perform "what-if" scenarios to assess different policy scenarios and decision processes (52, 57, 64). Scenario analysis is conducted by altering the AV of components to reflect a certain scenario (e.g., an intervention) and performing an inference process (63). To assess the scenario's impact on the components in the system, the AV of the components at equilibrium from the baseline scenario (the inference process before interventions are added) are then compared to the AV of the components at equilibrium from the inference process performed after the intervention is added to the model (63).

4.3.2 – Building the FCM structure

4.3.2.1 – Components

The nodes from a CLD created during a set of participatory modelling workshops with experts from within the broad One Health system (11), along with the findings from a scoping review (Chapter 2) and transcript analysis of the participatory modelling workshops (Chapter 3) were used to create the components for the FCM (Table 4.1). Six nodes from the original CLD had to be divided into sub-components when a single AV could not be determined. These nodes included: consumer demand, retailer demand, movement of animals, new and emerging food, on-farm production level, and market price per production unit. Consumer demand was divided into seven components, consumer demand for: antimicrobials (AMs), animal-based food products, non-animal based food products, new and emerging foods, organic food, animal welfare friendly food, and consumer choice, demand, and behaviour for and with all other products. Retailer demand was divided in a similar manner, this included retailer demand for: organic food, animal welfare friendly food, and all other food products. Movement of animals was divided into two component, domestic and international movement, as they were very different in terms of their AVs. New and emerging food was divided into four components based on the type of food product: genetically modified foods (GMOs), insects, lab-based meat and three-dimensionally (3D) printed food, and plant-based meat alternatives. On-farm production level was divided into three components: production of conventional animal-based food products, conventional non-animal based food products, and organic foods. Market price per production unit was divided into two components representing conventional and organic foods.

4.3.2.2 – Relationships

The relationships from the CLD were added to the FCM. Six relationships from the CLD did not get inputted into the FCM; these relationships were between *retail cost of food* and each of: 1) *AMU in terrestrial food-producing animal agriculture*; 2) *AMU in aquaculture*; and 3) *AMU in plant agriculture*, and between *market price per production unit* and the three previously mentioned components. This was because the directions of the causal relationships were not clearly defined within the workshop and the relationships were too complex or specific to a certain context to accurately reflect in the model. For example, in some instances, increased retail cost of food could reflect that these commodities are of high value, therefore, producers could increase the use of AMs to ensure no loss of such commodity. However, this may not always be the case. Therefore, it was not accurate to generalize, and not appropriate to put these relationships in the model. The other major change in relationships from those captured in the CLD were in reference to prescribing patterns, the reasons for use, and AMU (Figure 4.1). The node "prescribing behaviour" in the original CLD was a broad node that described the amount of prescribing done by prescribers as well as their other prescribing behaviours such as the use of diagnostics and the appropriateness of the prescribing (11). Therefore, to allow for a single value to represent the node, while still capturing an important and influential aspect of prescribing, this node was refined to reflect the appropriateness of prescribing in the FCM. This however changed the nature of the relationships in the model. In the original CLD (11) shown in Figure 4.1A, the participants described the relationships as: an increase in the reason for use (use for growth promotion, preventative purposes, and metaphylactic purposes, and treatment) leads to an increase in prescribing (node in CLD described as prescribing behaviour or the amount of prescribing), which in turn leads to an increase in AMU in humans, terrestrial animals, aquaculture, and plant agriculture. However, the node "prescribing behaviour" was refined to reflect the appropriateness of the prescribing practices, not the amount of prescribing or the total prescriptions written. Therefore, the relationships were altered in the FCM and were represented by the following the causal pathway (Figure 4.1B): the appropriateness of prescribing causes a decrease in the reason for use (with weights being strong for reduction in use for growth promotion, preventative purposes, and metaphylactic purposes and weak for use for treatment, as AMU is still required to treat sick humans and animals), which in turn causes an increase in AMU in humans, terrestrial animals, aquaculture, and plant agriculture. Additional relationships found through prior research (Chapter 2 and Chapter 3) were added to the FCM. Finally, the relationships that were a part of the broad nodes in the original CLD (11) were split between the relevant sub-nodes outlined above. For example, in the original CLD, the node for consumer demand had a positive correlation with animal welfare and with human AMU. However, in the FCM this would be reflected as: 1) a positive correlation between *consumer demand for animal welfare friendly products* and *animal welfare*; and 2) a positive correlation between *consumer demand for AMs* and *human AMU*.

4.3.3 – Parameterizing the FCM

After the structure of the FCM was defined, the AV for each component, and the weights of each relationship were defined. Fuzzy cognitive mapping uses fuzzy logic (61) to help assign the AV an initial value to the components, which take on a value between [0, 1]. In this model, the AV was divided into eight categories that represented the level of the component (none, very low, low, medium-low, medium, medium-high, high, very high), each of which had an associated value (Table 4.2, Figure 4.2). Eight categories were used instead of three (high, medium, low) for more granularity. The strengths of the relationships were weighted in a similar manner, in which the weights were divided into 15 categories (no relationship, very weak, weak, medium-weak, medium, medium-strong, strong, very strong) which had an associated value between [-1,1], with negative values representing an inverse correlation and positive values representing a direct correlation (Table 4.2).

4.3.3.1 – Activation values (AV)

The level for the AV of each component was assigned based on data found in the literature (Chapter 2) and within the workshop transcripts (Chapter 3). The assigned levels from the two chapters were combined and compared. When disagreement occurred, a level was assigned based on the available data and personal judgement (MC); all decisions were documented in a decision matrix (65). There was a total of 114 nodes from the original CLD, new nodes from the scoping review (Chapter 2) and transcript analysis (Chapter 3), and the six nodes which were divided into sub-nodes. Of these, 24 nodes were removed due to: lack of data; too specific or detailed; unable to be measured; or nodes that were not included in any relationships. The resulting 90 components with the assigned level and associated AV can be found in Table 4.1. A full detailed description of the data used (quantitative data and/or quotations from the literature and transcripts) to assign the final AV for each component can be found in the decision matrix (65).

4.3.3.2 – Weights of relationships

The data to generate the weights of the relationships were also collected through a literature search (Chapter 2) and transcript analysis (Chapter 3). However, finding data for the relationships was not the primary goal of the literature search (Chapter 2), and analysis of the transcripts found that the weights were not commonly reported by the experts (Chapter 3). Of the 491 relationships, 129 relationships had sufficient data to assign a direction and strength to the correlation of relationship, and an additional 122 relationships had sufficient data to suggest a direction of the correlation only. Therefore, weights (informed by the strength and direction of the correlation) were assigned to 362 relationships based on data, assumption and personal judgement. Most of the weight assumptions (n= 280) were based on previous knowledge and personal judgment (e.g., relative contact between companion animals and food-animals versus relative contact between companion animals and humans to assign the weights of AMR transfer). The data and assumptions are outlined in the decision matrix (65). The remaining relationships for which a strength was not available (n= 82) were assigned the weight of "medium" as a base assumption.

4.3.3.3 – Expert validation

To validate the AV and weights, intercoder reliability (66) was assessed between three independent researchers (EJP, SEM, CAC) on a sub-set (10%) of the components (n= 11) and relationships (n= 43). There was 92% consistency between coders and all discrepancies were discussed until consensus was reached. All decisions and changes to the components and relationships from the original CLD were documented (decision matrix; 65).

4.3.3.4 – Sensitivity analysis

Formal sensitivity analyses are not common-place in fuzzy cognitive mapping as the maps are usually expert-driven and created through discussion (67). However, since this FCM was generated from a previously conducted workshop and a scoping review in which defining the strength of these relationships was not the primary goal, there were numerous causal relationships with weights assigned based on assumptions and personal judgement. Therefore, an adjusted sensitivity analysis was performed to determine the influence of a subset of the relationships on the system. The outward relationships of the five components with the highest centrality (components with the most incoming and outgoing relationships; 37) for which assumptions had to be made were chosen for the sensitivity analysis because these components have the most influence within the system. The weights of the relationships that were assigned a baseline weight of "medium" due to lack of available information were adjusted to the lowest possible weight (0) and the highest possible weight (-1, or 1) as outlined in Appendix D, Table D1. The AV for the components that we were interested in (which will further be referred to as indicator components) were compared to the baseline to determine the sensitivity of these components to the changes in the weights of the relationships (Figure 4.3). The indicator components were: *AMU in humans, AMU in terrestrial food-producing animal agriculture, AMU in aquaculture, AMU in plant agriculture, antimicrobial resistant organisms (AROs) in humans, AROs in food-producing animals, AROs in plant agriculture, ARO in imported food, resistance in the environment, illness in humans, illness in food-producing animals, disease in plants, healthcare costs, retail cost of food, amount of imported products, domestic and international trade,* and *food security*.

4.3.4 – Implementing the model into software

All components and relationships were inputted into the software FCM Expert (57). The AVs and weights of the relationships were then added to the model. A weight matrix was exported (as a .csv file) and imported into the software Mental Modeler (40). An inference process was performed in FCM Expert to determine the pattern of behaviour; if the model would reach equilibrium, cyclical behaviour, or total chaos (67). Structural measurements of the model were calculated using Mental Modeler which are related to the network structure of the FCM including: the number of components and interconnections; the complexity score (40, 49, 68); and the density (9, 40, 69) of the system (Table 4.4), as well as the indegree (the number of incoming relationships); outdegree (the number of outgoing relationships); and centrality (the absolute value of either: (a) overall influence in the model (all + and – relationships indicated, for entire model); or (b) influence of individual concepts as indicated by positive (+) or negative (-) values placed on connections between components) of each component (Appendix D, Table D5). The hierarchical index (40, 68) was calculated manually using the outdegrees of all of the components (provided by Mental Modeler). This value shows how easily the system can be manipulated by outside influences (70). A purely hierarchical system (HI=1) relies heavily on internal pressures and therefore is not easy change with intervention or policy-change, whereas a democratic system (HI=0) is open to outside influences (70).

4.3.5 – Scenarios

A total of 18 scenarios (outlined in detail in Appendix E) were run to explore what could happen across the AMR system when certain interventions were implemented. Scenarios were performed in FCM Expert. Scenarios were initially implemented by altering the AV of the components to reflect how the intervention would impact the system. After the AVs were changed, an inference process was run until a new equilibrium was reached. The AVs for each component at steady state (equilibrium) were compared to the baseline scenario (inference process conducted with the initial AV of all components). Percentage change of the AV from the baseline for each of the indicator components at equilibrium was calculated for comparison purposes.

The following components were analyzed to assess the effect of each scenario on the system (indicator components): *AMU in humans, AMU in terrestrial food-producing animals, AMU in aquaculture, AMU in plant agriculture, AROs in humans, AROs in food-producing animals, AROs in plant agriculture*, and *resistance in the environment, illness in humans, illness in food-producing animals, disease in plants, healthcare costs, retail cost of food, amount of imported products, domestic and international trade,* and *food security*. These components were chosen because they cover the range of sectors (human, animal, and environment), they include important human and animal health indicators (e.g., illness in humans, illness in food-producing animals), important indicators for assessing AMR (e.g., AMU and AROs), and were of interest to the research team (e.g., impacts on healthcare costs, cost of food, food security, and trade).

4.3.5.1 – *A priori* scenarios

A total of nine scenarios were initially explored, which represented three interventions under current conditions and a climate change scenario (Table 4.3). The first two interventions arose from the set of participatory workshops with experts from within the Swedish food system (11,60). The first intervention, “Increased biosecurity and infection prevention and control (IPC) measures”, was one of the interventions that was discussed as an example of a successful intervention during a scenario planning workshop (60) and was therefore of interest to determine if it could be successful at reducing AMR in the FCM. This intervention aimed to increase (provide better) infection prevention and control, both on-farm (e.g., biosecurity) and in health and social-care settings. The second intervention, "Educational campaigns", was identified by a group of experts from within the broad One Health system as a potential high-leverage intervention during a participatory modelling workshops (11). This intervention aimed to increase knowledge about AMs and proper AMU through educational campaigns targeted to the public and prescribers. The third intervention "Antimicrobial stewardship" was a combination of the first two scenarios, increasing both IPC and educational campaigns. The fourth intervention, "Increased trade regulations" was based on France's 2022 decision to ban the importation of all animal-based food products from animals that have received growth promoters (71) and reflected increased trade regulations for AMU on farm. Climate change was also implemented into the model to determine how it may impact AMR and the other indicator components and to assess the sustainability of the interventions. The rationale and details for these four *a priori* interventions and climate change are outlined in Appendix E, how they were implemented into the model can be found in Appendix D, Table D2.

4.3.5.2 – *A posteriori* scenarios

During analysis of the initial nine scenarios, which were conducted by altering the activation values of components and performing an inference process, it was noticed that they were unable to significantly change the system. A significant impact was determined by a difference of greater than 1.0% in the AV of a component at equilibrium from the baseline compared to the scenario being tested. Therefore, we decided to test whether it was possible to alter the system by only altering activation values. We ran two test scenarios that altered the activation values of: 1) ten components with the highest centrality, and 2) the ten components with the highest outdegree, not including components for illness or resistance as these were outcomes of interest. These components were put to the highest or lowest value that would positively influence the system, for example animal welfare was increased to an AV of 1 because high animal welfare is associated with a reduction in AMU (Appendix D, Table D3). These scenarios were also unable to significantly shift the system. However, we noticed that through the sensitivity analysis, altering the weights of the relationships was able to change the activation values of the components at steady state. This was in line with the experts' views from the scenario planning workshop (60), in which experts shared that they did not believe that the interventions proposed (IPC and taxation) were enough to successfully tackle AMR, and that addressing underlying causes (e.g., poverty and inequality) and addressing the Sustainable Development Goals (SDG; 72) needed to be of top priority. Therefore, by using the experts' suggestions and the SDG as a framework, we created four new interventions that alter the relationships between components and tested these interventions under current and climate change conditions (Table 4.3). After analyzing the *a posteriori* scenarios it was evident that the interventions had impacts on many of the indicator variables, but they were not overly impactful at reducing AMR in any of the sectors (human, animal, plants, or the environment). Therefore, we decided to test all of the *a posteriori* interventions simultaneously to see if they could reduce AMR (the "Hail Mary" scenario). The details for the rationale and details these four *a posteriori* interventions are outlined in Appendix E and how they were implemented into the model can be found in Appendix D, Table D4.

4.4 – Results

The final FCM (Figure 4.4) consisted of 90 components with 491 connections between them. The density of the FCM was 0.06, with an average of 5.44 connections per component. The FCM had a complexity score of 0 and a hierarchical index of 0.01. All of the model features are listed in Table 4.4. The 90 components were made up of three driver components (*new and emerging food: 3D-printed food and lab-based meat, consumer demand for health tourism,* and *treatment of food productions post-harvest*) and 87 ordinary components. The features of each component can be found in Appendix D, Table D5. The components with the highest indegree (ID) were: *AROs in humans* (ID=10.85), *illness in food-producing animals* (ID=9), and *illness in humans* (ID=8.38). The components with the highest outdegree (OD) were: *type of production systems* (OD=9.52), *understanding and awareness* (OD=7.51), and *development of alternatives to AMs* (OD=6.5). The components with the highest centrality were*:* *AROs in humans* (15.73), *illness in food-producing animals* (C=13.25), and *illness in humans* (C=12.76). The model reached equilibrium (as opposed to cyclical or chaotic behaviour) and therefore could be used for scenario analysis (Figure 4.5).

4.4.1 – Scenarios

The AVs for each component during the inference processes that were conducted for each of the 18 scenarios are published on Borealis (65). Visual representations of the AVs for the 17 indicator components during the inference processes that were conducted for each of the scenarios can be found in Appendix F which include the eight interventions (Figures F1-17), the results of the high centrality and high outdegree test scenario (Figure F18), the "Hail Mary" scenario (Figure F19), and the results of the sensitivity analysis (Figure F20).

4.4.1.1 – Base scenario

The AVs for all of the components in the model over the nine iterations are shown in Figure 4.5. The AVs for the components of interest (indicator components) can be found in Table 4.6 and in Appendix F, Figures F1-F20 as the baseline. In general, the AVs for AMU were higher at equilibrium except for *AMU in plant agriculture* which decreased (reduced from and AV of 0.25 to 0.21, Table 4.5). *AMU in humans* increased the most, reaching steady state at medium-high (AV=0.58, Table 4.5). Resistance increased significantly with all components reaching steady state in the highest level, with *Resistance in the environment* and *AROs in humans* at the highest value (AV=0.99, Table 4.5). *Illness in humans* and *illness in food-producing agriculture* both reached equilibrium in the very low level, with food-producing animals being almost disease-free (AV=0.05, Table 4.5). *Healthcare costs* and *retail cost of food* both reached equilibrium at the very-high level, which was one level higher for *retail cost of food* (increased from high to very high), and three levels higher for *healthcare costs* (increased from medium to very high). *Domestic and international trade* remained in the high level, but *food security* reached equilibrium at the very-high level. Finally, *amount of imported product* had a steady state value that was one level lower than it started at, reaching equilibrium in the medium-high level. Therefore, if the system was to continue in its current state, although disease (and thus AMU) will remain very low, there may still be a large increase in AMR to a very high level which may have trade implications (increase in trade regulations) and economic impacts (increased healthcare costs and cost of food).

4.4.1.2 – *A priori* interventions, climate change conditions, high centrality, and high outdegree scenarios

Overall, the interventions that were created *a priori* and the climate change conditions had very little impact on the system, with a difference of less than 1.0% in the 17 indicator components. Similarly, the high centrality and high outdegree scenarios also had very little impact on the system. The results of the inference processes for these scenarios (Scenario 1-9) can be found in Appendix F, Figures F1-9.

4.4.1.3 – *A posteriori* interventions

4.4.1.3.1 – Scenario 10: Reducing cost as a barrier under current conditions

The results of the inference processes for the three intensities of Scenario 10 can be seen in Appendix F, Figure F10. Under current conditions, reducing the barrier by a small amount (Scenario 10.1) significantly reduced *illness in humans, illness in food-producing animals, and retail cost of food.* When the cost barrier was reduced further (Scenario 10.3), there was a significant change in six of the indicator components, causing a reduction in *retail cost of food, illness in food producing animals, illness in humans, AMU in terrestrial animals, AMU in aquaculture,* and an increase in *food security* (Figure 4.6). The largest impact was seen in *retail cost of food*, with a reduction from the very high level to the high level (16.5% reduction). There was also a moderate reduction in *illness in food producing animals* (5.7% reduction) and *illness in humans* (3.9% reduction), however, this did not cause a change to the level at equilibrium, which remained in the very low level for both components. A very small reduction was seen in *AMU in terrestrial animals* (1.7% reduction) and *AMU in aquaculture* (1.3% reduction), remaining in the medium-low level. Finally, *food security* slightly increased (1.7% increase) and remained in the very high level.

4.4.1.3.2 – Scenario 11: Increased international trade regulations under current conditions

The results of the inference processes for Scenario 11 can be seen in Appendix F, Figure F11. Under current conditions, a small increase in trade regulations (Scenario 11.1) slightly but significantly reduced *AMU in terrestrial food-producing animals, AMU in aquaculture, AMU in plant agriculture,* and *exposure to AROs from imported food,* and caused a slight increase in *illness in food-producing animals*. When trade regulations and enforcement of the trade regulations was strengthened further (Scenario 11.3), there were significant changes in ten of the indicator components, causing a reduction in *AMU in terrestrial food producing animals, AMU in plant agriculture, AMU in aquaculture, exposure to AROs from imported food, illness in humans, domestic and international trade regulations, and AROs in food producing animals*, and increases in *illness in food-producing animals*, *retail cost of food,* and *disease in plant agriculture* (Figure 4.6). The largest impacts were seen in AMU in agriculture, specifically in *AMU in terrestrial food-producing animals* (25.0% reduction), *AMU in plants* (23.3% reduction), and *AMU in aquaculture* (21.8% reduction). This caused *AMU in terrestrial food-producing animals* to fall from the medium-low level to the low level. *AROs from imported food* was also significantly improved (9.7% reduction) but remained in the high level. A moderate increase to *illness in food producing animals* was noticed (5.7% increase), however, it remained in the very low level. Minimal reductions occurred in *illness in humans* (1.4% reduction), and *AROs in food producing animals* (1.3% reduction). However, *domestic and international trade regulations* also experienced a slight reduction (1.4% reduction), and slight increases occurred to *retail cost of food* (1.8% increase), and *disease in plant agriculture* (1.1% reduction). The final levels of these components remained unchanged.

4.4.1.3.3 – Scenario 12: Technological advancements and innovation under current conditions

The results of the inference processes for Scenario 12 can be seen in Appendix F, Figure F12. Under current conditions, a small increase in technological advancements (Scenario 12.1) caused a significant reduction in AMU in all sectors (*AMU in humans, AMU in terrestrial food-producing animals, AMY in aquaculture, and AMU in plant agriculture),* however, caused slight increases in *illness in humans* and *illness in food-producing animals*. With even more effective technological advancements (Scenario 12.3), significant changes occurred in ten of the indicator components, including reductions in

AMU (*AMU in humans, AMU in terrestrial food-producing animals, AMU in aquaculture, and AMU in plant agriculture*), *AROs in food-producing animals,* and *domestic and international trade regulations*, and increases in *illness in humans, illness in food-producing animals, disease in plants,* and *retail cost of food* (Figure 4.6). The largest impacts were seen in AMU in all sectors, with large reductions in *AMU in plant agriculture* (29.5% reduction), *AMU in aquaculture* (27.8% reduction), *AMU in aquaculture* (21.6% reduction), and *AMU in humans* (20.8% reduction). These reductions caused *AMU in aquaculture* and *AMU in terrestrial food-producing animals* to move from a level of medium-low to low, and *AMU in humans* to move from medium-high to medium. *AMU in plant agriculture* remained in the low level. There were moderate increases to *illness in humans* (6.1% increase), moving from the very low to the low level, and *illness in food producing animals* (4.7% increase), remaining in the very low level. A minimal reduction in *AROs in food producing animals* (1.4% reduction) was also exhibited, however it remained in the high level. There were slight increases to *retail cost of food* (1.9% increase) and *disease in plant agriculture* (1.4%) but they were not enough to shift these components to a higher level. However, although *domestic and international trade* only experienced a small decrease (1.5% reduction), this increase was enough to force it to cross the threshold from the very high to the high level.

4.4.1.3.4 – Scenario 13: Addressing social inequalities and poverty under current conditions

The results of the inference processes for Scenario 13 can be seen in Appendix F, Figure F13. Under current conditions, slightly improving social inequalities and poverty (Scenario 13.1) only improved the system through the reduction of *AMU in humans, illness in humans,* and *illness in food-producing animals* by a minimal amount. However, through further improvements to addressing social inequalities and poverty (Scenario 11.3), greater reductions occurred in not only *AMU in humans, illness in humans,* and *illness in food-producing animals*, but reductions were also found in *AMU in terrestrial food-producing animals,* and *healthcare costs* (Figure 4.6). Improving vulnerable populations access to healthcare, social supports, and nutritious food caused a significant reduction to *illness in humans* (33.5% reduction). Additional moderate reductions were found in *AMU in humans* (3.4% reduction) and *illness in food producing animals* (3.7% reduction). There were also minimal reductions to *AMU in terrestrial food-producing animals* (1.5% reduction) and *healthcare costs* (1.4% reduction). However, none of these components exhibited a change to the predicted the level.

4.4.1.3.5 – Scenarios 14-17: a posteriori interventions under climate change

The results of the inference processes for Scenario 14-17 can be seen in Appendix F, Figure F14-17 and the impact of the four interventions at the highest intensity under climate change conditions

(Scenario 14.3, 15.3, 16.3, and 17.3) on the 17 indicator components can be seen in Figure 4.7. Overall, climate change conditions did not significantly change how the interventions impacted the system, except for technological advancements and innovation (Scenario 16). Addressing population vulnerabilities (Scenario 17) performed the same under climate change as it did under current conditions. Under climate change, reducing costs as a barrier (Scenario 14) had a slightly higher impact on reducing *AMU in terrestrial animals* (1.3% reduction under climate change compared to a 1.2% reduction under current conditions), and *illness in humans* (3.9% reduction under climate change compared to a 3.8% reduction under current conditions) compared to the same intervention under current conditions. Increasing trade regulations (Scenario 15) had a slightly larger impact on *retail cost of food*, with an increase of 0.1% more than the same intervention under current conditions. Technological advancements and innovations aimed at reducing AMU (Scenario 16), however, did have some significant difference in performance under climate change compared to the same intervention under current conditions. At the highest intensity of the intervention (Scenario 16.3), technological advancements and innovation was able to decrease *AMU in terrestrial animals* by 10% more under climate change than under current conditions (Scenario 12.3). It also led to a significant increase in *illness in food-producing animals* compared to under current conditions (5.9% increase compared to a 4.7% increase). Minor differences also occurred in *AROs in food-producing animals* (1.7% reduction under climate change compared to 1.4% reduction under current conditions), and in *retail cost of food* (2.2% increase under climate change compared to a 1.9% increased under current conditions). However, the negative outcomes associated with enhanced technology such as the increase in *illness in humans* (5.7% increase under climate change compared to 6.0% increase under current conditions), and *disease in plant agriculture* (1.3% increase under climate change compared to 1.4% increase under current conditions) were slightly reduced under climate change.

4.4.1.3.6 – Scenario 18: The "Hail Mary" Scenario

The "Hail Mary" Scenario tested all the *a posteriori* interventions (Scenarios 10-13) together, under current conditions. The results of the inference processes this scenario can be seen in Appendix F, Figure F19. These interventions in combination were able to significantly reduce AMU in all sectors, with the largest reduction seen in *AMU in food-producing animals* (50.1% reduction, Figure 4.8), moving from the medium-low to the low level. They were also able to significantly reduce *illness in humans* (32.6% reduction, Figure 4.8). However, these interventions were unable to significantly impact most resistant outcomes, aside from *AROs from imported foods* (9.2% reduction, Figure 4.8) and *AROs in food-producing animals* (3.3% reduction, Figure 4.8). The reduction in *AROs in food-producing animals* was able to shift the level from highest to the very high, but the reduction did not have an impact on the level of *AROs from imported foods*, remaining in the high level.

4.4.2 – Sensitivity analysis

The sensitivity analysis showed that altering the 10 relationships (Appendix D, Table D1) had varying results on the system, with some components being relatively unaffected (*amount of imported food, AROs in imported food, resistance in the environment, food security,* and *healthcare costs)* and some being significantly affected (*AMU in terrestrial food-producing animals, AMU in aquaculture, AMU in plant agricultural,* and *retail cost of food*). The results of the inference process for the sensitivity analysis can be found in Appendix F, Figure F20. When the 10 relationships were removed (set to a weight of 0), there was a significant increase in *AMU in terrestrial food-producing animals* (12.0% increase, Figure 4.3), *AMU in plant agriculture* (10.9% increase, Figure 4.3), *AMU in aquaculture* (9.6% increase), and *retail cost of food* (11.1% increase, Figure 4.3). There were also smaller but significant impacts on *illness in humans* (4.9% increase, Figure 4.3) and *illness in food-producing animals* (1.6% reduction, Figure 4.3). However, when the 10 relationships were increased to full strength (set to a weight of 1 or -1), there were significant reductions in three of the indicator components, *AMU in terrestrial food-producing animals* (9.3% reduction, Figure 4.3), *AMU in plant agriculture* (8.5% reduction, Figure 4.2), and *AMU in aquaculture* (7.8% reduction, Figure 4.3), but *retail cost of food* increased more than when the relationships were removed (13.1% increase, Figure 4.3). *Illness in humans* also experienced a reduction (3.3% reduction, Figure 4.3), and *illness in food-producing animals* increased (1.6% increase, Figure 4.3) when the relationships were at the strongest weight.

4.5 – Discussion

This study presents an innovative way to analyze the system of drivers for AMR, using a systems approach to analyze the effects of interventions to address AMR, including under a climate change scenario. The FCM presented in this study was created based on an expert-derived CLD which consisted of 17 experts from within the broad food system in Sweden (11). This FCM was extensive, with input from multiple experts and the literature, however, it was still confined to the factors and relationships identified within the workshop and to the availability of the data. The overall food system, therefore, could exist beyond the scope of this FCM, but the system must be bounded at some point. Using fuzzy cognitive mapping to analyze AMR within the Swedish food system highlighted many features of the system (e.g., centrality, complexity, density, and hierarchical index) and provided a tool that may be useful for decision-making and policy implications, as well as potential future scenarios under climate change conditions.

It was promising to find that the FCM was able to reach an equilibrium point, which was mandatory to be able to use our FCM for scenario analysis (57, 62, 73). The ability to reach equilibrium showed that the system was stable, and does not result in cyclical or chaotic behaviour, leading to the ability to make more confident decisions (57, 62, 73). The FCM consisted of many components and relationships, however many of the components were ordinary, with a small number of drivers and no receivers (Table 4.4). The complexity score is calculated based on the ratio of receiver components to driver components (40,49,68), and since there were no receiver components, the overall complexity score was zero. An FCM with many receiver variables (and thus a higher complexity score) is more likely to have multiple outcomes, that could lead to increased unintended consequences (73). Complex systems therefore have more outcomes, with less controlling forces, and thus are harder to manipulate in predictable ways (39). Our FCM also had a very low density score and hierarchical index. The density of the system is a measure of the number of connections compared to all of the possible connections (39). Systems that are less dense therefore are less entangled, with fewer causal relationships between variables. Higher density, and more interconnections, can imply more options for intervention, as a change in one variable may impact many other variables (39, 69). Therefore, with a low density score, the system may not have as many options for impactful intervention. However, this FCM could be missing many existing connections that were not outlined by the experts during the creation of the CLD. The FCM also had an extremely low hierarchical index. This indicated that the system is almost completely democratic, as opposed to hierarchical (73). Democratic systems are considered to be more adaptable to local changes, and therefore stakeholders are more likely to believe that the system can be changed by outside influences (70). Therefore, due to the low complexity, density, and hierarchical index, this implies that the system that drives AMR emergence and transmission within Sweden can be manipulated through intervention and policy changes and the outcomes may be more predictable, but less far reaching throughout the system. This could be one of the many reasons Sweden has been able to have so much success in implementing policy for antimicrobial stewardship and subsequent prevention of AMR (74-76).

This FCM also provided information about each component in terms of their ability to influence and be influenced by the system. This information may help identify high leverage factors that when altered, could have great impact on changing the system (77). The components with the highest centrality are factors that are most interconnected within the system. Thus, these factors are essentially the most important factors within the system and may be of particular interest when choosing where in the system to take action. The out-degree of each component is also of interest as these factors have many out-going connections, therefore have a high level of outward influence on the system. Many of the components found to have the highest centrality were expected as they are typically the target of current intervention strategies, such as: illness in food-producing animals, illness in humans, appropriate prescribing, and understanding and awareness. Many interventions are aimed at reducing illness on farm and in humans, through reducing the spread of disease via increased biosecurity (78-80) and hand washing (78,79), and through increasing immunity via vaccination (78-80). Similarly, many interventions aimed to increase appropriate prescribing by either education or through auditing prescribing practices and providing feedback have been assessed (81-82), as has interventions that aim to increase understanding and awareness in consumers to reduce the demand for AMs (83-85). However, animal welfare was the component with the fourth highest centrality, but is not typically the target of intervention. A group of experts from within the system (11), and the ReAct Group, an international network to provide education on AMR (86), have identified farming systems that enable high levels of animal welfare has been as a key factor in reducing the need for AMs. Therefore, this may be an important factor that is missing in current interventions. Similarly, production systems, such as organic and antimicrobial free farming, and good farm practices were two components with a lot of outward influence (high outdegree). These alternative production systems inherently have practices that promote high animal welfare (87-89), and therefore may also have a large influence on the system.

4.5.1 – Scenarios

4.5.1.1 – Baseline model

When the FCM was simulated with the initial AVs, all of the AMR indicators at final equilibrium were much higher than the initial values, especially in humans and the environment. *AMU in humans, AMU in aquaculture,* and *AMU in terrestrial food-producing animals* also increased to above the starting values. However, it is well documented that the levels of AMR in humans, animals, and the environment are quite low in Sweden, especially compared to other countries in the world (90-93), and have not been increasing rapidly, and in some cases have been decreasing in recent years (90, 92, 93). Therefore, it was of concern that the model predicted a rapid and large increase in AMR within all sectors of the system. This could indicate that some of the balancing factors may be missing from the system, or that the relationships that increase these factors may be too strong, or those that decrease them too weak. One hypothesis for this phenomena is to do with the aims of the participatory model that was used as the structure of the FCM (11). One of the main objectives of the workshop was to identify the drivers of AMR and how these drivers interact (11). Therefore, many of the factors identified would aim to drive (increase) AMR, but there may not have been as many factors identified that were aimed at reducing AMR. Also, the overarching factors (factors that influence the entire system) identified by the experts (11) were not included in the CLD and thus do not appear within this FCM. Therefore, large influences such as political power and social inequities have connections to every part of the system but their influences are not captured in this model. Overall, the over-estimated AMR levels and potential missing relationships and feedback loops would greatly impact the system behaviour and therefore limits the ability to accurately interpret the results of the interventions as it may not adequately reflect how these interventions may impact the true system. Further engagement with the experts and further exploration of the system structure is required to refine and simplify the system.

4.5.1.2 – *A priori* interventions, climate change, high centrality, and high outdegree scenarios

As mentioned above, the system had an extremely low density which indicated that interventions may not be as far-reaching within the system due to a lack of connectivity. This was exhibited through our *a priori* interventions, in which a change in the AV of a few components in the system were unable to cause system-wide changes. However, other FCMs that have been created to asses interventions through altering AVs have been able to enact change on the system, even in systems with low density (40, 54). However, these systems did not contain as many components, containing 8-42 components compared to 90 components in this FCM (40, 54). The large number of components, and relatively small number of connections may reduce the ability for these interventions to reach the outer edges of the system as there are fewer paths to get there. This was also reflected in the scenario planning workshops (60) in which experts stated that taxation of AMs and increased IPC were not enough to alter the system, and that multi-pronged interventions that tackle the underlying causes of AMR (e.g., poverty, social inequalities, basic hygiene and access to food and clean water) and a shift in world-views of the population (e.g., reducing capitalism, increased views on public health and the "greater good") were essential in reducing AMR (60). Therefore, altering one or two components in the system will not have an impact and thus we need to change the relationships and how the system operates.

The way in which climate change was modelled in the FCM, by only altering AVs, caused no significant changes in the system. However, AMR is predicted to increase under climate change conditions (17-19,28,30). Therefore, this may indicate issues in the FCM (e.g., missing relationships or inaccurate weights of relationships) or perhaps that it was modelled too simplistically (e.g., climate change may impact relationships as well as AVs).

Finally, high centrality and high outdegree components should have the most influence on the system when altered (37). However, with the number of components and the low density, altering the ten components with the highest centrality and high outdegree was still not enough to cause change in this system.

4.5.1.3 – Sensitivity analysis

The sensitivity analysis revealed two interesting things about the system. Firstly, by removing the 10 selected relationships completely, there was not as significant changes in the outcomes of AMU and AMR in the system as expected. Similarly, by setting the weights of these 10 relationships to the highest possible value, the relative change in the system only shifted slightly, especially in resistance outcomes. Therefore, these relationships may not have a huge influence on the system, especially in regards to AMR. Secondly, it was noted that the activation values of the components all reached equilibrium at the same value as the baseline scenario during the scenario analysis, when only the initial activation values were changed. However, during the sensitivity analysis, the final activation values were different than the baseline when the relationship weights were altered. Therefore, in order to change the final activation values of the components at equilibrium, thus providing sustainable change over time, the weights of the relationships must be altered, not just the values of the components. Overall, it was important to note that the weights of the relationships are important to the system, and therefore future work should be done to better define the weights of the relationships that did not have data available (such as how increased animal welfare impacts AMU for metaphylactic or preventative purposes, how appropriate prescribing relates to reducing AMR and how people may access AMs outside the system, or how AMR in humans impacts the development of new alternatives or the development of waste and waste water treatment facilities), either through further engagement of stakeholders or through a formal scoping review of the associations of these relationships.

4.5.1.4 – *A posteriori* interventions

Reducing cost as a barrier to sustainable food production systems and food had most impact on illness in food-producing animals. This was most likely due to the impacts of increased animal welfare both directly (through animal-welfare friendly practices) and indirectly (through organic production systems which inherently have more animal-welfare friendly practices). In this FCM, animal welfare is directly correlated with a reduction in animal illness, which was due to the relationship between poor animal welfare conditions and stressed animals and a reduction in immunity in these animals (11, 94, 95). Therefore, through reducing the cost barrier, more of the population may be able to afford to purchase animal-welfare friendly and organic food products, thus shifting the demand for these alternative production systems, and in turn improving animal welfare and disease burden in agriculture. This intervention had two positive unintended consequences: a reduction in human illness and an increase food security. Human illness and food security were most likely impacted by the increased access to nutritious foods due to the reduction in cost. This intervention was also the only intervention that was able to increase food security.

Enhanced diagnostic technology and development of better alternatives to AMs was the most effective at reducing AMU in humans, animals, and plants under current and climate change conditions. These interventions specifically targeted AMU, either through better prescribing from enhanced diagnostics or through better alternatives. Improving access to diagnostics has shown great promise on improving prescribing behaviour (96-98), therefore if diagnostics were to become more widely available and more specific (better at determining organisms), this could have great influence on improving prescribing and reducing AMU. The development and accessibility of alternatives to AMs (e.g., vaccines, phage therapy) compounded this effect by also targeting the reduction of AMU. Vaccines have been the most researched alternative to AMs, and have been shown to be associated with a reduction in AMU in animals (99) and in humans (100).

Increased trade regulations and enforcement of trade regulations was also effective at reducing AMU in agriculture. This intervention was also the only intervention to significantly reduce the importation of AROs through food, as restrictions to food with trace amounts of AROs or AM residues was also included. This was under the assumption that Sweden would conform to the trade restrictions by reducing the amount of AMs being used on farm in order to remain trading partners with France and other countries in the EU. A scenario analysis in the United States of America (USA) was performed in 2011 after some of their largest trading partners (e.g., South Korea and Russia) tightened restrictions on the use of certain AMs in feed for growth promotion and other AM practices (e.g., antimicrobial rinses), with other countries reviewing policy with intent to join (101). This scenario analysis assessed the economic impacts of the USA conforming, or not conforming to the restrictions and the implications for trade (101). This analysis estimated great economic losses due to reduced exports. However, if the USA were to conform, the current advantages they hold in terms of the low cost of their products could be reduced (due to increased costs of production), and thus reduce their competitive advantage in the trade market (101). Therefore, the intervention presented in this FCM may not account for the complex trade system. However, Sweden is less likely to be as largely impacted by these trade regulations compared to the USA due to their current AMU policies (74,102), the production systems they have in place (11,74), and the amount they rely on trade (103) and therefore the assumption that Sweden would conform to these regulations is valid.

Technological advancements and increased trade regulations, however, also caused an increase in the retail cost of food. This was most likely due to the reduction in AMU on farm, which would increase production costs due to an increased need for better farm practices and animal welfare (11). However, when Sweden and Denmark banned AMU for growth promotion, there were limited economic consequences to farmers (102), and thus this may not be as large of an issue within this context. If the cost of food were to increase, however, this could cause other negative impacts throughout the system such as a decrease in access to nutritious foods, especially to those in vulnerable populations, which could then impact health outcomes in these populations (11). Other negative unintended consequences due to the large reduction of AMU was an increase in illness in animals (from increasing trade regulations and technological advancements) and in humans (from enhanced technological advancements). AMs are still necessary for life-saving treatment, and therefore still need to be accessible when required.

Reducing the negative impacts to vulnerable populations was the most effective at reducing human illness, but did not have many other strong system-wide impacts. Although vulnerable populations are at higher risk of negative health outcomes and AMR (104, 105), and addressing poverty and social inequalities was identified as integral to combatting AMR by experts from within the system (60), this intervention was successful at reducing illness and AMU in humans, but it was the least impactful on broader factors within the system. This could indicate, either: 1) the factors associated with population vulnerabilities and social inequalities were not fully developed, and therefore there are missing relationships in the FCM that could be important to the system behaviour; 2) the level of population vulnerabilities, human illness, and human AMU are already low in Sweden, these components may not be the source of major issues within the system, and therefore reducing these further would not provide large changes to the other factors of the system; or 3) human centered interventions may not be enough to shift the system and multi-faceted approaches are required. However, this intervention did have one positive unintended consequence, which was a moderate reduction in illness in food-producing animals. This is most likely due to the relationships between farmers and their ability to care for their animals; healthy farmers (both physically and mentally) provide better care to their animals, thus improving animal welfare and reducing animal illness (11).

It was not surprising that climate change did not have great impacts on the interventions outcomes, as the way climate change was modelled did not have any impact on the system. However, there was one exception. The intervention that represented technological advancements and innovation was more effective at reducing AMU in terrestrial food-producing animals under climate change conditions than under current conditions. Further exploration of the system is required to determine the cause of this nuanced result.

Overall, none of the interventions, including under climate change, had significant impacts on resistance in any sector (humans, animals, or environment). As mentioned above, trade regulations had a significant impact on reducing the exposure to AROs from imported food, but this did not lead to a reduction in AROs in humans, meaning this may not be a significant source of resistance in humans in this FCM. However, literature is scarce on the relative contribution of imported food to overall resistance in humans (106). The largest impacts were seen from increasing trade regulations and through technological advancements which led to a small reduction in resistance in food-producing animals. Technological advancements also had a minor impact on resistance in humans and plant agriculture, which was most likely due to the large reductions in AMU. However, as the large reduction in AMU did not correlate to large reductions in resistance, it is clear that AMU is not a major driver of resistance in this model. Furthermore, components related to AMU were not found to have high centrality or high outdegree in the system. Therefore, this may highlight that interventions aimed to reduce AMU within these sectors may not be the best place to target action, and that downstream drivers (e.g., improving animal welfare and good farming practices) may provide larger impacts within the system.

4.5.2 – Strengths & Limitations

This study does have some limitations, both with the inherent limitations of fuzzy cognitive mapping and with the study itself. Firstly, FCMs are highly dependent on experts' knowledge and opinion, both within the creation of the structure and the values and weights in the model (113, 114). The FCM developed in this study was based off an expert-driven CLD (11), and expert opinion was used to help parameterize the model (Chapter 3). However, in this study, expert opinion was triangulated with data from the literature which can reduce bias and help to validate the existence of association between the factors (115).

Similarly, another limitation of fuzzy cognitive mapping is that the causality between the factors is defined with a high degree of credibility, based on experts' contributions, even if true causality does not exist (37). This was further limited by the way in which this FCM was developed. Since the FCM was developed as a secondary analysis, experts were not probed to define weights for each causal relationship. Therefore, many assumptions were made for the weights of the relationships in our FCM (outlined in the decision matrix; 65). Thus, there was a great deal of uncertainty for the relationships in this model, therefore reducing the ability to be certain in the behaviour of the system and the ability to adequately assess the interventions. Therefore, next steps should include presenting the FCM to the group of experts for further discussion on the weights and values.

Finally, although useful for comparing scenarios, it is challenging to interpret the intervention outcomes (116-118). In FCM, the time steps are arbitrary and the AVs, although numerical do not have an absolute meaning but rather relative ordinal interpretations (116-118). Therefore, it is not possible to quantify the impacts of the interventions (e.g., an intervention reduces the average cost of food from $10 per day to $8 per day) but can be used to compare interventions (e.g., one intervention reduces cost of food more than another). However, despite these limitations, the use of fuzzy cognitive mapping to model AMR provided invaluable insight into the system dynamics, helped to identify which factors may have the most impact on the system, and allowed us to compare interventions under climate change from a systems perspective.

Despite these limitations, this study highlighted the benefits of using fuzzy cognitive mapping as a method to combine expert knowledge (Chapter 2), and data from the literature and other sources (Chapter 3), to describe the system that drives the development and transmission of AMR in a Swedish food system context. The methodology allowed for a flexible and versatile way to model a complex system, especially because the data were lacking and unclear (58, 107). Creating purely quantitative models can be time-consuming, costly, and time- and resource-intensive and may still require many assumptions when data were not available (78). Another benefit of fuzzy cognitive mapping over purely quantitative modelling is that fuzzy cognitive mapping allows for the inclusion of factors that may be difficult to quantify (e.g., knowledge, understanding, and awareness) as they can be described using linguistic terms. This FCM methodology provided a clear and easy way to combine qualitative data from experts and the literature with available quantitative data. This FCM also has the ability to be updated and refined when new data become available and through further expert opinion and discussion. FCMs can also be created with different groups of experts and then combined or compared to better understand the system from different perspectives (108-110). Finally, FCMs allow for the comparison of different policies, interventions, or other scenarios within a complex system to allow for the analysis of unintended consequences, unforeseen interactions, and how multiple scenarios may play out within the system (57, 58, 109).

Current models of AMR are mainly quantitative, deterministic, compartmental models that models AMR within a single population (e.g., humans, animals, or the environment), or location (e.g., a single hospital or on a single farm), with limited connection across sectors (Chapter 3; 36, 111, 112). Furthermore, many of these models are hypothetical models of the system, and therefore, do not have data to inform the various factors or transmission pathways (111, 112). Therefore, the models which are currently being used to assess interventions within these systems are limited in their scope (e.g., not accounting for potential unintended consequences in the broader system) and contain a lot of uncertainty due to data limitations, thus limiting the ability to adequately assess how these interventions will play-out in the real world. Therefore, quantitative models, although still useful at a more fine-level, are unable to capture real world behaviour, are limited by data availability, and are unable to capture more abstract features that play important roles in the complexity such as human thoughts, opinions, decisions, and behaviour, and underlying power dynamics and political forces (36, 111, 112). FCMs, however, can broaden the factors included by using expert input to fill in the gaps in current empirical data (58, 107). This FCM was able to include many socio-ecological drivers of AMR from multiple sectors and provide a tool to assess interventions from a systems view, accounting for complex interactions between factors and potential unintended consequences.

4.6 – Conclusion

This study highlighted a novel method and provided a first attempt to create a simulation model for analyzing the system that drives AMR in a more holistic manner, allowing for the inclusion of a wider range of factors from the broad system than have currently have been modelled. Fuzzy cognitive mapping provided a way to bring expert opinion, data, and literature together to create a clearer picture of the system, with the flexibility to refine the system when more data becomes available. The use of fuzzy cognitive mapping allowed us to evaluate eight interventions under climate change conditions. Network analysis of the FCM allowed us to identify influential components for potential future intervention. We were able to determine that the food system, as described by experts, and refined by literature, was an adaptable system with low complexity, and therefore may be able to be intervened in with more predictable outcomes. Therefore, future work should further explore this system with experts and stakeholders from the broad system to further refine the system and provide more input into the inner-workings of this complex and everchanging system and advocate for further qualitative exploration of AMR and the complex One Health system that drives it.

4.7 – Tables

Table 4.1: List of all of the components in the fuzzy cognitive map of the emergence and transmission of antimicrobial resistance in a Swedish food system, with the component variable, the name of the component, the assigned level, the associated activation values[1] (which can range from 0-1) at which the different drivers (components) of AMR in the Swedish food system context exist and were informed by expert opinion and a literature review), and a description of the component.

Component	Name of component	Assigned level	Associated activation value[1]	Description of component
AD	Animal density	High	0.75	The level used to describe the number of animals in a given space
AH	Access to healthcare	High	0.75	The level used to describe the availability of adequate healthcare services to an individual physically and financially and the right to seek, receive and impart information and ideas concerning health issues as well as how and why patients access healthcare resources
AMa	Aquaculture AMU[2]	Low	0.25	The level used to describe the amount of use of antimicrobials in aquatic food-producing animals for all purposes (preventative, control, and treatment)
AMc	AMU[2] in companion animals	Low	0.25	The level used to describe the amount of antimicrobials in companion animals (e.g., dogs, cats, reptiles, rodents, horses) for all purposes (preventative, control, and treatment)
AMh	Human AMU[2]	Low	0.25	The level used to describe the amount of antimicrobials used in humans for all purposes (treatment, prevention, control)
AMp	Plant agriculture AMU[2]	Low	0.25	The level used to describe the amount use of antimicrobials in agricultural plants for all purposes (preventative, control, and treatment)
Amt	(Terrestrial) On-farm AMU[2]	Low	0.25	The level used to describe the amount use of antimicrobials in terrestrial food-producing animals for all purposes (preventative, control, and treatment)
AOS	Access to AMs[3] outside of the system	Very low	0.13	The level used to describe the amount of antimicrobials obtained from alternative sources that are outside of the regulations of the healthcare system (e.g., without a prescription from a physician or veterinarian)
AP	Appropriate prescribing, diagnosing, treatment practices	Medium-Low	0.38	The level used to describe the appropriateness of the practices of a prescriber (physician and veterinarian) in terms of how they diagnose, plan to treat, and prescribe medication
ARc	ARO[4] in companion animals	Very low	0.13	The level used to describe the amount of resistant organisms in all companion animals
ARe	Resistance in wider environment	Low	0.25	The level used to describe the amount of resistant organisms and genes in the surrounding environment (soil, water, plants)
ARf	AROs[4] in food products	Medium-Low	0.38	The level used to describe the amount of resistant organisms in all food products
ARh	AROs[4] in humans	Low	0.25	The level used to describe the amount of resistant organisms in all humans
ARi	AROs[4] in imported food	Medium	0.50	The level used to describe the amount of resistant organisms in imported food products
ARm	AROs[4] in food-producing animals	Low	0.25	The level used to describe the amount of resistant organisms in all food-producing animals
ARp	AROs[4] in plant agriculture	Low	0.25	The level used to describe the amount of resistant organisms in all plant crops
Arw	AROs[4] in wildlife	Very low	0.13	The level used to describe the amount of resistant organisms in all wildlife animals

Component	Name of component	Assigned level	Associated activation value[1]	Description of component
AW	Animal welfare (lack of stress)	Medium-low	0.38	The level used to describe how well an animal is coping with the conditions in which it lives both physically and mentally
CD	Consumer choice, demand, and behaviour: other	Medium	0.50	Individual level human choice, behaviour, and demand for all other products
CDa	Consumer choice, demand, and behaviour: AMs[3]	High	0.75	Individual level human demand for antimicrobials
CDh	Consumer choice, demand, and behaviour: Health tourism	Medium	0.50	Individual level human demand for health tourism
CDi	Consumer choice, demand, and behaviour: Imported food	High	0.75	Individual level human demand for imported food
CDm	Consumer choice, demand, and behaviour: Meat/egg food products	Medium	0.50	Individual level human demand for animal food products
CDn	Consumer choice, demand, and behaviour: New and emerging foods	Medium-low	0.38	Individual level human demand for new and emerging food products
CDp	Consumer choice, demand, and behaviour	Low	0.25	Individual level human demand for plant-based meat alternative products
CDo	Consumer choice, demand, and behaviour: Organic	High	0.75	Individual level human demand for organic food products
CDv	Consumer choice, demand, and behaviour: Non-meat/egg food products	Low	0.25	Individual level human demand for non-animal food products
CDw	Consumer choice, demand, and behaviour: Animal welfare	Medium-high	0.63	Individual level human demand for animal welfare friendly food products
CP	Corporate profits from AMs[3]	Low	0.25	The level used to describe the amount the pharmaceutical industry profits from selling antimicrobials
Cm	Meat/egg consumption	High	0.75	The level used to describe the amount of animal-based food products consumed by the general population
Cnm	Consumption of other (non-meat/egg) foods	Medium	0.50	The level used to describe the amount of non-animal based food products consumed by the general public
Csf	Consumption of seafood	Medium	0.50	The level used to describe the amount of animal-based seafood products consumed by the general population
D	Diagnostics	Medium-low	0.38	The level used to describe the amount and availability of all resources used to diagnose a disease in humans and animals
DAA	Development of alternatives to AMs[2]	Low	0.25	The level used to describe the amount of creation, development, and production of any product that can be used instead of antimicrobials
Dh	Death (Human)	Low	0.25	The level used to describe the human death rate (includes all reasons for death)
Dhe	Digital health	Medium	0.50	The level used to describe the amount of access to healthcare through the internet or phone
DIT	Domestic and international trade	High	0.75	The level used to describe the strength or amount of trade regulations for international and domestic trade of food products

Component	Name of component	Assigned level	Associated activation value[1]	Description of component
DNA	Development of new AMs[2]	Low	0.25	The level used to describe the amount of creation, development, and production of antimicrobials
DP	Amount of product in the domestic market	Medium	0.50	The total amount of food products available for sale in Sweden’s domestic market
FS	Food and water security	Low	0.25	The level used to describe the amount of people with reliable access to a sufficient quantity of affordable, nutritious food and clean, potable water from domestic production only
GFP	Good farming practices	Medium	0.50	The level used to describe the quality of the principles to apply for on-farm, resulting in healthy animals, and safe and healthy food and non-food agricultural products, while taking into account economical, social, and environmental sustainability
HC	Healthcare costs	Medium	0.50	The level used to describe the actual costs of providing services related to the delivery of health care, including the costs of procedures, therapies, and medications
HM	Healthy host microbiome	Medium	0.50	The level used to describe the health and balance of a hosts’ microbiome and the ability to properly function
HR	Healthcare resources	Medium	0.50	The level used to describe the amount and type of staff, training, waiting time, money, equipment/technology within the healthcare system
Ic	Companion animal illness	Medium	0.50	The level of disease in all companion animals (infectious and chronic)
Ih	Human illness	Low	0.25	The level of infectious disease in the human population
Ihc	Chronic, non-communicable diseases	Medium	0.50	The level of chronic disease in the human population
Ihp	Psychological illness	Medium	0.50	The level of the psychological health (mental health issues) in the human population
Im	Food-producing animal illness	Low	0.25	The level of diseases in all animals (incl. poultry, livestock, aquatic animals) raised in agriculture
IP	Amount of imported product	High	0.75	The level used to describe the total amount of food products available for sale that have been imported from a different country
Ip	Disease in plant agriculture (crops, horticulture)	Medium	0.5	The level of disease in all plants used for agriculture
MAd	Movement of animals: domestic	High	0.75	The level used to describe the amount of physical movement of wild and food-producing animals from one location to another (domestic)
MAi	Movement of animals: international	Low	0.25	The level used to describe the amount of physical movement of wild and food-producing animals from one location to another (international)
MP	Movement of people	Medium	0.50	The level used to describe the amount of physical movement of humans from one location to another (domestic and international)
MPc	Market price per production unit: conventional food	Medium	0.50	The level used to describe how much whole-sale conventional food products are valued at
MPo	Market price per production unit: organic food	High	0.75	The level used to describe how much whole-sale organic food products are valued at
NAf	Non-AM disease prevention: food-producing animal farms	Medium	0.50	The level used to describe the amount of use of all other forms of disease prevention and control done in the farming of food-producing animals
NAh	Non-AM disease prevention: health and social-care settings	Medium	0.50	The level used to describe the amount of use of all other forms of disease prevention and control done in healthcare and social-care settings

Component	Name of component	Assigned level	Associated activation value[1]	Description of component
NFg	New and emerging food: GMO[5]	Low	0.25	The level used to describe the amount of genetically modified food being produced and consumed by humans and/or animals in Sweden
Nfi	New and emerging food: insects	Very low	0.13	The level used to describe the amount of insects being consumed by humans and/or animals in Sweden
NFt	New and emerging food: lab meat/3-D printed food	Low	0.25	The level used to describe the amount of lab-meat and 3-D printed food being produced and consumed by humans and/or animals in Sweden
NFv	New and emerging food: plant-based meat	High	0.75	The level used to describe the amount of plant-based alternatives to animal food-products being produced and consumed by humans and/or animals in Sweden
NQ	Nutritional quality of diet	Medium	0.50	The level used to describe the value of the product for the consumer's physical health, growth, development, reproduction and psychological or emotional well-being.
PC	Production costs	Medium	0.50	The level used to describe the amount the costs related to production of food-products
PLm	On-farm production level: conventional food animal-based product	Medium-high	0.63	The level used to describe the amount of conventional food product (animal-based) that is produced for sale from all farms in Sweden
PLo	On-farm production level: organic food products	Low	0.25	The level used to describe the amount of organic food product (animal-based and plant-based) that is produced for sale from all farms in Sweden
PLp	On-farm production level: conventional plant-based products	Medium-low	0.38	The level used to describe the amount of conventional food product (plant-based) that is produced for sale from all farms in Sweden
PMS	Pharmaceutical market, public relations, sales	Low	0.25	The amount of money put into marketing and the reputation of pharmaceutical companies and the regulations around pharmaceutical marketing and pharmaceutical representatives
PP	Producer profitability	Low	0.25	The level used to describe the producer's ability to use their resources to generate revenues in excess of their expenses
PS	Type of production systems	High	0.75	The level used to describe the relative number of non-conventional (e.g., organic, AB-free) farms to the number of conventional farms in Sweden
PV	Population vulnerabilities	Low	0.25	The level used to describe the amount of the population made up of groups and communities at a higher risk for poor health as a result of the barriers they experience to social, economic, political and environmental resources, as well as limitations due to illness or disability.
RAm	Retail availability of animal-based food products	Medium	0.50	The level used to describe the amount of food products of animal origin make it to retail and are available for purchase from consumers
RC	Retail cost of food	High	0.75	The level used to describe the relative cost of food in retail stores
RD	Retailer demand for product	Medium	0.50	The level used to describe the types and standards of food products which retailers want to stock in their stores
RDi	Retailer demand for product: imported food	Medium	0.50	The level used to describe the types and standards of imported ood products which retailers want to stock in their stores
RDo	Retailer demand: organic	Medium-high	0.63	The level used to describe the amount of organic food products which retailers want to stock in their stores
RDw	Retailer demand: animal welfare products	Medium	0.50	The level used to describe the amount of animal-welfare friendly food products which retailers want to stock in their stores

Component	Name of component	Assigned level	Associated activation value[1]	Description of component
SA	Science and academia	High	0.75	The level used to describe the amount of research and scientific evidence done in the scientific and academic communities
TPH	Treatment of food productions post-harvest	None	0	The level used to describe the reliance on treatment of food productions post-harvest (e.g., chloride washes) compared to the reliance on on-farm prevention
TWW	Treatment of waste and waste-water	High	0.75	The level used to describe the effectiveness, availability, and access to treatment of waste (human and animal) and waste-water to remove harmful pathogens and
UA	Understanding and awareness	Medium	0.50	The level used to describe the overall understanding and awareness of the human population on major aspects of the food and health system (e.g., availability and access to surveillance, scientific evidence, knowledge translation, communication)
Ugp	Use for growth promotion	None	0	The level used to describe the amount of antimicrobial used in healthy animals to increase rate of growth and feed efficiency
Um	Use for metaphylactic purposes	Medium	0.50	The level used to describe the amount of antimicrobial used in animals to control the spread of an infection and prevent getting an infection from nearby infected animal
Up	Use for preventive purposes	Low	0.25	The level used to describe the amount of antimicrobial used in healthy animals to prevent an infection
Uph	Use for prevention in humans	Low	0.25	The level used to describe the amount of antimicrobial used in non-infected humans to prevent getting an infection
Upp	Use for treatment post-procedure	None	0	The level used to describe the amount of antimicrobial used in healthy animals after a medical procedure (usually for prevention of disease or injury, e.g., tail docking, de-horning)
Ut	Use for treatment	High	0.75	The level used to describe the amount of antimicrobial used in animals to treat an infection
Uth	Use for treatment in humans	High	0.75	The level used to describe the amount of antimicrobial used in humans to treat an infection
VDM	Viability of domestic meat production	Low	0.25	The level used to describe the ability of the meat production system to continue operating successfully
Vh	Human vaccination	Very high	0.88	The level used to describe the proportion of the human population which have been vaccinated against common pathogens

[1]Activation values represents the level at which the different drivers (components) of AMR in the Swedish food system context exist and were informed by expert opinion and a literature review, and a description of the component. The activation value can take on a value between [0,1] and was divided into eight categories to represent the different levels with the following cut-off values: none (0), very low (0.13), low (0.25), medium-low (0.38), medium (0.5), medium-high (0.63), high (0.75), very high (0.88).

[2]AMU – Antimicrobial use

[3]AM – Antimicrobial

[4]ARO – Antimicrobial resistant organism

[5]GMO – Genetically modified organism

Table 4.2: The activation values[1] and relationship weights[2] assigned to each level category in a fuzzy cognitive map of the emergence and transmission of antimicrobial resistance in a Swedish food system.

Component activation value categories	**Activation value[1] assigned (range)**	**Relationship weight categories**	**Weight[2] assigned**
None	0.00	No relationship	0.00
Very low	0.13 (0.01-0.13)	Very weak	+/- 0.13
Low	0.25 (0.14-0.25)	Weak	+/- 0.25
Medium-Low	0.38 (0.26-0.38)	Medium-Weak	+/- 0.38
Medium	0.50 (0.39-0.50)	Medium	+/- 0.50
Medium-High	0.63 (0.51-0.63)	Medium-Strong	+/- 0.63
High	0.75 (0.64-0.75)	Strong	+/- 0.75
Very high	0.88 (0.76-0.88)	Very strong	+/- 0.88
Highest	1.00 (0.89-1.00)	Highest	+/- 1.00

[1]Activation values (AV) represent the level at which the different drivers (components) of AMR in the Swedish food system context exist and were informed by expert opinion and a literature review, and a description of the component. The activation value can take on a value between [0,1]. Each level has a cut-off value that was used to assign the AV, but during simulations the values can change. Therefore, the component is assigned a level based on the given range in which the AV falls at equilibrium.
[2]Weights represent the strength of the correlation between two drivers (components) of AMR in the Swedish food system context exist and were informed by expert opinion and a literature review, and a description of the component. The weights can take on a value between [-1,1] in which positive (+) values represent a positive correlation and negative (-) values represent a negative correlation between the two components. The weights do not have a range as the weights do not change during simulation.

Table 4.3: Scenarios assessed in a fuzzy cognitive map of the emergence and transmission of antimicrobial resistance in a Swedish food system, for their ability to reduce antimicrobial resistance and other negative impacts associated with antimicrobial resistance.

***A priori* interventions**		
	Under current conditions	**Under climate change conditions**
Status quo	Baseline scenario	Scenario 5
Increased infection prevention and control	Scenario 1	Scenario 6
Educational campaign	Scenario 2	Scenario 7
Antimicrobial stewardship intervention (Both increased infection prevention and control and educational campaign)	Scenario 3	Scenario 8
Trade implications	Scenario 4	Scenario 9
***A posteriori* interventions**		
	Under current conditions	**Under climate change conditions**
Cost as a barrier	Scenario 10	Scenario 14
Trade regulations	Scenario 11	Scenario 15
Technological advancements	Scenario 12	Scenario 16
Addressing population vulnerabilities	Scenario 13	Scenario 17

Table 4.4: The model features of the fuzzy cognitive map of antimicrobial resistance in the Swedish food system context.

Model Feature	**Value**
Total components	90
Total connections	491
Density[1]	0.06
Average connections per component	5.46
Number of driver[2] components	3
Number of receiver[2] components	0
Number of ordinary[2] components	87
Complexity score[3]	0
Hierarchical index[4]	0.01

[1]Density is calculated by the number of relationships out of the total number of possible relationships (9,40,69)

[2]Driver components only "forcing" functions (outgoing relationships), receiver components only receiving functions (inward relationships), and ordinary components have both inward and outgoing relationships

[3]Complexity score is the ratio of receiver variables to driver variables (40,49,68)

[4]Hierarchical index (HI) shows how easily a system can be manipulated by outside influences. A purely hierarchical system (HI=1) relies heavily on internal pressures and therefore is not easy change with intervention or policy-change, whereas a democratic system (HI=0) is open to outside influences.

Table 4.5: The initial level and the level at equilibrium with associated activation values[1] of the components of interest after the inference process was performed on the fuzzy cognitive map of antimicrobial resistance in the Swedish food system under the baseline scenario.

Component	Component name	Initial level (activation value[1])	Level at equilibrium (activation value[1])
AMh	Antimicrobial use in humans	Low (0.25)	Medium-high (0.58)
AMt	Antimicrobial use in terrestrial food-producing animals	Low (0.25)	Medium-low (0.28)
AMa	Antimicrobial use in aquaculture	Low (0.25)	Medium-low (0.33)
AMp	Antimicrobial use in plant agriculture	Low (0.25)	Very low (0.21)
ARh	Antimicrobial resistant organisms in humans	Low (0.25)	Highest (0.99)
ARm	Antimicrobial resistant organisms in food-producing animals	Low (0.25)	Highest (0.89)
ARp	Antimicrobial resistant organisms in plant agriculture	Low (0.25)	Highest (0.92)
ARe	Resistance in the environment	Low (0.25)	Highest (0.99)
Ih	Illness in humans	Low (0.25)	Very low (0.13)
Im	Illness in food-producing animals	Low (0.25)	None (0.05)
Ip	Disease in plant agriculture	Low (0.25)	High (0.65)
HC	Healthcare costs	Medium (0.5)	Very high (0.88)
IP	Amount of imported product	High (0.75)	Medium-high (0.62)
ARi	Exposure to antimicrobial resistant organisms from imported food products	Medium (0.5)	High (0.75)
RC	Retail cost of food	High (0.75)	Very high (0.83)
DIT	Domestic and international trade regulations	High (0.75)	Very high (0.76)
FS	Food security	High (0.75)	High (0.78)

[1]AV - Activation values represents the level at which the different drivers (components) of antimicrobial resistance in the Swedish food system context exist. The initial AVs were informed by expert opinion and a literature review), and a description of the component. The value at equilibrium is the final AV based on how the incoming relationships impact the component. The activation value can take on a value between [0,1] and was divided into eight categories to represent the different levels: none (0), very low (0.01-0.13), low (0.14-0.25), medium-low (0.26-0.38), medium (0.39-0.50), medium-high (0.51-0.63), high (0.64-0.75), very high (0.76-0.88), and highest (0.89-1.00).

4.7 – Figures

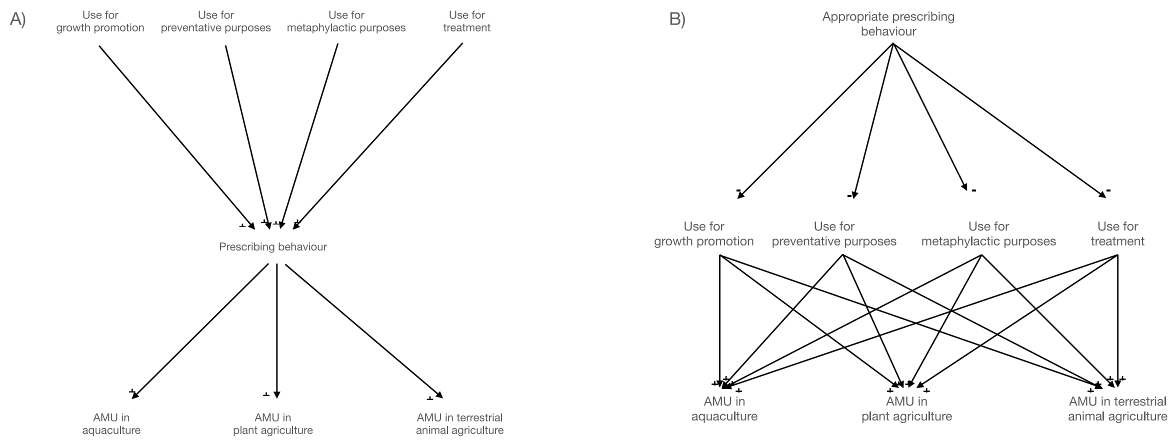

Figure 4.1: Changes in causal relationships between the reason for use (use for growth promotion, use for preventative purposes, use for metaphylactic purposes, and use for treatment), prescribing behaviour, and antimicrobial use (AMU) in aquaculture, plant agriculture, and terrestrial animal agriculture from the original causal loop diagram created during a participatory modelling workshop with experts from the broad One Health system that drives antimicrobial resistance in a European food system context (11) on Panel A, and the changes made to these components (prescribing behaviour became appropriate prescribing behaviour) and relationships when implemented into a fuzzy cognitive map of the drivers of antimicrobial resistance in the Swedish food system context on Panel B.

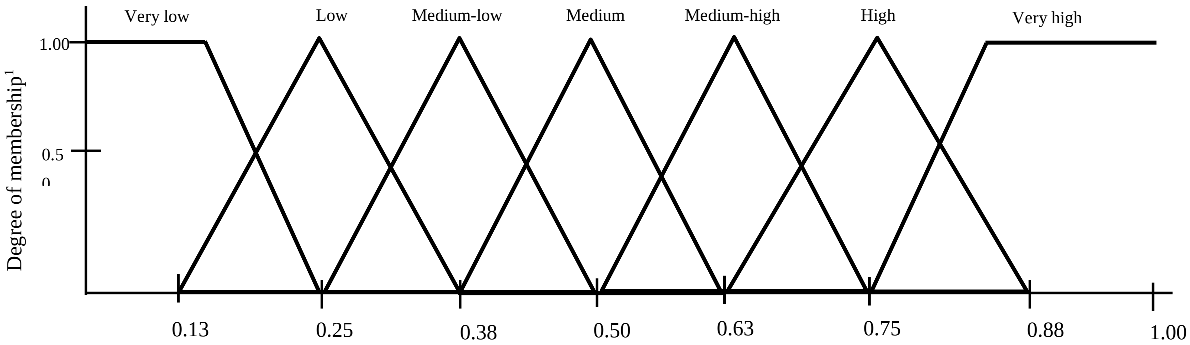

Figure 4.2: An example of how fuzzy logic was used to create the categories for the activation values for the components and the weights of the relationships in the fuzzy cognitive map of the development and transmission of antimicrobial resistance in a Swedish food system context.

[1]Fuzzy logic uses “”degree of truth” as opposed to “true or false”, or Boolean logic (0 or 1). Therefore the degree of membership refers to the relative amount the factor belongs within each category. If the factor belongs fully to a category, it will have a degree of membership of 1.

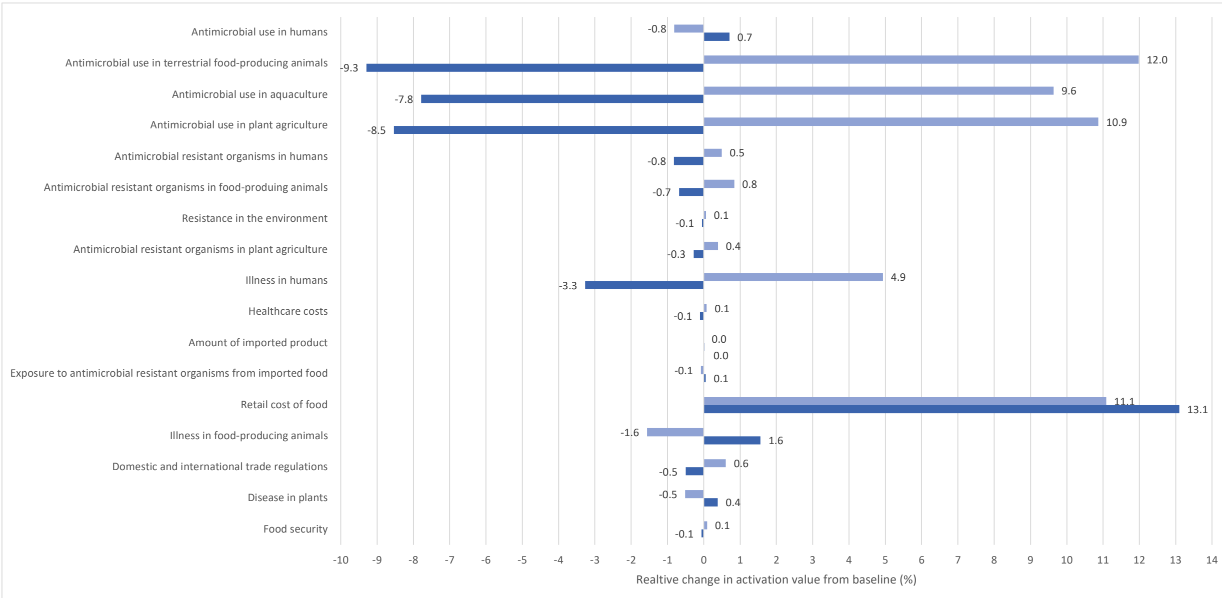

Figure 4.3: Results of the sensitivity analysis performed on a fuzzy cognitive map of the drivers of antimicrobial resistance in the Swedish food system context on the 17 components of interest when the weights were set to their lowest value (represented by dark blue) and their highest value (high represented by light blue).

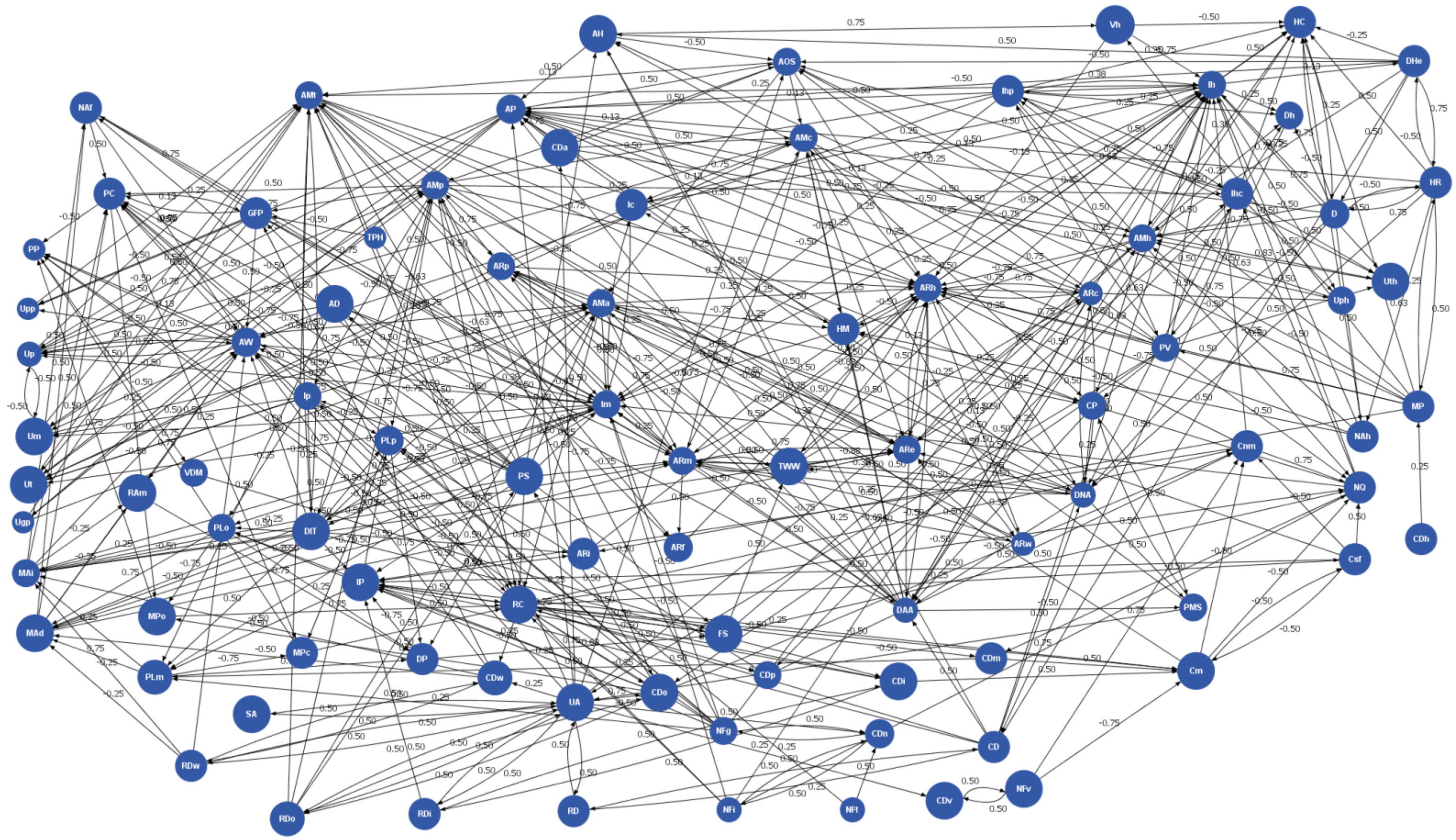

Figure 4.4: The fuzzy cognitive map of AMR emergence and transmission in the Swedish food system made up of 90 components (represented by the blue circles, in which the size of the circle represents the activation value of the component) and 491 relationships (represented by the arrows, in which the value represents the weight of the relationship, with negative values representing negative relationships).

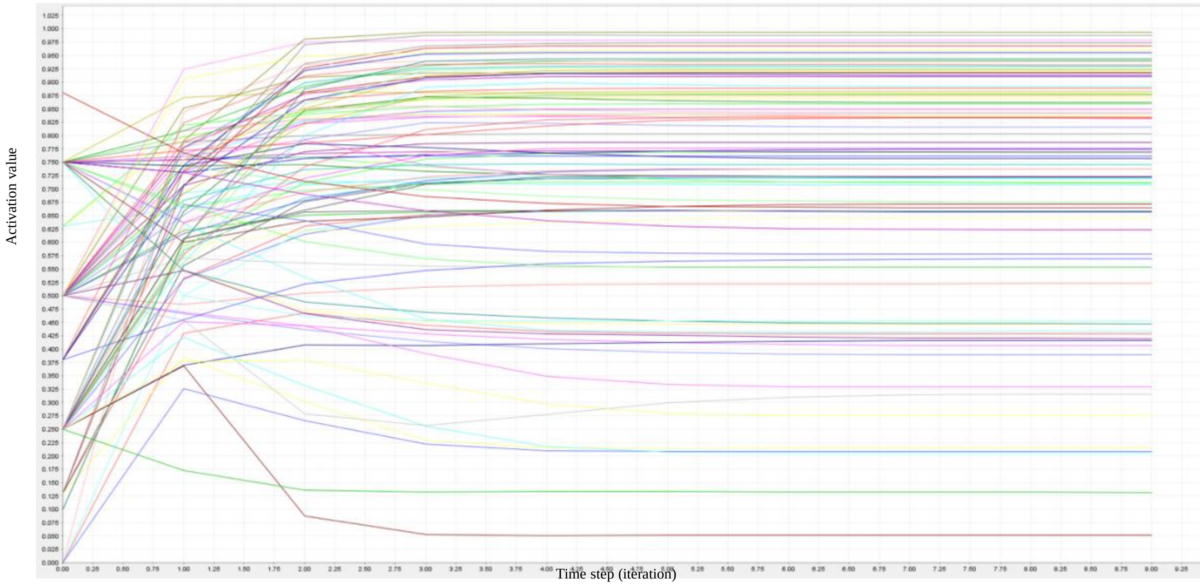

Figure 4.5: The output from the software FCM Expert (57) for the inference process of the baseline fuzzy cognitive map of AMR in the Swedish food system to indicate that the model reaches equilibrium after nine iterations (x-axis) and the activation values of each component at each iteration (y-axis). Each line represents a component in the FCM but these are not labelled.

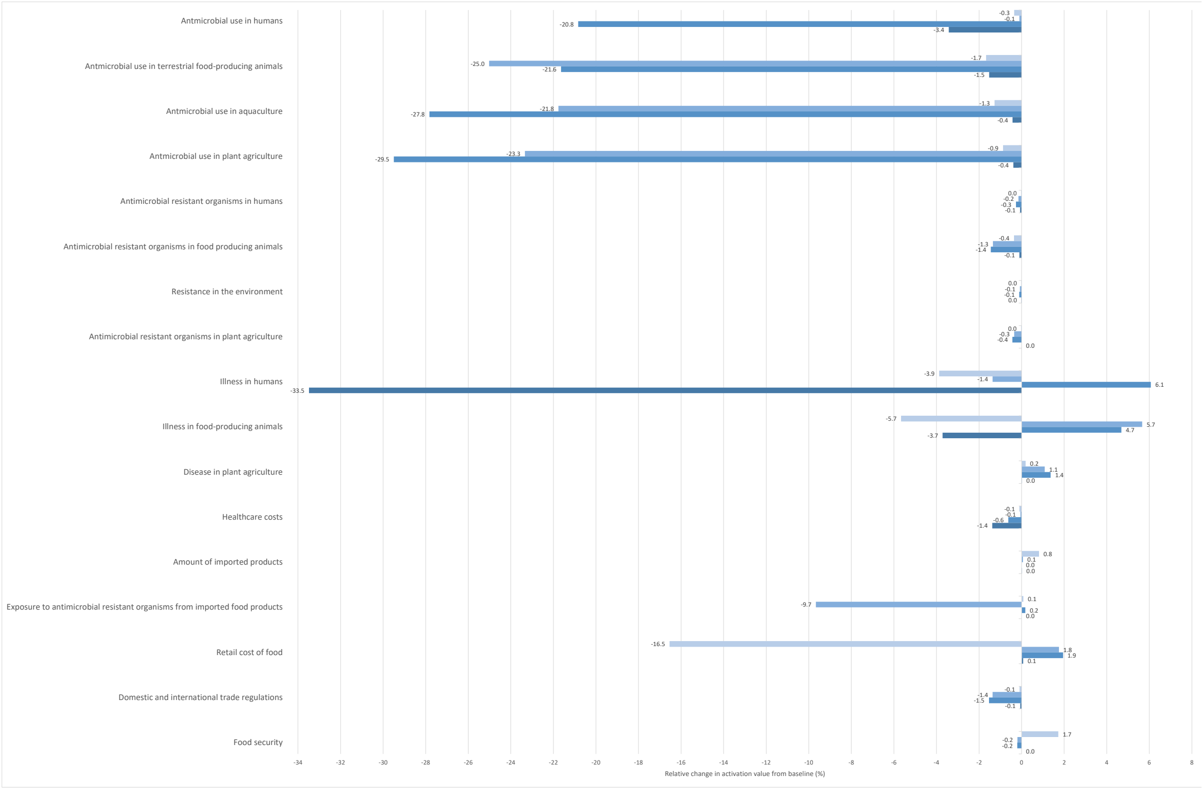

Figure 4.6: The relative reduction in the activation value of the indicator components at equilibrium from Scenario 10 to 13 at the highest intensity (with Scenario 10.3 represented by the lightest blue, Scenario 11.3 by light blue, Scenario 12.3 by medium blue, and Scenario 12.4 by dark blue) compared to the baseline scenario. Scenario 10 represents a reduction in barrier as a cost for nutritious food and sustainable production practices under current conditions. Scenario 11 represents increased international trade regulations and implantation under current conditions. Scenario 12 represents technological advancement and innovation under current conditions. Scenario 13 represents addressing poverty and social inequalities under current conditions.

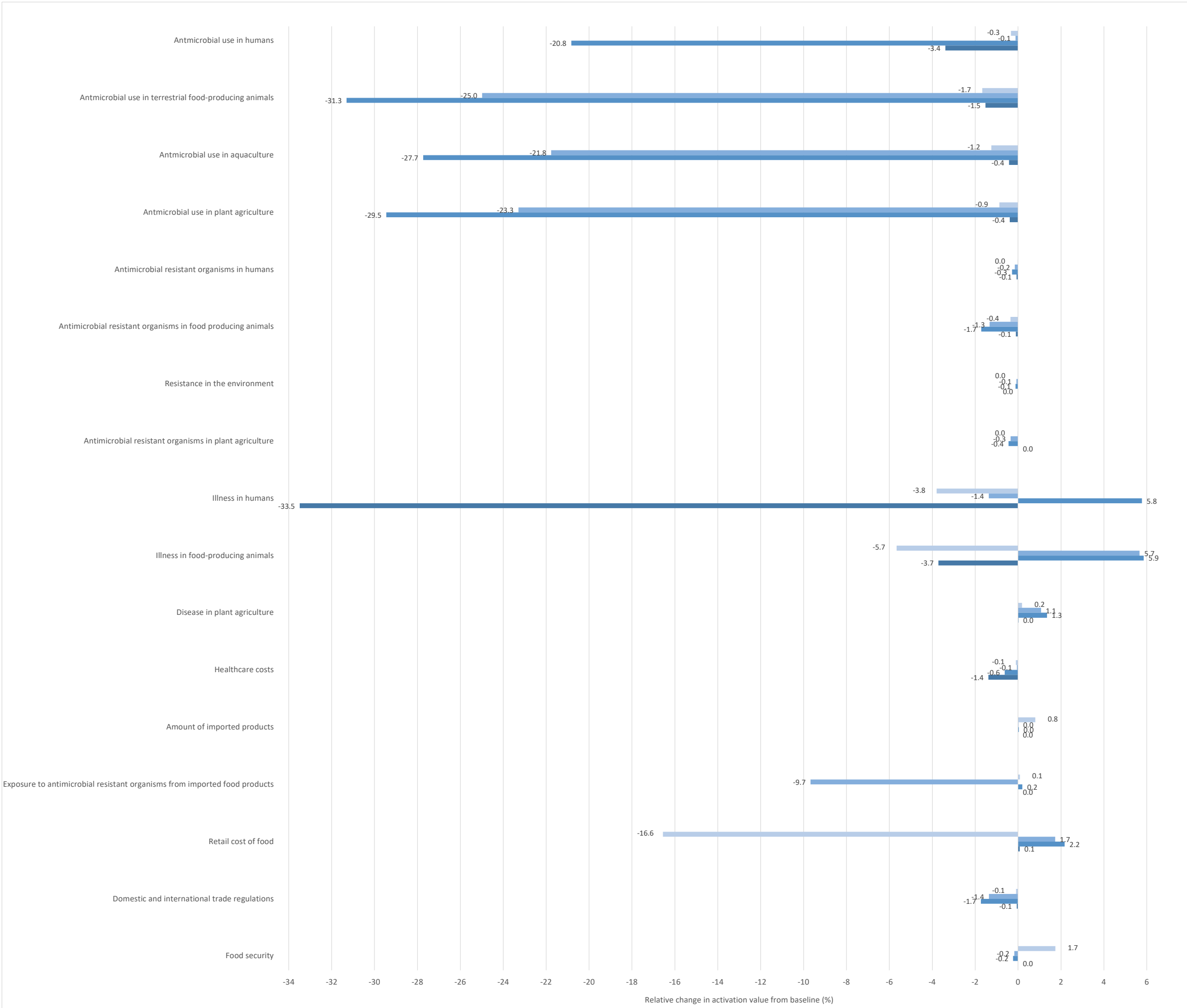

Figure 4.7: The relative reduction in the activation value of the indicator components at equilibrium from Scenario 14 to 17 at the highest intensity (with Scenario 14.3 represented by the lightest blue, Scenario 15.3 by light blue, Scenario 16.3 by medium blue, and Scenario 17.4 by dark blue) compared to the baseline scenario. Scenario 14 represents a reduction in barrier as a cost for nutritious food and sustainable production practices under climate change conditions. Scenario 15 represents increased international trade regulations and implantation under climate change conditions. Scenario 16 represents technological advancement and innovation under climate change conditions. Scenario 17 represents addressing poverty and social inequalities under climate change conditions.

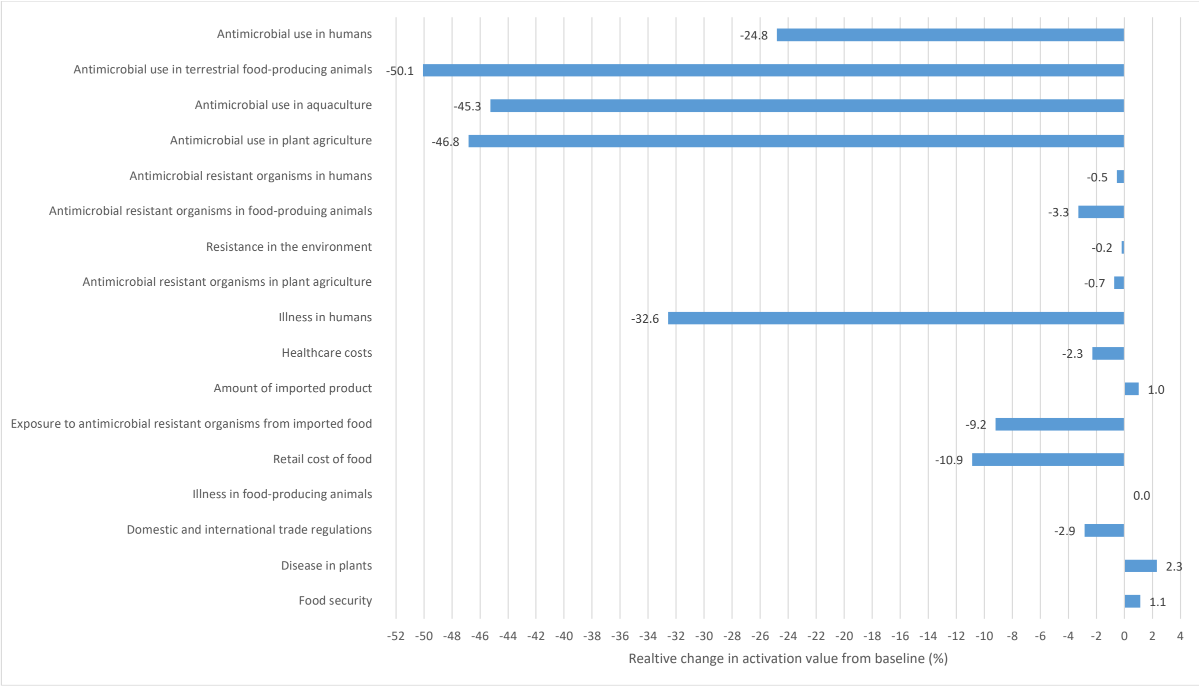

Figure 4.8: The relative reduction in the activation value of the indicator components at equilibrium from Scenario 18 which represent Scenarios 10-13 in combination at the highest intensity. Scenario 10 represents a reduction in barrier as a cost for nutritious food and sustainable production practices under climate change conditions. Scenario 11 represents increased international trade regulations and implantation under climate change conditions. Scenario 12 represents technological advancement and innovation under climate change conditions. Scenario 13 represents addressing poverty and social inequalities under climate change condition.

Chapter 5

Expert and literature-driven fuzzy cognitive mapping as a new method to model complex public health issues: Using antimicrobial resistance in the Swedish food system as an example

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5.1 – Abstract

Many public health issues, including antimicrobial resistance (AMR), develop from a complex system of drivers that traditional epidemiological methods cannot account for. By recognizing these complex interaction, more effective and sustainable solutions can be developed and implemented. Therefore, there is a need for participatory and systems thinking approaches to engage stakeholders from within the broad system to advance the understanding of the complexity and underlying social-ecological drivers of these issues. Participatory modelling is gaining popularity as a transdisciplinary approach to better characterize complex systems in public health. Fuzzy cognitive mapping is a semi-quantitative, participatory modelling technique that has shown promise in other disciplines but has yet to be widely applied to public health. This paper outlines the process of creating a fuzzy cognitive map of the development and transmission of AMR in a Swedish food system context to: 1) provide a working example of how to use FCM in a public health context; 2) highlight the benefits of using fuzzy cognitive mapping to help address the challenges of established methods to address complex public health issues; 3) identify mitigation strategies for challenges faced throughout the process; and 4) advocate for future participatory and semi-quantitative research in AMR as well as other complex public health issues.

5.2 – Introduction

Many public health issues, such as antimicrobial resistance (AMR), are the product of a complex system of drivers that involve actors from multiple sectors (including humans, animals, and the environment), and are intimately connected and span across multiple ecological scales [1-5]. Traditional quantitative epidemiological methods are not able to adequately address the complexity of these issues due to the complex, nonlinear, and indirect relationships that exist between the factors [6, 7]. Participatory modelling is gaining ground as a way address these public health issues due to the transdisciplinary and integrated nature of the approach through the engagement of stakeholders from multiple disciplines [6, 7]. Participatory modelling involves the engagement of stakeholders to create a formalized and shared representation of a real-world system based on the implicit and explicit knowledge of the stakeholders [8]. One modelling method which is based in participation is fuzzy cognitive mapping [9]. Fuzzy cognitive mapping has been used to model systems in many disciplines such as ecology [10-12], economics [13-15], and sociology [16, 17], but has yet to be widely adopted to address complex public health problems. Fuzzy cognitive mapping has the power to bring stakeholders together from multiple disciplines to co-create semi-quantitative simulation models for use in decision making and policy analysis. Due to their semi-quantitative nature, these models can be expanded to include other forms of data beyond expert opinion, such as empirical data from literature. This makes fuzzy cognitive mapping a useful tool to integrate quantitative, empirical data typically used in public health research with data generated using qualitative methods and through stakeholder engagement. By capturing a breadth of perspectives, fuzzy cognitive mapping can help widen the scope and better our understanding of the system [9, 15, 18, 19].

5.2.1 – Using participatory and semi-quantitative modelling techniques to address complex public health problems: Using AMR as an example

5.2.1.1 – AMR as product of a complex system

Complex systems are systems composed of many elements with multiple interactions between them, in which the elements adapt and react to the patterns the interactions create [20]. The three main components of complex systems are non-linearity, emergence, and unpredictability [20,21]. Nonlinearity refers to disproportionate causation, in which small changes in one element do not necessarily cause a small change in another [21]. Alternatively, small shifts in one part of the system can lead to sudden and large changes throughout the system [21]. This is typically due to multiple interactions that interact to create the overall behaviour of the system [21]. For example, multiple factors may be acting in opposing ways on an element in the system, which may also be connected to other factors in the system. Therefore, changes in one element can cause non-linear effects [21]. The second feature is emergence, which refers to the emergence of macroscopic patterns (system-wide change) resulting from microscopic interactions between elements (an association between two elements) [21]. Together, the non-linearity and emergence cause great uncertainty and unpredictability within the system [20,21]. For example, changing one small part of the system, could have large and unpredictable consequences elsewhere in the system. The system that produces AMR is comprised of many drivers across many sectors and ecological scales and involves many moving parts. The human, animal, and environmental sectors are intimately connected, and AMR can develop and spread across these sectors with ease [1, 3, 5]. Therefore, changes in one sector can have large and unpredictable consequences across of the system [1, 3, 5].

Antimicrobial use (AMU) has been identified as a major driver of AMR [1-3, 22], however, there are many socio-ecological factors which impact why and how we use antimicrobials, and how antimicrobials and antimicrobial resistant pathogens may spread throughout the system [1-5, 22-24]. Past solutions to combat AMR have been unsuccessful long-term as they have failed to address the entire system due to a lack of integration and communication between the multiple actors involved [3, 23]. When interventions and policies are “siloed”, with action being taken in only one part of the system, unintended consequences can occur in other parts of the system [25]. Systems thinking and participatory modelling can identify and bring the important actors and stakeholders (e.g., government, organizations, scientist, sociologists) together and to consider AMR with a more holistic view.

5.2.1.2 – Participatory modelling to address complexity

Due to the inherent One Health nature of AMR and the involvement of multiple actors from a variety of sectors, integrated and transdisciplinary methods are required to be able to fully understand this issue [6]. Participatory methods support engagement of stakeholders from many different disciplines and knowledge systems to come together and discuss the issue from their individual perspectives and explore how they may fit into the overall picture. By combining different perspective, participatory modelling approaches facilitate the integration of different knowledges to form a more holistic picture of the system [5, 6]. Not only do we get a broader overview of the system, we can also get better insight into the practical or real-world aspects of how the system may perform, as opposed to how the system may theoretically behave [26, 27].

Participatory modelling is becoming recognized as an effective and important tool for addressing complex public health problems [6, 7]. There are multiple types of participatory model building activities (e.g., group model building, spatial group model building, companion modeling, agent-based modeling) but their overall aim is to engage stakeholders to co-create models. Ultimately, these approaches can lead to a better understanding of systems and enhanced applicability of models to a specific context of interest and use for decision- and policy-makers [6, 7]. Participatory modelling is an iterative and adaptive process in which stakeholders can be engaged at multiple points in the modelling process. These models outline the major elements and improve the quality of the model outputs by adapting them to reflect their specific context. Participatory modelling also allows for conversations around socio-ecological issues such as power dynamics and political issues that may underpin decisions and behaviour in the system that could not be identified or captured using quantitative modelling techniques [6, 7].

Fuzzy cognitive mapping is a semi-quantitative modelling technique that traditionally includes a participatory model building process [9, 18, 19]. Fuzzy cognitive mapping has shown great promise in modelling complex dynamic systems in ecology [10-12], engineering [28], economics [13-15, 29, 30], energy efficiency [31-33], waste and waste water management [34], sociology [16, 17], and some health system [35-38]. Fuzzy cognitive maps (FCMs) are made up of concepts (or components or nodes) which represent the elements or factors of a system, which are connected by weighted causal relationships. Both concepts and relationships are defined in linguistic terms [9, 18]. For example, the amount of antimicrobial use (AMU) in Sweden could be considered “low” compare to other countries which may have “high” AMU. Similarly, the relationship between AMU and the burden of illness may be “strong” but the relationships between understanding and awareness about proper AMU and consumer demand for antimicrobials may be considered “weak”. This modelling approach typically engages stakeholders to not only define the system (in terms of the major factors and interconnections) but to also provide estimates of the values associated with the strengths and directions of the interconnections (further referred to as relationships) and the current states of the major factors (further referred to as components) of the system in linguistic terms [9, 18, 19]. These linguistic terms are broken into categories (e.g., high, medium, low) using fuzzy logic (computing based on "degrees of truth" rather than "true or false" or Boolean logic) [39] and take on a value between [0,1] for the components, and [-1,1] for the weights of the relationships (which will be further described in Section 5.4.3). When constructed, this type of model can then be used for simulations and scenario analysis [9, 18]. The benefit of fuzzy cognitive mapping is that the model building process can be asynchronous and iterative. Models can be created and combine through multiple collaborative processes with stakeholders from different areas at different times and then combined or compared [18, 19].

5.2.2 – Rationale and objectives

As mentioned, FCMs are typically created through participatory model building. However, the semi-quantitative nature of these models creates a unique opportunity to integrate expert opinion and the linguistic definitions of the components and relationships with available empirical evidence. Fuzzy logic allows for the combination of quantitative and qualitative data using categories and degrees of truth (Figure 5.1). Mixed methods research such as this could combine the breadth, generalizability, and measurable evidence of quantitative research and the depth and context-specific nature of qualitative research [40-46]. By combing the benefits of participatory modelling and expert engagement along with the benefits of empirical evidence and existing quantitative data, fuzzy cognitive mapping could provide a powerful tool for simulation modelling of complex public health issues. Therefore, the aim of this paper was to provide an overview of the process I undertook to create a semi-quantitative model of the development and transmission of AMR in a Swedish food system context using outputs from a participatory modelling workshop with experts from within the broad One Health system. The main objectives were to: 1) provide a working example of how to use FCM in a public health context; 2) highlight the benefits of using fuzzy cognitive mapping to help address the challenges of established methods to address complex public health issues; 3) identify mitigation strategies for challenges faced throughout the process; and 4) advocate for future participatory and semi-quantitative research in AMR as well as other complex public health issues. In the next section I will provide an example of using fuzzy cognitive mapping to create a simulation model of the Swedish food system that drives AMR which was based on a participatory modelling workshop and a literature review.

5.3 – A working example of using fuzzy cognitive mapping to address complex public health issues: AMR in a Swedish food system context

To create a simulation model of the development and transmission of AMR in a Swedish food system context, I converted an expert-derived causal loop diagram (CLD) [5], validated and expanded by literature (Chapter 3), into a mixed methods model using the semi-quantitative modelling technique called fuzzy cognitive mapping [9]. This method was used to model AMR in a Swedish food system context and assess the sustainability of interventions to combat AMR under a changing climate, but this process could be applicable to other complex public health issues. The steps below are outlined in Figure 5.2.

5.3.1 – Step 1: Defining the structure and informing the model

As opposed to traditional FCMs, the model constructed was created *a posteriori*, and was based on a set of participatory modelling workshops in which experts from within the broad One Health System mapped out the major drivers of AMR in a European context [5]. Therefore, the structure (the components and relationships) of the FCM was outlined by the experts using participatory methods and the creation of a CLD [5]. CLDs are a visual dynamic thinking tool used in systems thinking to describe the elements that make up a system and the connections between them, which can then be used to look for patterns and behaviours to better understand the system [47, 48]. The expert-derived CLD consisted of 91 nodes (also called factors or drivers), 331 interconnections (or relationships between the factors), and six overarching factors that impacted the entire system [5]. The expert-derived CLD provided the base structure for the FCM, and the estimates of the values for the weights of the relationships and the current states of the components were informed by a literature search (Chapter 2) and a secondary analysis of the transcripts of the participatory modelling workshops (Chapter 3).

As mentioned above, CLDs are a visual depiction of the parts of the system and how they interact [47, 48]. These visual maps, however, can be used as a basis for computer-based simulation models. This is done by converting the CLD to a stock-and-flow model, which essentially is a quantified version of the CLD [49]. The elements of the CLD become the stocks which represent the value of the element at a given point in time that can accumulate or drain over time based on the influence of the flows. The interconnections act as the flows, which represent the rate that the stock is changing (increasing or decreasing) over time. Together, the stock-and-flow model can simulate changes in the elements of the system over time [49]. A specialized stock and flow model which has had many implications in public health are compartmental models in which the population is divided into compartments based on their disease status (e.g., susceptible, infectious, recovered) and can flow between these compartments based on rates of flow (e.g., recovery rate, death rate, transmission rate) [50].

Therefore, the next step in creating a complex model of AMR was to try and use the CLD as a basis for a stock and flow model. However, stocks and flows require quantitative values for the level of the stocks (e.g., how many people have AMR infections) and for the flow rates (e.g., the prescribing rate – number of people who receive a prescription for an antimicrobial per week) in order to be used for simulation.

A literature search was performed to find: 1) existing models of AMR, and 2) data to inform the stocks and flows. A modified scoping review was conducted to fulfil these two needs (Chapter 2). The first objective was to find models related to AMR and the broad system as these models could provide insight into where research has already been conducted and parameters have been identified, as to not duplicate efforts and use well-defined peer-reviewed methods. An ideal model to use as a basis would be a compartmental models that crossed sectors at an international scale. However, this type of model was not identified in the literature. The models that were found were developed for specific settings within a given sector (e.g., a hospital, a single farm) and the inter-sector relationships were not well-defined. Therefore, creating a model to include all of the important factors and connections identified by the group of experts would need to be built from the ground up, based directly on the CLD [5].

The scoping review was kept broad when searching for data, in both the sources (e.g., blog posts, news articles, government reports) and types of data (e.g., quantitative and quantitative indicators, surveillance, interviews, surveys) to inform the model by using broad search terms and a wide variety of sources. Based on what the experts said in the participatory modelling workshops [5] about the availability of data, or lack of data, along with the wide variety of factors that drive AMR (some of which might not be quantifiable), minimal quantitative data was expected. One of the major outcomes of the literature search was a database which contained data (e.g., quantitative indicators, quotes from the literature) to inform 64 of the 91 nodes from the CLD [51]. The database also contained data to inform the weights of the relationships that were mentioned within the literature, however, these were not explicitly searched for. Because the literature search revealed that the data to inform the model was not detailed or sufficient in many cases, a fully quantitative model would be challenging to create without including many assumptions for the parameters and initial values, or without falling back into the same small-scaled sector-specific models that already exist. Therefore, a mixed methods or semi-quantitative model was the most appropriate way to capture the breadth of the system, advance the understanding of AMR, and create a model to test interventions and aid in decision-making from a system-wide perspective.

The decision to include qualitative data in the model led to two other decisions: 1) to include qualitative data from the workshops to help inform the model; and 2) to use fuzzy cognitive mapping, a semi-quantitative modelling technique. Although not the initial purpose of the participatory-modelling workshop, the experts sometimes described the nodes and relationships in terms of amounts or strengths during the discussion [5]. Therefore, the workshop transcripts were re-analyzed to identify instances in which experts provided semi-quantitative indicators for the nodes (e.g., there is “very little” AMR in Sweden), and relationships (e.g., as illness increases on farm, there is a “huge increase” in AMU) (Chapter 3). Overall, the experts inadvertently provided insight into the state of the many of the nodes in the CLD in semi-quantitative terms [52]. However, the experts were more likely to use examples to show how the factors were connected and were not as inclined to put strengths to the relationships when describing the system.

Mixed methods or semi-quantitative modelling are used in many other disciplines [28-38], but their application in public health is limited. When searching for a way to combine the quantitative and qualitative data to create a simulation model, fuzzy logic and fuzzy cognitive mapping appeared to be a pragmatic solution [9, 39]. This modelling technique provided a way that would allow the use of quantitative and qualitative data and has the power to conduct simulations and scenario analysis [9, 18]. With the model approach chosen, the next step was to set up the model.

5.3.2 – Step 2: Setting up the model (assigning the activation values and weighted relationships)

To combine the data from the scoping review and the transcript analysis, the data needed to be presented in a common format. Fuzzy cognitive mapping uses fuzzy logic to combine quantitative and qualitative data, which essentially creates categories or levels (e.g., high, medium, low) and uses degrees of truth for inclusion within a category (Figure 5.1) [39]. Fuzzy logic uses “degrees of truth” as opposed to “true or false” or Boolean logic. Therefore, a factor can partially belong in two categories, which is determined by the degree of membership [39]. For example, according to The Centre for Disease Dynamics, Economics, and Policy, Sweden’s antibiotic use in 2015 was 4.72 defined daily dose (DDD) per 100,000 population and Turkey’s was 18.10 DDD per 100,000 [53]. According to the categories outlined in Figure 5.1, this would put Sweden within the low category and Turkey within the high category (Figure 5.1). However, France, with antibiotic use of 13.04 DDD per 100,000 [53] would partially belong to the medium (degree of membership = 0.45) and high category (degree of membership = 0.55). This concept of dividing the data into categorical levels was used to combine the quantitative and qualitative data from the literature (Chapter 2; [51]), and the statements from the experts of the participatory modelling workshop (Chapter 3; [52]). The details for how the levels were assigned in the scoping review (Chapter 2), the transcript analysis (Chapter 3), and how they were combined (Chapter 4) to inform the model are outlined in the previous three chapters. Overall, assigning the levels was relatively subjective and was approached differently for the quantitative data and qualitative data.

However, this process allowed for the inclusion of more nodes than would have been possible with either process individually. The literature provided data to fill in nodes or relationships that expert described but did not quantify, and the experts were able to provide insights into the nodes or relationships that were not found in the literature.

Once the nodes were assigned a level, the nodes from the original CLD [5] that contained data were included in the FCM as the components and the relationships from the CLD that existed between the remaining components were listed and additional relationships found through the literature search and transcript analysis were added. Where data existed, weights were assigned in a similar manner as above. However, data for the relationships were much less abundant. Conducting a literature search for all 331 relationships from the CLD was not feasible, as it took three months to do the 91 nodes alone. The strengths of the relationships were also not stated explicitly by the group of experts as this was not a primary goal of the workshop [5]. Therefore, many of the relationships were informed by personal judgement and background knowledge and were validated by the broader research team. Those that were not easily deciphered were assigned a strength of medium as a base assumption.

5.3.2.1 – Validation of the FCM structure, nodes, and relationships

The structure of the original CLD was validated with the experts [5] and therefore which provided validation to use it as a basis for the FCM [5]. However, changes had to be made to the initial structure due to nodes that were removed due to lack of data or nodes that were unable to be assigned a single value, or were separated into sub-nodes due to the nodes being too broad. Therefore, the final structure of the FCM was discussed and validated with the broader research team to ensure the major pathways remained in the model even when nodes were removed (e.g., if an intermediate node was removed, the main relationship still existed).

Given the subjective nature of the process required to define and categorize the data to assign the levels and relationships, discussion and validation with the broader research team was an integral part of the process. Inter-coder reliability was conducted during the literature search (Chapter 2), transcript analysis (Chapter 3), and during the model building when data from the literature was combined with data from the transcript analysis (Chapter 4). In all instances, discussions took place between the group of researchers and when disagreement existed, discussions occurred until consensus was reached. However, as mentioned above, there were many instances in which data did not exist to inform the relationships. In these cases, a level was informed by my personal judgement and background knowledge which were validated by the broader research team. There were many relationships that were not easily assigned a level based on the knowledge of the research team, and therefore the strength of medium was assigned as a base assumption. Once all of the components and relationships had values assigned, the next step was to find a software that could be used to construct and analyze the model.

5.3.3 – Step 3: Finding the right software

There were a total of 11 different FCM software found in an initial scan of the literature. However, being new to the method, it was unclear the features that would be required for implementation or analysis. There were two especially useful articles that compared newer software (FCM Wizard [55] and FCM Expert [18]) to existing FCM software in terms of their usefulness and the available. Using these articles as a basis, the software packages outlined in the two articles were researched. There were 10 different software packages reviewed, with an additional one that was identified through a preliminary Google search (iModeler [56]). Three of the software packages (FCM Expert [18], iModeler [56], and Mental Modeler [57]) were tested, two of which were used for analysis (Table 5.1). The pros and cons for the software tested (and used) as well as the reasons the others were not used are provided in Table 5.1.

Mental Modeler and iModeler were the first two software tested as they were web-based and easy to access. A small portion of the model was built in both software to determine if it was worth pursuing. Mental Modeler provided the means to analyze the system using network metrics (e.g., density, centrality, indegree, outdegree, hierarchical index) and allowed for scenario analysis. However, the model was based on relationships alone, and did not allow for activation values (initial states) for the components. Inputting the activation values for the components was important to this model as there was more data (from the literature review and the transcript analysis) to inform the activation values than the weights of the relationships. The software iModeler was similar to Mental Modeler in that it was based solely on relationships and did not allow for activation values to be inputted in the qualitative model stage. iModeler was of great interest due to its ability to be converted into a quantitative model once data became available. Future work may use this feature. However, a software that allowed for inputting activation values as well as the weighted relationships was required. The next software tested was FCM Expert, a modelling software that was free to install but only worked on PC computer systems. This software provided many useful features including: a user-friendly interface; allowed for the inclusion of activation values; multiple inference process options; performed simulations; and allowed for scenario analysis. Another benefit of FCM Expert for future research is the ability to refine the model using machine learning (e.g., estimate activation values and weights of relationship based on datasets) when data becomes available. Finally, FCM Expert had the ability to export the relationships from the model as a weight matrix (as a .csv or .xls file) which was a very useful feature that allowed me to easily move between Mental Modeler and FCM Expert to utilize the features of both of these software packages.

5.3.4 – Step 4: Building the model and using the model for scenario analysis

Once the software was chosen, the model building process began. FCM Expert uses a user-friendly point and click graphic user interface, making this software more accessible to the average user, without the need for coding. First, the components and their associated activation values were added. FCM Expert allows for only three-letters to represent the component, however it allows the full name and details to be put in a comment box that appears when clicking on the component. Relationships were then added to the model. The weights of the relationships were added and details about the relationship were noted in the comment box. Once all components and relationships were added to the model, it was ready to be analyzed and used for simulation.

FCM Expert has a built-in inference process function, which is used to run simulations and perform scenario analysis. During an inference process, FCM Expert re-calculates the activation value of the components at every discrete time step using an updating rule (e.g., Kosko's activation rule with self-memory; 18) and the transformation function (e.g., Sigmoid function), which is informed by the combination all of the relationships connected to each component [18, 59]. There are three updating rules (Standard Kosko's activation rule, Kosko's activation rule with self-memory, and Rescaled activation rule with self-memory) and five transformation functions (bivalent, saturation, trivalent, hyperbolic, and sigmoid) to choose from, in which the standard options were used: Kosko's activation rule with self-memory as the updating rule as it allows for the activation value to be based on the value in the previous step (has memory), and the Sigmoid transformation function which allows for improved convergence of the model [18, 59]. An inference process was performed in FCM Expert to determine if the model could reach equilibrium, which is essential to be able to analyze scenarios [18]. If the model does not reach equilibrium, it can either have cyclical behaviour (oscillating activation values over time), or chaotic behaviour (activation values never reach steady state) [60]. The FMC converged and reached equilibrium which allowed for scenario analyses to be conducted, in which multiple interventions under current and climate change conditions were assessed (outlined in Chapter 4).

Scenario analysis, in FCM Expert, is done by altering the activation values of desired components, running an inference process, and comparing the activation values of the components at equilibrium to those of the inference process of the original FCM (baseline) [18]. In all of the examples of FCMs in the literature, altering the activation value was able to create change in the system (activation values changed at equilibrium). However, in this FCM these alterations were not enough to make a change to any of the components at steady state (Chapter 4). This could have been because of the size of the FCM (e.g., models in example articles had less than 30 components compared to 90 in this FCM; [11, 36]), or internal issues with the structure of the model (e.g., missing connections or feedback loops).

Therefore, new interventions that altered the weights (strengths) of the relationships were created. The same process was undertaken: the weights of the relationships were changed, inferences processes were performed, and percent reduction was calculated for the subset of components compared to the baseline. Changing the weights of the relationships was able to create change in the system, but was not able to significantly reduce AMR. The outcomes of all the scenarios can be found in Chapter 4.

Finally, the analysis features included in Mental Modeler were utilized because the features of the model that it calculated (density, centrality, indegree, outdegree, average connections per node) were important in better understanding the system. The ability to export the weight matrix of the FCM from FCM Expert and import it into Mental Modeler allowed for the advantages of both software to be used without having to re-create the model in each software. Finally, there was one other model feature, hierarchical index (HI) [57], that had been reported in many of the example FCMs but was not calculated in Mental Modeler. This value shows how easily the system can be manipulated by outside influences [62]. A purely hierarchical system (HI=1) relies heavily on internal pressures and therefore is not easy to change with intervention or policy-change, whereas a democratic system (HI=0) is open to outside influences [62]. This value was manually calculated using the outdegrees (number of outgoing connections) of all the components which were provided by Mental Modeler.

5.4 – Benefits of using fuzzy cognitive mapping to address AMR and its application for public health research

The use of FCM informed by participatory approaches and existing data from the literature proved to be a novel and beneficial method to enhance our understanding of the system that drives AMR in Sweden. This method goes beyond a visual model of AMR (the CLD created through the participatory modelling workshops; [5]) to gain a better sense of how the system may change over time, and allow for the assessment of interventions under uncertain conditions through simulation modelling. Through the participatory modelling workshops and the engagement of experts from across the food system, a broader range of factors that influence AMR were identified and provided further insight into how the various parts of the system may interact [5]. Analysing experts' statements also gave insight into the current states of the components and relationships in semi-quantitative indicators (Chapter 3). Combining the views and opinions of a group of experts with data from the literature allowed for further understanding of the current states of the main factors in the system. The data found in the literature provided more detailed descriptions of the current states of the components and strengths of the relationships with quantitative or qualitative indicators, and expanded the available data for components and relationships in which the experts did not quantify. Alternatively, the experts provided insight into components or relationships in which data were not available and provided more context-specific information. Together, these two sources of data complemented each other to provide a better understanding of the system.

Current quantitative models of AMR are limited by the data that is available to inform the parameters, and they are limited by the current knowledge about the quantitative associations and relative contributions of the various transmission pathways [63, 64]. Using semi-quantitative modelling allowed for the inclusion of more aspects of the system than purely quantitative modelling techniques can account for, including areas in which data are not yet available, data are incomplete or patchy, or areas that are hard to quantify. Furthermore, since existing models of AMR are limited in the factors that they can include, they typically model small, isolated, parts of the system (e.g., a single hospital or a single farm) [63, 64], the interventions that are assessed using these models are also limited in scope and cannot adequately assess how the interventions may impact the broader system. Similarly, these models may not be able to account for unintended factors that may prevent the ability for an intervention to work. This FCM provided the first simulation model that, through the use of systems thinking, included more parts of the overall system that drives AMR in one unified model. Therefore, this model accounted for more of the complex interactions between different areas of the system and thus can better identify unintended consequences when interventions are put in place.

Qualitative methods have been used to try and better understand the more complex drivers of AMU, such as how and why people use and access antimicrobials (AMs) for themselves, their children, and their animals and the motivations behind prescriber behaviour [65-71]. Similarly, qualitative and participatory methods have been used to develop and assess interventions [72-74]. This type of research is important to tailor the interventions to the specific context and to work with populations to understand why an intervention may or may not work [72-74]. Therefore, FCMs may provide a tool for government and industries to explore how interventions may impact the system, test policy-implications, and aid in decision-making from a system-wide perspective, and allow for stakeholder input through the process to tailor the model to reflect their context. For example, government could explore potential unintended consequences of imposing taxes for AMs, such as how it may impact access to lifesaving treatment or nutritious food. Furthermore, FCMs could be used for testing interventions under various future scenarios (e.g., climate change) and could be used in tandem with other participatory methods, such as foresight methods [75] and scenario planning [76], to explore various scenarios with participant input. Qualitative and mixed methods research have been used to predict how the issue of AMR may develop in the future. For example, in Sweden, a group of experts were engaged to discuss what the European food system would need to look like for two interventions (taxation of AMs at point of sale and increased infection prevention and control measures) to be successful at combating AMR in the year 2050 under uncertain climate change conditions [77]. Another study used expert opinion as a tool to assess the uncertainty in the statistical projections of AMR based on historical data from the European Antimicrobial Resistance Network [78]. These highlight the benefit that experts provide to the research, especially when there is large uncertainty in the quantitative data.

Finally, the use of fuzzy cognitive mapping allowed for exploration of the system using metrics from network modelling, such as: centrality, indegree, outdegree, density, and hierarchical index. Centrality measures [57] allowed for the identification of highly connected and highly influential components, which may indicate areas where high-leverage interventions (interventions that may have wide-spread impact through the system) could be implemented [79, 80]. Density [62] and hierarchical index [62] measures highlighted how the system behaves and how outside influences (e.g., interventions) may impact the system. For example, the density of this model was extremely low, meaning that although there were 491 connections, this was comparatively small compared to the 4,095 potential connections that could occur between the 90 nodes [61]. This indicated that the system was not densely connected and therefore interventions may not have wide-spread influence in the system but there may be fewer unintended consequences. The hierarchical index was also very low, which indicated a democratic system; the system can be more easily manipulated by outside influences (e.g., intervention) [62]. These indicators provided great insight into the system behaviour and allowed us to learn more about where and how interventions may impact the system.

5.5 – Challenges and mitigation strategies

Creating a FCM of the complex system that drives AMR based off of an expert-derived CLD was an extremely beneficial exercise, however it did have its challenges, which are outlined below with how they were mitigated, to aid future public health research.

5.5.1 – Language and jargon

The first major challenge was keeping track and making sense of all the different language and jargon used within each methodology and modelling discipline. Being from an infectious disease modelling background, I was most familiar with terms used in this discipline of modelling, most specifically in compartmental modelling. When conducting the transcript analysis and delving into literature on systems thinking, many parallels between infectious disease modelling and systems thinking were noticed. When making the transition into FCM, things became unclear, with many different names for things with very similar meanings (Table 5.2). This use of varying language creates barriers between disciplines that could easily have conversations about modelling and systems dynamics if they were to understand each other's terminology.

Furthermore, confusion also occurs when the same words are used to described different things across disciplines. One major obstacle being the term "model". Model can mean different things to different people, depending on their background and expertise. For example, throughout this process a CLD was used and a concept map was created which are examples of visual models, a search for dynamic models of AMR and the broader system was performed, and a FCM, a semi-quantitative model, was created. This can cause confusion when trying to discuss results to audiences from different disciplines. For example, a 20% reduction in an FCM does not equate to 20% less AMs being taken per year (as might be the output of a quantitative dynamic model) but describes a relative change compared to its initial value, which is described by an associated level. Similarly, terms such as inference process, exist in multiple disciplines and have different meanings. In psychology, an inference process is the process a person goes through when trying to create a conclusion based on the given evidence and internal reasoning [81, 82]. In machine learning and artificial intelligence an inference process uses mathematical algorithms to sort and analyze incoming information (e.g., from a large dataset) to make deductions on how to sort and differentiate the data and provide an output based on how it was trained to interpret the data [83, 84]. In infectious disease modelling, inference is used when estimating parameters [85, 86]. In this case, the inference process in FCM Expert calculates how the components of the FCM change over each time-step based on how all the incoming relationships impact that component [18]. In all these cases, the overall idea is the same: an inference is essentially generating an output based on multiple different inputs. However, without outlining the separate definitions for each discipline, confusion can occur. Therefore, there is a need for separate terminology for different disciplines (e.g., inference process) but there is also a need for more inclusive language when portraying the same ideas (e.g., node vs factor vs component vs stock).

5.5.2 – Conducting a formal scoping review to inform the model

The second major challenge occurred during the literature review phase (Chapter 2) in which the breadth of data that was to be included was of much greater volume than anticipated. When creating a compartmental model, a useful first step is to research similar models (e.g., similar organism, similar transmission dynamics, similar population) to find well-formed models to use as a basis that can be adapted to fit your specific context. It was necessary to identify models to cover the various areas of the system, with AMR as part of the model but also beyond AMR (to include any micro-organisms) when models specific to AMR were not available. This led to many models being found and organized (e.g., by type, host, organism, and main features) to be able to determine what was available and where we might be missing parts of the system (Chapter 2). This proved to be a larger amount of work than anticipated, and since it provided a lot of insight into the modelling landscape of AMR and the One Health system, it was decided to publish this work to make it accessible to other researchers who may be wanting to undergo a similar process (Chapter 2). This process was helpful for understanding the current modelling landscape of AMR and would be a useful exercise when addressing other public health issues, and a scoping review methodology would be a beneficial method.

A similar process occurred for the scoping review for the data to inform the model (Chapter 2). The objective was to find data to parameterize a model (a quantitative model, most likely stock and flow, at the time) including the 91 nodes from the CLD. A formal scoping review is not common procedure when finding data to parameterize a compartmental model and therefore was not part of the initial process. The literature was searched, and the references and associated data provided in the literature (e.g., numerical indicators or quotations) were extracted to be organized at a later date. However, after searching the first few nodes, it was noticed that there was going to be a lot of data that would need to be sifted through and a formal procedure was required for collecting and organizing the data. Therefore, the search continued with a more formal search strategies, but the data were not organized until the search concluded. Thus, adding a significant amount of work that needed to be done after the search was completed and required the addition of a research assistant to sort and organize the data into a useable format (an excel database). Using data extraction forms, commonly used in scoping reviews, would have streamlined the process and would not have required a duplication of effort [87] .

Overall, to streamline this process and aid in writing and dissemination of the information, a protocol for two formal scoping reviews (one for the models and one for data to inform the model) should be created *a priori*, multiple reviewers should be used to reduce the amount of time required, and data extraction forms should be used to facilitate data extraction and organization.

5.5.3 – Doing an FCM *a posteriori*

Creating a FCM *a posteriori* provided additional challenges. FCMs are typically created based on expert input, in which experts discuss the system of drivers as well as provide estimates for the weights of the relationships and the activation values through interviews or other participatory methods (e.g., model building workshops) [9, 55, 56]. Therefore, they are solely expert-driven and every part of the model is informed by expert opinion. In this process, the structure of the FCM was created through expert opinion (the CLD [5]), however it was not "quantified" explicitly with the experts. Because the transcripts used came from a workshop in which the experts were not probed to provide insight into the strengths of the relationships [5], many relationships were mentioned without a weight (Chapter 3). In some instances, experts used linguistic indicators such as "*strongly*" impacts or "*very important driver for…*" but overall, these were few and far between (Chapter 3). Thus, by creating a FCM *a posteriori*, a lot of valuable information that could have helped to inform this model was missed.

There were also too many relationships to research in the literature without using a lot of resources and time (Chapter 2). However, the relationships in the FCM are very important to the system [9, 55, 56] and therefore getting access to better information to inform these is a priority. Not only do the stakeholders have tacit knowledge from their experiences within their field, but stakeholders also have access to or knowledge of where data does and does not exist. Therefore, stakeholders can also help identify other sources of data that can be used to enhance the model and aid in the literature review (Chapter 2). Engaging experts throughout the entire modelling process, either in a single workshop to outline the structure and quantify it, or through a series of workshops in which experts are engaged at multiple time-points throughout the process (e.g., create a CLD and then later quantify the model) should be common procedure. A proposed process is presented in Figure 5.4. Another option would be to present the current FCM to the experts and allow them to refine the model. For example through a follow-up set of interviews or workshops with the experts from the initial workshop [5] in which they would be asked to explicitly provide estimates for the current states of the main components, and strengths and directions of the relationships.

5.6 – Recommendations for future participatory and semi-quantitative research to address complex public health issues

One way to advance research in this specific field would be to further refine model with experts within and outside the disciplines that were originally engaged. Using expert knowledge to better inform the relationships could create a stronger model for use in decision-making. Experts should not only be engaged in describing the structure of the system (e.g., creating the CLD) but be explicitly asked to outline the current states of the components and the strengths and directions of the correlations of the relationships from their personal knowledge and opinion. This would provide estimates for these values and context-specific examples to inform the model that may not be able to be identified in the literature. The FCM created *a posteriori* contained many assumptions for relationships which did not have data to inform them. Therefore, expert opinion could be used to fill these gaps. Also, with the number of relationships involved, this would require a significant amount of resources and time to research estimates for the weights for the relationships within the literature, and this may not be feasible. For example, there were 491 relationships in my FCM, which was not densely connected. In contrast, a workshop with multiple experts could populate the model from multiple perspectives in a much shorter amount of time (e.g., a two or three day workshop format). Finally, experts could give insight to the most important drivers and relationships to direct future research (e.g., a literature review) to ensure these relationships are well-defined. Overall, engaging experts to define the values for the components and especially the relationships could strengthen the model by decreasing the number of assumptions and informing the model from a first-hand local perspective.

Expert engagement, as well as mathematical methods, to simplify the model would also create a more refined model [88, 89]. This can involve mathematical methods that remove weak or redundant pathways and organize the FCM to reduce the amount of uncertainty without losing the complexity that it captures [88, 89]. Similarly, further discussion with experts can be conducted to determine the most important pathways and relationships that could be removed [71,72].

Performing participatory-modelling workshops and engaging experts from different contexts (e.g., from high income vs low- and middle-income countries) could also allow us to better understand how AMR may develop and spread within different areas of the world. Current research has used participatory approaches to understand the underlying system in Europe, South-East Asia, New Zealand, and Tanzania [91-93], but has yet to use expert knowledge to being to "quantify" the system to be able to use it for simulation purposes. However, through fuzzy cognitive mapping and the engagement of experts from various backgrounds and contexts, we could gain a better understanding of how the underlying system of drivers of AMR behaves in multiple contexts, which would enable us to better understand how to address this issue at a local or national scale. By creating and contrasting FCMs from different contexts (e.g., the drivers of AMR in a high income vs low- and middle-income context), we can see if there are similarities in which global action can address this issue (e.g., reduce AMR) or if context-specific interventions need to be created. There is current interest in systems approaches to address AMR, with a call for global action to create a "global systems map" and global sharing of data to help better understand the system of drivers of AMR and the relative contributions of the various transmission pathways [94]. Fuzzy cognitive mapping could provide a method to collect data from experts across the globe and begin to map the system at a global scale.

The second recommendation for future research, beyond AMR, is to develop a procedure for FCM building to address other complex public health issues (such as presented in Figure 5.3). Fuzzy cognitive mapping provides a promising way to better understand the behaviour of the system that drives complex public health issues by: 1) including a wider range of factors and relationships identified by experts from within the system; and 2) allowing us to account for specific contextual factors, thus allowing for the assessment of system-wide impacts when creating policy. It is especially useful when addressing health issues in vulnerable or marginalized communities by engaging members of these communities. For example, fuzzy cognitive mapping has been used to model the drivers and outcomes of diabetes and cervical cancer in Aboriginal communities in Canada [95, 96]. Using participatory approaches allowed members of the community to provide input into the inner-workings of their community, the challenges they face, and the way the community members think, feel, and behave from a first-hand perspective [95, 96]. Therefore, these practices could be adopted to model AMR and other complex systems in marginalized communities, which may have different perspectives, barriers, and drivers that underline their motivations and behaviour, and may not be captured in current research.

Finally, this research has shown that by using qualitative methods and tapping into participants' tacit knowledge and real-world experiences, we can learn more about the underlying complexity and create a better understanding of how the system works, where to intervene, and how and why certain policies may or may not work when put into place. Relying on quantitative methods, although still useful at a more microscopic scale (e.g., within-host, within hospital, local level), are unable to capture the more complex interactions and are limited by data availability [63, 64]. Quantitative epidemiological models to address public health issues at a population level are not yet able to accurately capture more abstract features that play important roles in the complexity, such as human thoughts, opinions, decisions, and behaviour, which are not necessarily inter-linked in predictable ways [63, 64]. Furthermore, the data required to create quantitative models are not currently available, especially in low- and middle-income countries [1, 23, 25, 63, 64, 97, 98], and thus other forms of research are required to understand the system. Although, qualitative methods, such as intervention mapping [99], foresight methods, [75] and scenario planning [76], have shown great insight into what experts believe are useful interventions, what would or would not work in real life, consequences that could occur within their sectors, and what the world would need to look like for certain interventions to work [72-74, 91], there is still a need for more inclusion of qualitative research in public health research [100].

5.7 – Conclusion

Fuzzy cognitive mapping is a novel and powerful method with application to AMR and other complex public health issues. This semi-quantitative modelling technique combines the powers of participatory methods and stakeholder engagement with empirical data, which can complement each other to create a well-informed model from a transdisciplinary and systems perspective to be used for decision-makers, policy-analysts, and future planning. This paper highlighted that fuzzy cognitive mapping can help better understand the underlying system of drivers for AMR and allowed for the assessment of intervention from a systems perspective, accounting for potential unpredictable outcomes. It also highlighted that using novel methods for use in public health comes with challenges that could be mitigated during future use such as: becoming comfortable with the language; performing a formal scoping review; and engaging experts throughout the entire model building process. Finally, it highlighted that mixed methods can enable the use of wider ranges of data and the inclusion of more factors from within the system allowing for a more holistic view of the system, and provided recommendation for a more stream-lined procedure for implementing fuzzy cognitive mapping for use in future public health research. It was evident from this process that fuzzy cognitive mapping needs to be implemented as a participatory modelling method from the beginning stages of research and must be an iterative process in which stakeholders are an integral part throughout the entire model building experience to best capture the system in their context, tailor the model for their decision-making needs, and to be able to refine and validate the model throughout every stage. Stakeholders embedded in the system can provide incredible insights into the underlying drivers of the system and have integral tacit knowledge that needs to be utilized. Overall, through this example shows fuzzy cognitive mapping to be a powerful tool to better understand complex public health issues and be used for exploration of interventions and future scenarios.

5.8 – Tables

Table 5.1: A summary of the pros and cons for the fuzzy cognitive map (FCM) software that exist and reasons for using or not using them when creating a fuzzy cognitive map to describe the development and transmission of antimicrobial resistance in a Swedish food system context based on an expert-driven causal loop diagram.

SOFTWARE	PROS	CONS	USED/NOT USED (REASON FOR NOT USING)
FCM Expert[1]	• Can add activation values • Sophisticated scenario analysis • Can be refined with machine learning methods • Can import/export framework matrix	• Does not include analysis of the model features	Used • Created model • Performed simulation and scenario analysis
Mental modeler[2]	• User friendly • Visually appealing • Can analyze model features • Has scenario analysis • Can import/export framework matrix	• Does not allow for inputting of activation values • Scenarios only based on relationships	Used • Analyzed model features
iModeler[3]	• Visually appealing (can group components by theme with colour) • Can run scenarios • Create framework matrix that shows which have most impact in the short, medium, and long term • Can convert into quantitative simulation model (when data becomes available)	• Does not allow for inputting of activation values • Scenarios only based on relationships • Can't easily import model from other software or formats	Attempted to use but stopped due to lack of ability to add in activation values for components
FCM-Analyst[4]			Did not use • Could not access because could not find source to download software
FCM Wizard[5]			Did not use • Could not access because requires login
FCM Modeler[6]			Did not use • Could not access because could not find source to download software

FuzzyDANCES[7]			Did not use • Could not access because could not find source to download software
FCMapper[8]			Did not use • It was Excel-based which was not user friendly and had limited functions
FCM designer[9]			Did not use • Uses a Spanish interface
JFCM[10]			Did not use • Too specific to its one application (traffic analysis) • Requires knowledge of coding in Java
Comprehensive R Archive Network (CRAN): 'fcm' [11]			Did not use • Did not find online in initial search of software

[1]Nápoles G, Espinosa ML, Grau I, Vanhoof K. FCM Expert: Software Tool for Scenario Analysis and Pattern Classification Based on Fuzzy Cognitive Maps. Vol. 27, International Journal on Artificial Intelligence Tools. 2018.
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[11] Dikopoulou, Z., Papageorgiou, E., 2017. Inference of Fuzzy Cognitive Maps (FCMs). The Comprehensive R Archive Network (CRAN)

Table 5.2: Definitions for parts of a system or a model used in system thinking, dynamic modelling (stock and flow and compartmental) and fuzzy cognitive maps to display the overlap in language, as well as how these terms can be used in the context of antimicrobial resistance (AMR).

PART OF THE SYSTEM/MODEL	EXAMPLE IN THE CONTEXT OF ANTIMICROBIAL RESISTANCE	DISCIPLINE	DISCIPLINE SPECIFC NAME	ALTERNATIVE NAMES	DEFINITION
Factor	• Hospital • Physician • Patient • Antimicrobial • Farm • Slaughterhouse • Proportion of the population with a resistant infection	Systems thinking	Node	Element, factor	The individual part of the system.
		Stock and flow	Stock	Variable	Represents a part of a system whose value at any given instant in time depends on the systems past behaviour.
		Compartmental model	Compartment	State, variable	A division of a population into groups (compartments) based on each individual's infectious status.
		Fuzzy cognitive map	Component	Concept, elements, nodes	Variable (measurable) concepts that make up the important parts of the system.
Connection between factors	• The use of antimicrobials causes the development of antimicrobial resistance. • The amount of food produced causes the market price of food to change. • The access to nutritious food a person has is related to their ability to fight disease (immune status).	Systems thinking	Interconnections	Links	Relationships or the flow of information between the elements.
		Stock and flow	Flow	Outflow, inflow	Flows represent the rate at which the stock is changing at any given instant, they either flow into a stock (causing it to increase, inflow) or flow out of a stock (causing it to decrease, outflow).
		Compartmental model	Rate of transfer	Flow of elements, transition rate	The flow of individuals from one compartment to another.
		Fuzzy cognitive map	Interrelationships	Causal relationships, edges, edge relationships	The the amount of influence one component can have on another.

PART OF THE SYSTEM/MODEL	EXAMPLE IN THE CONTEXT OF ANTIMICROBIAL RESISTANCE	DISCIPLINE	DISCIPLINE SPECIFC NAME	ALTERNATIVE NAMES	DEFINITION
Current state of the factor	• The amount of food a country imports each year. • The number of hospital beds available in a country. • The amount of money spent on antimicrobials in food-producing animals in a year.	Stock and flow	Level		Represents a quantity of a stock existing at the point in time in which it was measured
		Compartmental model	Initial condition		A set of starting-point values belonging to or imposed upon the variables in an equation that has one or more arbitrary constants.
		Fuzzy cognitive map	Activation value		Numbers from the unit interval [0,1] assigned to the concepts to describe the state of the concept.
The value that describes the connection	• The connection between the patient and obtaining an antibiotic is determined by the physician's antibiotic prescribing rate • The connection between the animals on the farm and the slaughterhouse is determined by the number of days to market • The connection between the people who are exposed to resistant organisms through food and those who become infected is partially determined by the consumption rate.	Stock and flow	Rate		The rate at which the stock is changing at any given instant.
		Compartmental model	Parameter		A variable that represents the temporal progression of the number of individuals in each of the states of the system (e.g., transmission rate, contact rate)
		Fuzzy cognitive map	Weight		The amount of influence between components translated into quantitative values between -1 (high negative) to 1 (high positive) values.

5.9 – Figures

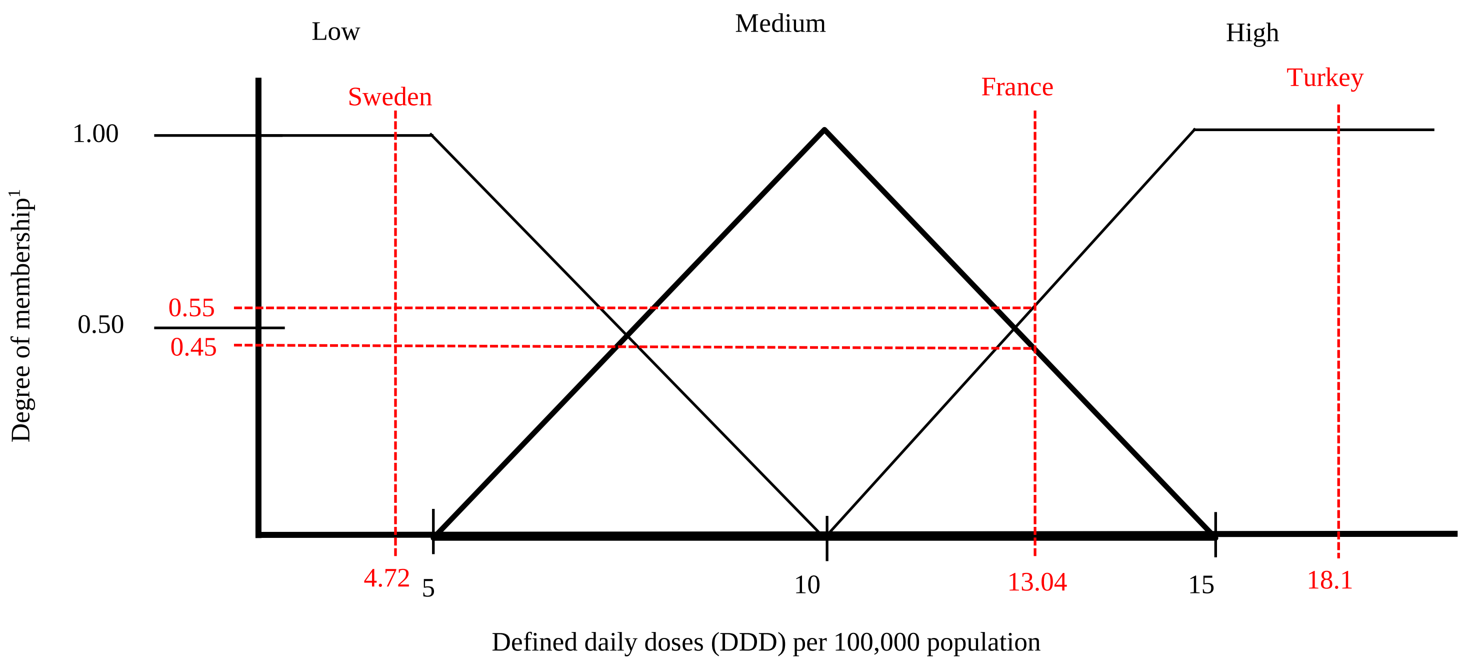

Figure 5.1: An example of how to use fuzzy logic to describe antimicrobial use (measured in daily defined dose (DDD) per 100,000 population) with Sweden, France, and Turkey as an example.

[1]Fuzzy logic uses "”degree of truth” as opposed to “true or false”, or Boolean logic (0 or 1). Therefore the degree of membership refers to the relative amount the factor belongs within each category. If the factor belongs fully to a category, it will have a degree of membership of 1.

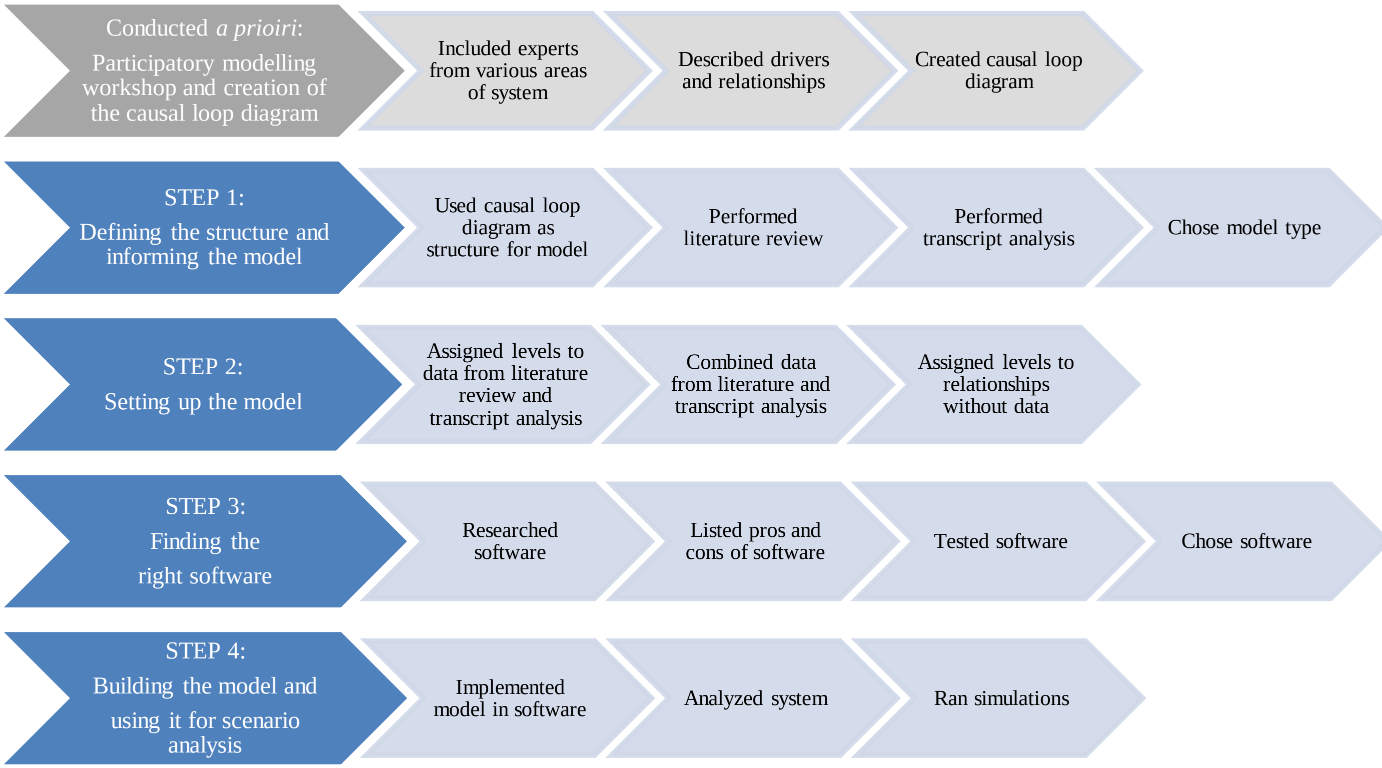

Figure 5.2: The steps taken when creating a fuzzy cognitive map to describe the development and transmission of antimicrobial resistance in a Swedish food system context *a posteriori* based on an expert-driven causal loop diagram. The grey boxes represent the steps that were done *a priori* to inform the structure of the fuzzy cognitive map but were not conducted as part of the model building process and the blue boxes represent the steps included in the model building process.

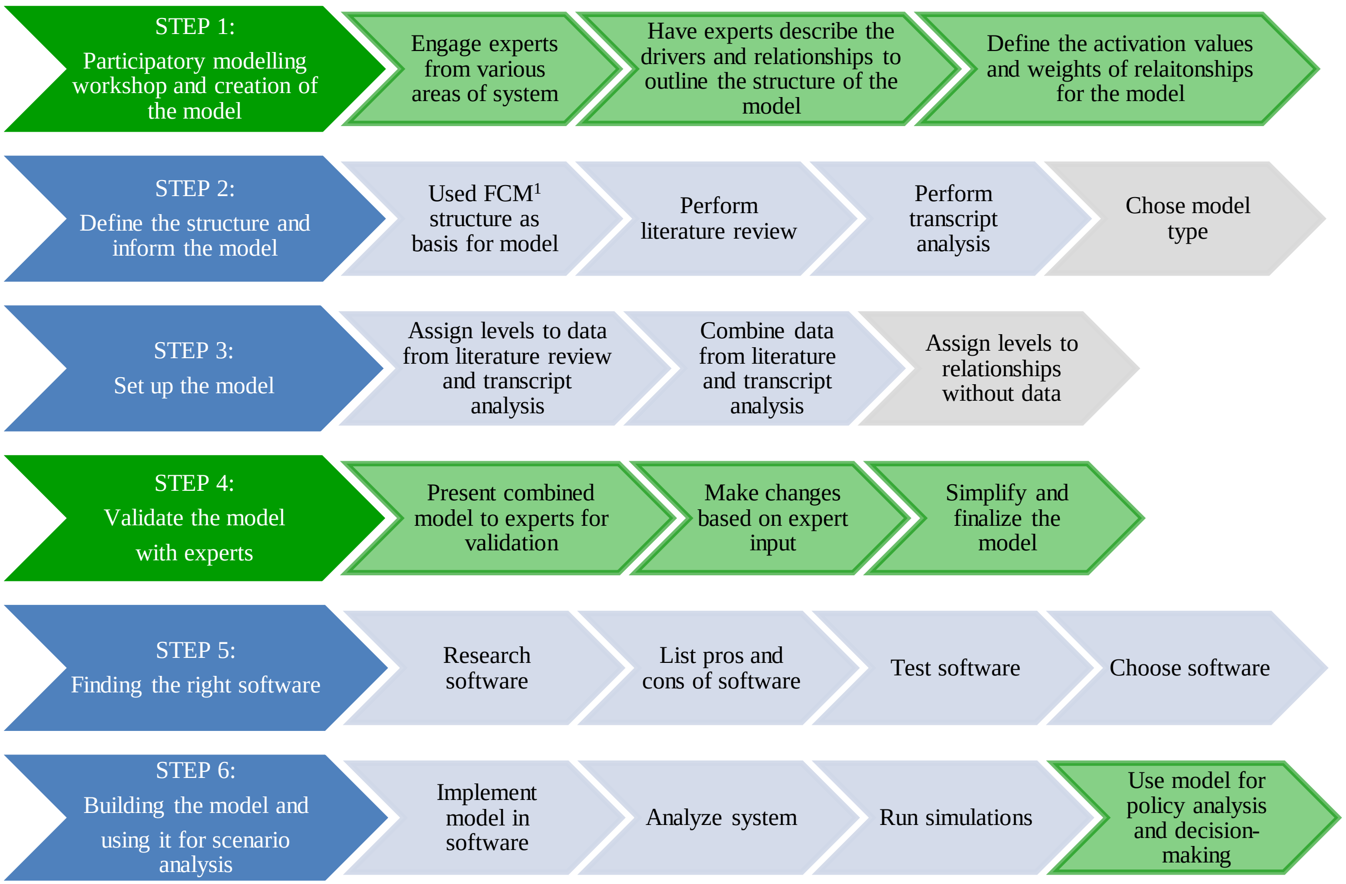

Figure 5.3: An outline of a proposed procedure for the process of creating a fuzzy cognitive map (FCM) using participatory modelling and literature which represents a refined version of the process that was conducted when creating a FCM of the development and spread of antimicrobial resistance in a Swedish food system context based on a participatory modeling workshop. The green boxes represent the new steps that were added to refine the original process (blue boxes). The grey boxes represent steps from the original process that are no longer required.

Chapter 6: Conclusion

6.1 – Overview

Antimicrobial resistance (AMR) has become one of the leading causes of death world-wide and has caused great health and economic burden [1-3]. There are many drivers of AMR within the human, animal, and the environment sectors, which are intimately interconnected [1-3]. However, current policy to address AMR are sector-specific and fail to account for factors in the broader system [3]. Therefore, this One Health issue requires systems thinking theory and could benefit from mixed methods dynamic modelling techniques to be able to adequately address the complexity and better understand the system of drivers of AMR. For this purpose, this thesis defined the evidence landscape to inform a broad One Health model of AMR in a high-income (Swedish) food system context, by identifying existing models and quantitative data from the literature (Chapter 2), extracting data from a participatory modelling workshop with experts from within the broad Swedish food system context (Chapter 3), and creating a semi-quantitative simulation model of the development and transmission of AMR in a Swedish food system context and applying it to assess the sustainability of select interventions to reduce AMR under climate change conditions (Chapter 4). Finally, this thesis provided a reflection on the process of using the novel method of participatory, semi-quantitative modelling to address AMR and its application for addressing complex public health issues (Chapter 5).

6.2 – Summary of key findings

This thesis identified a multitude of simulation models from various parts of the One Health system as depicted by experts in a prior study [4]. The models identified covered most of the major areas of the system (e.g., healthcare, agriculture, environment), however, they were not integrated to capture the system in one unified model (Chapter 2). Many of the AMR-specific models were human-focused, compartmental, and deterministic. They were also limited in scope and at very fine-level populations (e.g., one hospital emergency department, one species of animal on a single farm). The models did not capture the more complicated socio-ecological drivers identified by the experts from the participatory modelling workshop, such as human knowledge, experience, and associated behaviours, or complex drivers of political decisions and their implications [4].

There were also a wide variety of data, both quantitative and qualitative, to inform factors in a model of the emergence and transmission of AMR in a Swedish food system context (Chapter 2). Some of the factors were only able to be informed by qualitative data, especially the factors that were abstract and hard to quantify. For those that did have quantitative data, the data were often not in a format useable for many quantitative modelling techniques. Thus with the available data in the literature and the models that currently exist, it was clear that quantitative modelling would not suffice, but that semi-quantitative (mixed methods) modelling techniques could be able to make use of the data collected to capture the broader system.

Due to the limited quantitative data to inform many of the factors in the previously-created model structure [4], expert opinion was critical to infill missing data and help inform the model of the factors that drive AMR (Chapter 3). Knowledge from experts' personal and professional backgrounds provided insights (through semi-quantitative indicators) into the current states of the main factors that were identified by the experts during the participatory modelling workshop [4], and the strengths and directions of the correlations between the factors (relationships). Experts mainly used tacit knowledge (personal and professional knowledge and opinion) when describing factors, using language to indicate whether the state of a factor was either "a lot" or "a little". However, in most instances the experts described relationships without indication of strength. Overall, expert insight provided additional data to be used to inform a One Health model of AMR.

Together, the existing quantitative (Chapter 2) and qualitative (Chapter 3) data were enough to inform a semi-quantitative model of the development and spread of AMR in a Swedish food system (Chapter 4). The fuzzy cognitive map (FCM), consisting of 90 components and 491 relationships, was not as highly connected as it could have been (very low density; the number of connections compared to all of the possible connections [5]), meaning although the FCM is open to outside influence (very low hierarchical index [6]), interventions would likely not provide wide-spread change in the system. The FCM provided an opportunity to assess eight interventions (increased prevention and control measures, educational campaigns about proper antimicrobial use (AMU), antimicrobial stewardship (increased prevention and control measures and educational campaigns combined), increased trade regulations, reducing cost as a barrier to nutritional and sustainable food, enhanced technological advancements, addressing poverty and social inequities, and increasing trade regulation enforcement and compliance) as well as the effects of climate change. Most interventions were unable to enact a shift in the system and those that did have an impact on some of the indicators (e.g., AMU or illness), were unable to reduce AMR. The application of FCM to address AMR provided a novel way to model a complex public health issue from a systems lens, included a broader range of factors, and used participatory approaches to gain a better understanding of the system in a real-world and Swedish context.

The process of creating an FCM based on a participatory modelling workshop and literature search came with many challenges and learning opportunities, highlighting the need to engage experts throughout the model building process (Chapter 5). Although the participatory modelling workshop provided a basis for the model though the creation of a causal loop diagram [4], it would have been beneficial to quantify the model with the expert input [7]. This would have provided a fuller description of the current states of the components and the weights of the relationships from the experts' tacit and explicit knowledge. The experts could also have provided input about the data landscape, such as available data sources, concrete examples, or where data may not yet exist, to help tailor the literature review. Overall, through outlining the steps taken, the associated barriers and mitigation strategies, and the benefits of using FCM to model AMR, this thesis highlights the importance of expert engagement and advocates for using expert opinion to explicitly inform models that represent complex public health issues as experts provide insight into the context being explored, and can provide input into elements of the system for which external data does not exist. Therefore, this thesis also provides recommendations for a refined process for the application of this method to public health research.

6.3 – Contributions to the literature and implication for public health research

This thesis provides a novel methodology for modelling AMR from a systems and One Health lens that combines participatory methods and empirical data from the literature. The scoping review (Chapter 2) provides a comprehensive list of existing models of AMR and quantitative and qualitative data that currently exists in the literature to inform a model of AMR in Swedish context, and places it within the One Health system. Existing scoping reviews of dynamic models of AMR tend to be situated within one sector (e.g., human, agricultural and aquaculture, or wildlife models), and are often aimed at describing purely quantitative models [8-10]. Two of the most current scoping reviews for models of AMR were more inclusive and identified models for humans and animals within their reviews [10, 11]. However, these reviews highlight that many of the models that currently exist for AMR are still limited to a single sector and represent small sections of the system (e.g., a single hospital or farm) and therefore provide limited use for One Health modelling [10, 11]. Therefore, by expanding the scoping review to include models of organisms beyond AMR-specific organisms and the inclusion of qualitative and mixed methods models, this thesis compiles a wider variety of models that can be adapted for modelling AMR and provides one convenient and organized place to view these models.

This thesis also provides a comprehensive review of the evidence landscape, describing where quantitative data currently exists and where there are gaps in the literature for the main drivers of AMR that need to be addressed before empirically-driven models can be created (Chapter 2). This thesis provides a framework for future One Health model building in which scoping reviews may need to become the norm. Due to the complexity of One Health issues there are a typically a large number of factors that need to be included in the model [12, 13]. Therefore, scoping reviews to collect data to inform these factors are gaining in popularity as a first step in the model building process [14-16]. This methodology can be used to help collect data to inform models of AMR in other contexts as well as other complex public health problems. It also provides an organized and detailed description of the state of many health, agricultural, and environmental factors that could be included in the systems that drive other public health or animal health problems (e.g., the level of healthcare resources, the burden of illness, the type of agricultural practices, the level of the population that is vulnerable).

This thesis also provides evidence that quantitative models may not be the most appropriate way forward, and that focusing research towards mixed methods or qualitative methods may provide more insight into the system than quantitative methods can, at least at this current time before data becomes more widely available (Chapter 2). A recent scoping review was conducted to identify the research gaps in the current understanding of AMR development, transmission, and impacts across the human-animal-environment interface and identified 300 research gaps, with most gaps being in human health, environmental health, animal health, food and feed, and plant crops [17]. These gaps included a lack of surveillance data, but also limited studies, models, and understanding of the interface between reservoirs [17]. Similarly, Allock et al. found that on the human side, despite the growing recognition of AMR as a threat to health, there are considerable limitations in the understanding of the current burden of AMR as well as the determinants at a population level [18]. Many of the current mathematical models that exist for AMR are theoretical, in that they do not contain supporting data to inform or validate them [12]. Therefore, despite the number of models that exist, there is still a large gap in the knowledge for the underlying mechanisms and data to inform the models, which thus limit the usefulness of these models [12]. Therefore, it is clear that the data required to model the system that drives AMR, and therefore assess interventions, are not currently available and other methods may need to be used. Whole genome sequencing provides a promising way to enhance the understanding of the transmission of AMR and quantifying the transmission pathways (e.g., relative contributions of the various pathways to overall resistance), however, this research is not yet widely accessible [19-22].

Qualitative methods have shown promise in better understanding the underlying system [4, 23, 24], major drivers such as human motivation, decision-making, and behaviour [25-31], and the current discourse around AMR and AMR policy [32-37]. A scoping review on how the social determinants of health, equity, and gender have been included in studies about AMR revealed that these major underlying factors are currently missing from research in this field [38]. Therefore, through the inclusion of qualitative research, we may be able better understand how and why people use antimicrobials, health seeking behaviour for themselves or their pets or food-producing animals, how prescribers make decisions and understand their prescribing behaviours, and how people think and feel about AMR, which will help to understand the underlying system of drivers of AMR.

The data collected in Chapter 2 and Chapter 3 of this thesis were combined to inform a semi-quantitative simulation model of the development and transmission of AMR in a Swedish food system context (Chapter 4). To the best of my knowledge, this is the first attempt to create a simulation model with the entire One Health system that drives AMR in one unified model that accounts for the complex socio-ecological, political, and economic drivers that can influence AMR. The use of fuzzy cognitive mapping allowed for the combination of quantitative and qualitative data to expand the system beyond the scope that currently exists in models found in the literature. This model goes beyond the creation of a causal loop diagram (CLD), as was done in Europe, South East Asia, and New Zealand [4, 23, 24], and attempts to associate data, both from literature and expert opinion, to each of the nodes and relationships to be able to use the model for simulation modelling. Using expert knowledge and participatory approaches as a starting point in creating and informing the model helped fill in the data gaps identified in the literature review (Chapter 2), refined the literature search by providing concrete examples to search (e.g., 3-D printed food as an example for new and emerging food), provide insight into where data may or may not be found, and helped tailor the model to the local context (Chapter 3). FCMs are typically based solely on expert input [7,39], however, the inclusion of literature expanded the available data, provided detailed numerical inputs to help refine the assigned levels, and filled in gaps in parts of the model that were not quantified by the experts. Therefore, mixed methods research provided the means to integrate expert tacit knowledge and empirical data to create a well-informed model.

FCMs can capture the complexity, and the non-linearity of the various interconnections that may not have been quantitively measured through traditional epidemiological methods (e.g., logistic or linear regression) [7, 39]. Therefore, the simulation model in this thesis encompasses the broader system and provides a decision-making tool that can be used to assess interventions, policy implications, and other future scenarios while accounting for potential unintended consequences or unforeseen interactions that could occur throughout the system. Quantitative models that are currently being used to assess interventions to reduce AMR are done so in a sector-specific (siloed) manner and are usually at a very specific setting (e.g., in a hospital or on a single farm), and are unable to account for the broader system [11, 12]. For example, a scoping review of dynamic models of AMR found that 90% of the models included assessment of interventions such as decreasing AMU or changing the antimicrobials being prescribed, policy aimed to reduce AMU, and increasing hygiene and infection prevention control measures [11]. However, due to the limited scope of the models [11], the ability to assess these interventions impact on AMR in the broad system is not possible, and due to the limited data available to inform the models [11], the confidence in the intervention performance is also limited. The FCM presented in this thesis provides a flexible tool that has the ability to be refined and expanded with continued participant engagement and data availability and can be tailored to ask specific questions and explore different scenarios and thus can become a powerful tool for AMR research and exploration. Furthermore, other qualitative methods can be of great use to assess interventions and to gather information about how or why they may work (before implementation) or why they did or did not (after implementation). Methods such as intervention mapping [40] or scenario planning and foresight methods [41-43] allow stakeholders to discuss various aspects of the intervention and how it may impact their context. Finally, research using qualitative theories such as constructionist perspectives to address social problems [44] could help to better understand how the population views the social problem of AMR, how it is being portrayed in in the media and by the politicians or the science community, and how the general population thinks and feels about it, and why current actions are not yet able to combat the impacts of AMR.

Finally, this thesis provides an outline of how to create a FCM of a complex public health issue (AMR) to highlight its usefulness and advocate for future use of mixed methods research (Chapter 5). FCMs have been used to address modelling complex systems [45] and have been used in many disciplines to model phenomena such as complex social [46], strategic [47], and financial systems [48-50]. However, use for public health is limited [51-53] making it difficult to find examples to use as a basis for applying this method in a public health context. These FCMs are also solely expert driven [45-53], and therefore the method to integrate data from the literature was not discussed. Through sharing the details of the process taken and the challenges that had to be overcome, this thesis provides a useful tool for future researchers to learn from as: 1) to not repeat mistakes; 2) to refine the process; and 3) to eventually create a well-defined procedure for the use of FCM in public health research. Through the sharing of experiences of applying a novel method to a public health context, this thesis can promote the necessary conversations to be initiated for disciplines to be crossed in order to share knowledge and promote transdisciplinary collaboration.

Overall, by highlighting the benefits of fuzzy cognitive mapping and how the engagement of experts can widen the understanding of the complex system that drives AMR, the largest contribution that this thesis provides to advancing public health research is to help advocate for the inclusion of transdisciplinary, participatory, and qualitative methods in the modelling of AMR. Although quantitative modelling and traditional epidemiological techniques provide detailed descriptions of the associations between factors, they are currently unable to account for the complexity of the interactions, unpredictability of the real-world, and capture the breadth of factors within the system [11, 12]. However, the technology, funding, and compliance does not yet exist to report, collect, and share the detailed quantitative (e.g., surveillance) data required to model the system in purely quantitative terms, especially in low- and middle-income countries [11, 12, 54-58]. However, even if it did exist, quantitative models would not yet be able to address the underlying socio-ecological drives such as human decision-making and behaviours [7, 39]. Although quantitative models can provide an in-depth understanding of individual parts of the system from a biological level, it does not allow for an understanding of how these pieces fit together to drive AMR throughout the system. Therefore, when assessing interventions, although the intervention may appear to reduce AMR within the model in the context in which it is being assessed, it could in reality be: a) missing underlying factors that may not allow the success it had in theory (e.g., compliance, competing interest, motivation); and b) creating negative impacts in other parts of the system (e.g., unintended consequences). For example, in a scenario planning workshop with experts from Sweden [43], the taxation of antimicrobials was said to be able to adequately reduce AMU in Sweden, however, it could reduce accessibility to those who cannot afford antimicrobials when truly needed, which could lead to increased deaths due to treatable illnesses or cause a shift to black-market sales or illegal trading of antimicrobials [43]. Thus highlighting that understanding the system as a whole is essential to be able to adequately address AMR. Qualitative methods can allow for the inclusion of stakeholders from various disciplines and facilitate conversations across sectors, leading to a better understanding of how the individual parts of the system fit together. Therefore, the mixed methods approach used to model the One Health system that drive AMR provided a broad description of the system of drivers with expert input as well as empirical data to create a more well-defined and systems view of AMR in the Swedish food system context.

6.4 – Limitations

Due to the complexity, breadth, and novel methods used, this thesis does have some limitations. The main limitation of the scoping review (Chapter 2) was due to the broad nature of the nodes that were to be searched. Creating search strings to capture nodes in their entirety sometimes proved difficult; for example, consumption of non-animal based food products can include fruits, vegetables, nuts and seeds, grains, etc. Also, there were nodes that were hard to define in quantifiable terms, such as consumer behaviour, diverse experiences, culture, and trust. Thus, it is likely that relevant data were missed, meaning the model is less specific and may contain more uncertainty than our actual collective knowledge base. It would be beneficial to work with experts to refine and properly define these nodes in quantifiable terms to aid in the search process. In qualitative participatory research, the participants should be engaged through the entire research process, and it should be an iterative process between data collection, data analysis, and expert validation [59, 60]. However, due to the COVID-19 pandemic, plans to interview experts and allow them to review and provide further input did not occur. Furthermore, certain individual characteristics would not be possible to capture in a population-level model at a national level due to the wide differences that occur at the individual level. For example, an individual's cultural and educational background along with their past experiences can greatly shape how they view different aspects of the system, such as: what they eat, how they access the healthcare system, their trust in doctors and medicine, etc., and this can then shape their exposures and risk of AMR [4]. To model these factors would require individual-level modelling techniques such as agent-based models [60, 61]. For example, one agent-based model studied how price and individual knowledge impact food decisions [62]. Future research may be able integrate semi-quantitative and participatory approaches with individual-based modelling.

The analysis of the transcripts from the participatory modelling workshop was conducted as a secondary analysis with the goal of identifying semi-quantitative indicators from expert statements, which lead to two limitations (Chapter 3). First, as it was not the main goal of the workshop, experts were not encouraged to "quantify" the nodes and relationships during the discussions and group model building process. Therefore, the data collected were the product of the conversations that took place but were not deliberately asked of from the participants. This was a missed opportunity to get richer descriptions of the current states of the nodes and strengths of the relationships from participants' tacit and explicit knowledge. Traditional fuzzy cognitive mapping engage experts throughout the process and work with the experts to provide estimates for the weights of the relationships and the current states of the components in linguistic terms [39, 45-53]. Therefore, the experts can explicitly provide information to inform the model from their tacit and explicit knowledge. The experts can also refine the model, provide insights into the most important factors and relationships, and provide insight into details from a local context perspective. Future research should not only create the structure of the system, but inform the model with expert input.

Secondly, the coding and extraction of the data from the transcripts was done with a relatively strict coding scheme to fit the overall objective to use the data to inform the semi-quantitative model. Therefore, this could have limited the scope of the data identified. However, framework analysis is a method that has been adapted for qualitative research to be used to answer specific questions [64] and provides a pragmatic, flexible, rigorous approach for data analysis [65]. Furthermore, using a framework matrix allowed for the ability to easily integrate the qualitative data from the transcripts with the data found from the scoping review. Even with this strict coding framework, the interpretation of the experts' statement was still subjective and therefore could have been influenced by internal biases. Qualitative research is criticized for the subjective nature of the data interpretation [66], and therefore there are certain methods to help to reduce bias, such as intercoder reliability [66] and triangulation [67]. Intercoder reliability was conducted with two researchers to determine the data were assigned to the appropriate level (Chapter 2). The data from the transcript analysis were also integrated with data from the literature search (triangulation) for inclusion in the FCM (Chapter 4) which also helped to minimize the impacts of personal bias.

The use of fuzzy cognitive mapping provides some inherent bias in the methodology, that was exacerbated by the procedure taken in this thesis (Chapter 4). One of the main criticisms of FCMs is that there is too much emphasis placed on the causality in the relationships defined by the experts, even if true causality does not exist [68, 69]. This was further limited by the large uncertainty around the strengths of many of the relationships because they were not explicitly search for in the literature or stated in the transcripts. Therefore, this added uncertainty to the model and limited the ability to assess the impacts of the interventions. It was clear from the sensitivity analysis and scenario analysis that the strength of the relationships can have large impacts on the system and therefore further research is needed to better define these relationships. This could be through further expert engagement, as mentioned above. However, other systems dynamic tools, such as behaviour-over-time graphs, graphical functions, and structure-behaviour pairs could be used to look deeper into the underlying structure of the system, identify patterns in the relationships, and help to better understand the relationships that were not clearly defined [70-72]. For example, graphical functions look to quantify the effect between non-linear components that are hard to measure by graphing them against each other (e.g., as AMU goes up, AMR goes up) compared to graphing them over time (e.g., AMU increases over time and AMR increases over time) [70-72]. Similarly, structure-behaviour pairs aim to connect the behaviours over time with the underlying systemic structures [70-72]. For example, if AMU increases over time and AMR increases over time, this suggests a reinforcing loop. Alternatively, if AMU increases over time but disease decreases over time, this suggests a negative feedback loop. These tools could also verify that although the relationships may not in fact be “causal”, a relationship or association does exist between the factors, even if there are intervening variables that may not have been identified. Therefore, future research could break down and analyze the individual relationships to better inform the weights for the relationships in the FCM.

It was also apparent from the analysis of the system that there were either missing relationships or feedbacks, or the strengths of some of the relationships were not accurate, within the model created (Chapter 4). This was evident because when the system was simulated over time, AMR became extremely high in all parts of the system even though the literature and experts expressed that AMR in Sweden is relatively low (Chapter 2 and 3). Similarly, the interventions, although able to alter many of the drivers of

AMR, were unable to reduce resistance in the system. This was most likely due to way in which the original CLD was built [4]. Since the goal of the participatory workshop was to identify the drivers of AMR, there were a lot of factors aimed at driving (increasing) AMR, however, less attention may have been paid to the factors that may reduce AMR. Expert engagement and further refinement with the experts could improve the model. However, other systems tools, such as systems archetypes and structure-behaviour pairs could also help to analyze the system [71-73]. Systems archetypes aim to understand the underlying systemic structures that are working to generate an issue (e.g., AMR) [72, 73]. This tool could be used to analyze the current FCM to identify the problem areas that are causing AMR to increase, and can be used to suggest ways in which these issues could be fixed [72, 73]. Structure-behaviour pairs, as described above, could be used to identify missing feedback loops [70-72].

Overall, the methods in this thesis took place within the context of the Swedish food system. The experts engaged were from Europe, with many from Sweden and northern Europe. Therefore, the system that was defined based on the CLD [4], which served as the structure for the model and the basis for the literature search, was from a Swedish perspective. The experts in the participatory modelling workshop described Sweden as an affluent and peaceful country with a culture of obedience, compliance, trust in political figures, and high regard for public health and socialism [4]. Sweden also has many regulations in place that limit AMU and promote animal-welfare friendly farming practices [4, 74, 75]. Therefore, Sweden may not be representative of the average country. This can limit the generalizability of the findings and therefore it is unclear if this model can be used to model other high-income contexts or be able to accurately reflect other contexts (e.g., low- and middle-income countries). In general, participatory approaches are used to define and tailor the research to the local context [76, 77], and therefore the results of this research are context-specific and further research will need to be conducted to expand the generalizability of this model. This could include conducting FCM-building workshops with experts from other contexts (e.g., other high-income countries to test the generalizability to other high income countries and to low- and middle-income countries to assess the generalizability globally) and comparing and contrasting the model structure and behaviour using simulation modelling and systems dynamics tools.

6.5 – Recommendations for future research

This thesis highlights that the use of participatory methods, systems and One Health approaches, and FCM can provide great insight into the system that drives AMR in a Swedish food system context. Using these methods broadened the scope (compared to current models) by allowing for the inclusion of more aspects of the system that purely quantitative modelling techniques could not account for, including areas in which data are not yet available, data are incomplete, or areas that are hard to quantify. Through network analysis and simulation, the FCM provided insight into the structure and behaviour of the system (e.g., that it is not densely connected and is open to intervention), and helped to gain a better sense of how the system may change over time. Also, the FCM provides a tool to be used for simulation modelling and scenario analysis from a holistic, systems lens. However, this was a first attempt at creating a model of this breadth and therefore requires further research to refine the model. To improve this FCM, further expert engagement and participatory modelling workshops to simplify and refine the structure of the system as well as explicitly define the activation values (initial states) and weights of the relationships is required. Further research is also required to be able to explicitly incorporate economical drivers and impacts to be able to assess how money impacts the system. To expand the understanding of the systems that drive AMR in other contexts, participatory FCM-building workshops should be performed in other high-income and low- and middle-income contexts. These FCMs can then be compared and used for decision-making and policy analysis to determine if interventions behave the same within the various contexts or if context-specific interventions are required to adequately address this issue. Furthermore, a proper procedure for the process of building a FCM using participatory and literature input should be created and accessible for use for other complex public health problems. This method could help advance research and understanding in other areas of public health. Finally, this thesis provides evidence and advocates for the wider inclusion of participatory qualitative methods to address complex public health issues such as AMR as they provide a broader understanding of the system and can provide great insight into the underlying drivers of the issue from a local perspective.

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Chapter 5:

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APPENDICES

Appendix A: Additional Tables – Chapter 2

Table A1: Search strings used in the scoping review for the different types of existing models across various parts of the broader One Health system.

Model type	Search strings used
Mathematical models pertaining to the transmission of pathogens between humans, animals, and their environment	model AND disease transmission AND (human OR cattle OR chicken OR swine OR pig OR environment OR companion animal OR cat OR dog) (infectious disease model OR simulation model) AND One Health (infectious disease model OR simulation model) AND food-borne (infectious disease model OR simulation model) AND (hospital OR community OR on-farm OR abattoir OR veterinary hospital) (infectious disease model OR simulation model) AND (E. coli) AND (hospital OR community OR on-farm OR abattoir OR veterinary hospital)
Mathematical models of AMR transmission or emergence	model AND antimicrobial resistance AND (humans OR animals OR One Health) model AND antimicrobial resistance AND (human OR cattle OR chicken OR swine OR pig OR environment OR companion animal OR cat OR dog) (infectious disease model OR simulation model) AND antimicrobial resistance AND One Health (infectious disease model OR simulation model) AND antimicrobial resistance AND food-borne (infectious disease model OR simulation model) AND antimicrobial resistance AND (hospital OR community OR on-farm OR abattoir OR veterinary hospital) (infectious disease model OR simulation model) AND (antimicrobial resistance OR resistant E. coli) AND One Health (infectious disease model OR simulation model) AND (antimicrobial resistance OR resistant E. coli) AND (hospital OR community OR on-farm OR abattoir OR veterinary hospital)
Models of AM decay and residue build up in waste, waste-water, and other settings	model AND antimicrobial decay model AND antimicrobial decay AND (environment OR water or waste water OR river OR effluent OR farm) model AND antimicrobial resistance AND (environment OR water or waste water OR river OR effluent OR farm)
Economic models of agriculture and the food system	model AND consumer demand AND food (economic OR supply-demand OR consumer demand) AND model AND (food OR chicken OR beef OR pork OR fish OR vegetables OR fruit)
Economic models of health systems	model AND economic AND health*

Table A2: Search strings used in the scoping review the data sources and evidence to inform the 91 nodes that represent the major factors that drive AMR in the Swedish food system.

Node	Search strings
(Terrestrial) On-farm AM use	(Farm OR agriculture OR cow OR pig OR chicken) AND (Antimicrobial OR Antibacterial OR Antibiotic) AND (Use OR usage OR Consumption) AND (Sweden OR Europe)
Access to AMs outside of the system	(Antimicrobial OR Antibacterial OR Antibiotic) AND (without prescription OR non-prescribed OR non-prescription OR self-medication OR unregulated) AND (Sweden OR Europe)
AM use in companion animals	(Companion Animal OR pets OR cat OR dog) AND (Antimicrobial OR Antibacterial OR Antibiotic) AND (Use OR usage OR Consumption) AND (Sweden OR Europe)
AM use in plant agriculture	(Crop OR agriculture OR fruit OR vegetable) AND (Antimicrobial OR Antibacterial OR Antibiotic OR pesticide OR herbicide) AND (Use OR usage OR Consumption) AND (Sweden OR Europe)
AM use in wildlife	(Wild life OR wild animal) AND (Antimicrobial OR Antibacterial OR Antibiotic) AND (Use OR usage OR Consumption) AND (Sweden OR Europe)
Amount of imported product	Import AND (food OR meat OR fruit OR vegetable OR chicken OR beef OR pork OR fish)AND (Sweden OR Europe)
Amount of product in the domestic market	(Production OR avail*) AND domestic AND (food OR meat OR fruit OR vegetable OR chicken OR beef OR pork OR fish) AND (Sweden OR Europe)
Animal density	Animal density AND (Sweden OR Europe)
Animal welfare/stress	Animal welfare AND (Sweden OR Europe)
Aquaculture AM use	(Aquaculture OR aquatic OR fish) AND (Antimicrobial OR Antibacterial OR Antibiotic) AND (Use OR usage OR Consumption) AND (Sweden OR Europe)
AROs in companion animals	(Companion Animal OR pets OR cat OR dog) AND (Antibiotic OR Antimicrobial) AND (Resistance OR resistant) AND (infection OR death OR prevalence OR incidence OR susceptibility OR isolate OR surveillance) AND (Sweden OR Europe)
AROs in food products	(Food OR meat OR fruit OR vegetable OR chicken OR beef OR pork OR fish) AND (Antibiotic OR Antimicrobial) AND (Resistance OR resistant) AND (prevalence OR incidence OR susceptibility OR isolate OR surveillance) AND (Sweden OR Europe)
AROs in food-producing animals	(Farm OR agriculture OR cow OR pig OR chicken) AND (Antibiotic OR Antimicrobial) AND (Resistance OR resistant) AND (infection OR death OR prevalence OR incidence OR susceptibility OR isolate OR surveillance) AND (Sweden OR Europe)
AROs in humans	Human AND (Antibiotic OR Antimicrobial) AND (Resistance OR resistant) AND (infection OR death OR hospitalization OR prevalence OR incidence OR susceptibility OR isolate OR DALY OR surveillance) AND (Sweden OR Europe)
AROs in imported food products	(Food OR meat OR fruit OR vegetable OR chicken OR beef OR pork OR fish) AND (Import* OR foreign) AND (Antibiotic OR Antimicrobial) AND (Resistance OR resistant) AND (prevalence OR incidence OR susceptibility OR isolate OR surveillance) AND (Sweden OR Europe)
AROs in plant agriculture	(Crop OR field OR plant OR fruit OR vegetable) AND (Import* OR foreign) AND (Antibiotic OR Antimicrobial) AND (Resistance OR resistant) AND (prevalence OR incidence OR susceptibility OR isolate OR surveillance) AND (Sweden OR Europe)
AROs in wildlife	(Wild life OR wild animal) AND (Antibiotic OR Antimicrobial) AND (Resistance OR resistant) AND (infection OR death OR prevalence OR incidence OR susceptibility OR isolate OR surveillance) AND (Sweden OR Europe)
Chronic, non-communicable diseases	(Chronic OR non-communicable) AND human AND (illness OR disease OR death OR hospitalization OR prevalence OR incidence OR DALY OR surveillance)
Companion animal illness	(Companion Animal OR pets OR cat OR dog) AND (illness OR disease OR death OR morbidity OR prevalence OR incidence surveillance)
Consumer choice, demand, and behaviour	Consumer demand AND (antibiotic OR antimicrobial OR organic OR food OR meat) AND (Sweden OR Europe)

Consumption of other (non-meat/egg) foods	(Consumption OR consume OR eat OR purchase OR buy) AND (food OR fruit OR vegetable) AND (Sweden OR Europe)
Corporate profits from AM	(Profit OR sales) AND (Pharmaceuticals OR Antibiotic OR Antimicrobial) AND (Sweden OR Europe)
Cost per unit (kg, L) set by quota	Cost per unit AND quota AND (Sweden OR Europe)
Death (Human)	Human AND (Sweden OR Europe) AND (death OR burden OR mortality OR morbidity OR fatality OR death rate) Human AND (antibiotic OR AMR OR antimicrobial) AND (Sweden OR Europe) AND (death OR burden OR mortality OR morbidity OR fatality)
Development of alternatives to AM	(Development OR new OR make) AND (alternative OR natural) AND (antibiotic OR antimicrobial) AND (Sweden OR Europe)
Development of new AMs	(Development OR new OR make) AND (antibiotic OR antimicrobial) AMD (Sweden OR Europe)
Diagnostics	Diagnostic AND (Sweden OR Europe)
Digital health	(Digital health OR e-prescription) AND (Sweden OR Europe)
Disease in plant agriculture (crops, horticulture)	(Crop OR field OR plant OR fruit OR vegetable) AND (disease OR death OR morbidity OR prevalence OR incidence surveillance)
Disposal of AMs (e.g., unused, unmetabolized)*	
Diverse experiences, opinions, training, and culture*	
Domestic and international trade*	
Existing farm infrastructure	Existing farm infrastructure AND (Sweden OR Europe)
Existing healthcare infrastructure	Existing healthcare infrastructure AND (Sweden OR Europe)
Exposure to AROs in imported products	(Food OR meat OR fruit OR vegetable OR chicken OR beef OR pork OR fish) AND (Import* OR foreign) AND (Antibiotic OR Antimicrobial) AND (Resistance OR resistant) AND (prevalence OR incidence OR susceptibility OR isolate OR surveillance) AND (Sweden OR Europe)
Feed efficiency	Feed efficiency AND (Sweden OR Europe)
Feed quality	Feed quality AND (Sweden OR Europe)
Food and water security (personal, national)	(Food OR water) AND security AND (Sweden OR Europe)
Food-producing animal illness	(Farm OR agriculture OR cow OR pig OR chicken) AND (illness OR disease OR infection OR prevalence OR incidence OR surveillance) AND (Sweden OR Europe)
Good farm practices	Good farm practices AND (Sweden OR Europe)
Healthcare costs	Healthcare cost AND (Sweden OR Europe)
Healthcare resources	Healthcare resources OR (number of physicians OR number of hospitals) AND (Sweden OR Europe)
Host microbiome	Host microbiome AND (Sweden OR Europe)
Human AM use	Human AND (Antibiotic OR Antimicrobial OR penicillin) AND (Use OR Usage OR Consumption) AND (Sweden OR Europe) human AND (Antibiotic OR Antimicrobial OR penicillin) AND (Use OR Usage OR Consumption) AND (Sweden OR Europe) AND ("Defined daily dose" OR dose OR DDD OR "Drug utilization")
Human illness	Human AND (illness OR infection OR death OR hospitalization OR prevalence OR incidence OR DALY OR surveillance OR food-borne) AND (Sweden OR Europe)
Human vaccination	Human AND (vaccination rate OR vaccines) AND (Sweden OR Europe)
Level of resistance in other countries*	
Market price per production unit (e.g., kg, L)	Market price AND (Food OR meat OR fruit OR vegetable OR chicken OR beef OR pork OR fish) AND (Sweden OR Europe)
Meat/egg consumption	(Consumption OR consume OR eat OR purchase OR buy) AND (Food OR meat OR chicken OR beef OR pork OR fish) AND (Sweden OR Europe)

Movement of animals	(Movement OR transport) AND (Farm OR agriculture OR cow OR pig OR chicken) AND (Sweden OR Europe)
Movement of people	(Movement OR transport OR travel OR tourism OR health tourism) AND human AND (Sweden OR Europe)
National budgets, money, funding*	
New and emerging foods	(Genetically modified OR GMO OR 3D OR 3D printed OR insect) AND food AND (Sweden OR Europe)
Non-AM disease prevention and control in plant agriculture	(Biosecurity OR infection prevention) AND (Farm OR agriculture OR crop OR field OR plant OR fruit OR vegetable) AND (Sweden OR Europe)
Non-AM disease prevention and infection control in health and social care settings	(Infection prevention OR isolation OR hospital acquired infection OR nosocomial) AND (hospital OR long-term care OR nursing home OR healthcare) AND (Sweden OR Europe)
Non-AM infection control in food-producing animal agriculture	(Biosecurity OR infection prevention) AND (Farm OR agriculture OR cow OR pig OR chicken) AND (Sweden OR Europe)
Non-AM infection prevention and control by the public*	
Non-AM infection prevention and control in other social institutional settings*	
Number of units (e.g., kg, L) set by quota	Number of units set by quota AND (Sweden OR Europe)
Nutritional quality of diet	Nutrition AND quality AND diet AND (Sweden OR Europe)
On-farm production level (e.g., kg, L)	(Production OR yield) AND (Food OR meat OR chicken OR beef OR pork OR fish) AND (Sweden OR Europe)
Pharmaceutical market, sales, and PR	Pharmaceutical AND (market OR sales OR representatives) AND (Sweden OR Europe)
Population vulnerabilities	Vulnerable population AND (Sweden OR Europe)
Prescribing, diagnosing, treatment practices (appropriateness)	Appropriate* AND (prescrib* OR diagnos*) AND (Sweden OR Europe)
Producer profitability	Producer Profit AND (Food OR meat OR fruit OR vegetable OR chicken OR beef OR pork OR fish) AND (Sweden OR Europe)
Production costs	Production Cost AND (Food OR meat OR fruit OR vegetable OR chicken OR beef OR pork OR fish) AND (Sweden OR Europe)
Production systems	Organic AND (agriculture OR farm) AND (Sweden OR Europe)
Psychological health	(Psychological OR mental) AND human AND (illness OR disease OR death OR hospitalization OR prevalence OR incidence OR DALY OR surveillance)
Research, development, and innovation*	
Resistance at the abattoir/processor	(Abattoir OR food process OR food plant) AND (Antibiotic OR Antimicrobial) AND (Resistance OR resistant) AND (prevalence OR incidence OR susceptibility OR isolate OR surveillance) AND (Sweden OR Europe)
Resistance in the wider environment	(Environment OR water OR soil) AND (Antibiotic OR Antimicrobial) AND (Resistance OR resistant) AND (prevalence OR incidence OR susceptibility OR isolate OR surveillance) AND (Sweden OR Europe)
Restocking with animals/eggs at higher risk for infection	Restocking with animals/eggs at higher risk for infection AND (Sweden OR Europe)
Retail availability of meat/eggs in domestic market	Retail availability AND (Food OR meat OR fruit OR vegetable OR chicken OR beef OR pork OR fish) AND (Sweden OR Europe)
Retail cost of food	Retail cost AND (Food OR meat OR fruit OR vegetable OR chicken OR beef OR pork OR fish) AND (Sweden OR Europe)
Retailer demand for product	Retail demand AND (antibiotic OR antimicrobial OR organic OR food OR meat) AND (Sweden OR Europe)
Science and academia*	
Time to market weight	Time to market weight AND (Sweden OR Europe)

Treatment of waste and waste-water	(Treat* or sani* OR clean) AND (waste OR manure OR sewage OR waste water) AND (Sweden OR Europe)
Treatment post-procedure	(Farm OR agriculture OR cow OR pig OR chicken) AND (Antimicrobial OR Antibacterial OR Antibiotic) AND (Use OR usage OR Consumption) AND (tail dock OR de horn) AND (Sweden OR Europe)
Understanding and awareness*	
Unregulated meat sales	Unregulated meat AND (Sweden OR Europe)
Use for controlling spread of illness in humans	Human AND (Antibiotic OR Antimicrobial OR penicillin) AND (Use OR Usage OR Consumption) AND (metaphylaxis OR control*) AND (Sweden OR Europe)
Use for growth promotion	(Farm OR agriculture OR cow OR pig OR chicken) AND (Antimicrobial OR Antibacterial OR Antibiotic) AND (Use OR usage OR Consumption) AND growth promotion AND (Sweden OR Europe)
Use for metaphylaxis/control	(Farm OR agriculture OR cow OR pig OR chicken) AND (Antimicrobial OR Antibacterial OR Antibiotic) AND (Use OR usage OR Consumption) AND (metaphylaxis or control*) AND (Sweden OR Europe)
Use for prevention in humans	Human AND (Antibiotic OR Antimicrobial OR penicillin) AND (Use OR Usage OR Consumption) AND prevention AND (Sweden OR Europe)
Use for preventive purposes	(Farm OR agriculture OR cow OR pig OR chicken) AND (Antimicrobial OR Antibacterial OR Antibiotic) AND (Use OR usage OR Consumption) AND prevention AND (Sweden OR Europe)
Use for treatment	(Farm OR agriculture OR cow OR pig OR chicken) AND (Antimicrobial OR Antibacterial OR Antibiotic) AND (Use OR usage OR Consumption) AND treatment AND (Sweden OR Europe)
Use for treatment in humans	Human AND (Antibiotic OR Antimicrobial OR penicillin) AND (Use OR Usage OR Consumption) AND treatment AND (Sweden OR Europe)
Viability of domestic meat production	Viability of domestic meat production AND (Sweden OR Europe)
What is being farmed*	

*****Greyed out boxes represent the nodes for which search strings were not created due to the abstract nature of the node.

Table A3: Characteristics of the 18 identified economic model studies (including 4 models considered a combination of economic and disease transmission models) found from the scoping review for the different types of existing models across various parts of the broader One Health system (objective 1).

	Total number	***Percent***
Sector/Population		
Human	4	22
Food (human demand)	12	67
Food-producing animal	2	11
Main issue addressed		
Hospital AMR interventions	1	6
Infection prevention and control	2	11
Consumer behaviour	1	6
Future supply and demand for food	6	33
Food scares and food demand	4	22
Financial impacts of livestock disease	2	11
Supply and demand on agriculture trade	2	11
Model process		
Supply-demand	3	17
Econometric	5	28
Network	-	
Agent based	2	11
Compartmental	-	
Cost analysis	1	6
Bio-econometric	1	6
Structural time series	2	11
Combination	4	22
Type of article		
Single model	14	78
Review	4	22
Total	18	100%

Appendix B: Additional References – Chapter 2

Due to the number of separate searches performed, the scoping review was time and resource intensive. Therefore, per recommendations by Arksey & O'Malley [14], a three month cut-off date was used (December 31st, 2020), and a separate list of articles that were scanned in by title and abstract was created. Below provides a list of additional references that could be used to model the different parts of the Swedish food system that were extracted but did not undergo the full review for inclusion and data extraction.

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Appendix C: Additional Figures – Chapter 2

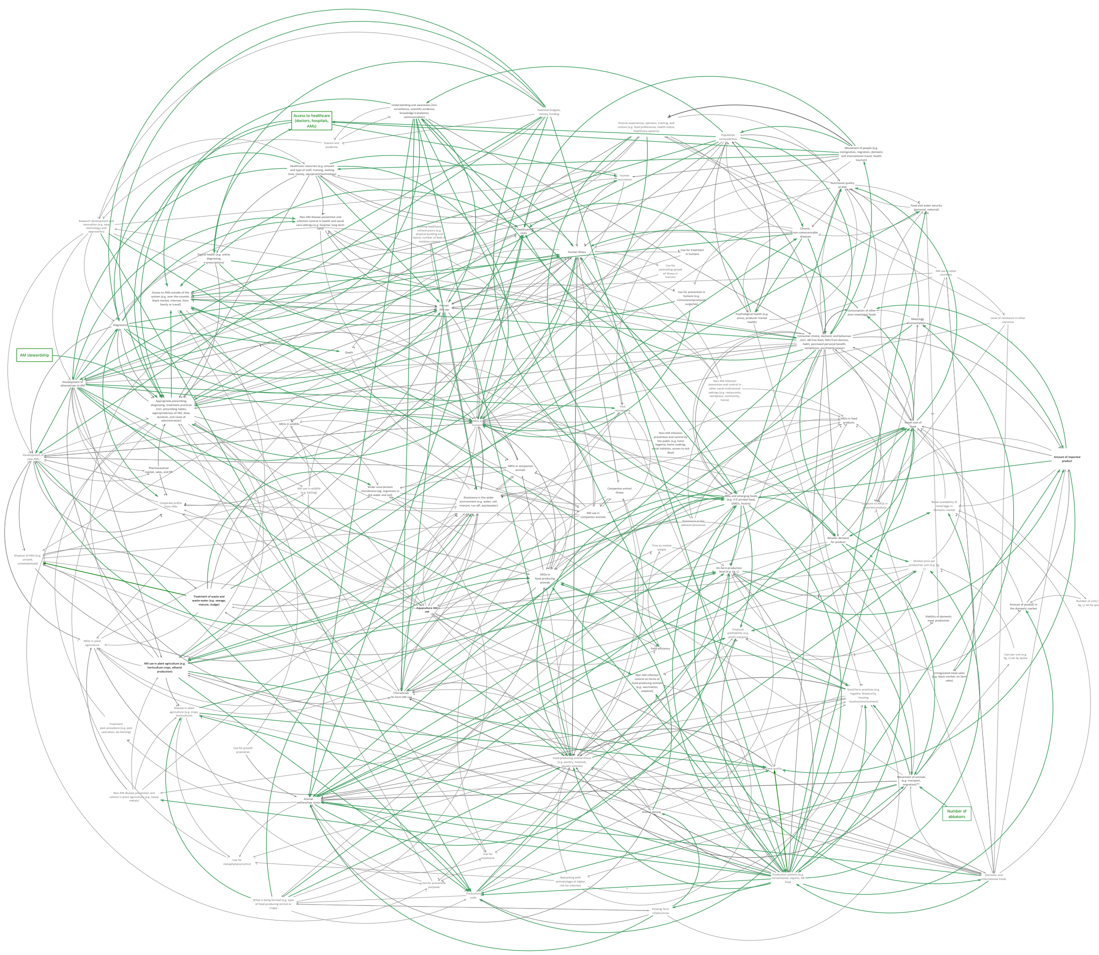

Figure C1: The diagram of AMR adapted from Lambraki et al. (13) with the new relationships identified in the scoping review to identify the data sources and evidence to inform the a model of the drivers of AMR in the Swedish food system (objective 2). The grey lines represent the relationships identified in the original diagram and the green arrows represent the new relationships identified. Note: this figure is zoomable in the PDF version of this thesis to legible font size.

Appendix D: Additional Tables – Chapter 4

Table D1: The weights[1] of the relationships (from component 1 to component 2) that were altered (set to their lowest possible weight and highest possible weight) in a fuzzy cognitive map of the emergence and transmission of antimicrobial resistance in a Swedish food system to determine the sensitivity of components to ten relationships.

Component 1	Component 2	Initial weight[1]	Lowest weight[1]	Highest weight[1]
Animal welfare	Antimicrobials use for metaphylactic purposes	Medium (-0.5)	No relationship (0)	Strongest relationship (-1)
Animal welfare	Antimicrobials use for preventative purposes	Medium (-0.5)	No relationship (0)	Strongest relationship (-1)
Appropriate prescribing	Antimicrobial resistant organisms in humans	Medium (-0.5)	No relationship (0)	Strongest relationship (-1)
Appropriate prescribing	Access to antimicrobials outside the system	Medium (0.5)	No relationship (0)	Strongest relationship (1)
Antimicrobial resistant organisms in humans	Development of alternatives to antimicrobials	Medium (0.5)	No relationship (0)	Strongest relationship (1)
Antimicrobial resistant organisms in humans	Treatment of waste and waste water	Medium (0.5)	No relationship (0)	Strongest relationship (1)
Illness in food producing animals	Antimicrobials use for metaphylactic purposes	Medium (0.5)	No relationship (0)	Strongest relationship (1)
Illness in food producing animals	Antimicrobials use for preventative purposes	Medium (0.5)	No relationship (0)	Strongest relationship (1)
Illness in humans	Antimicrobials use for preventative purposes in humans	Medium (0.5)	No relationship (0)	Strongest relationship (1)
Antimicrobial resistant organisms in food producing animals	Antimicrobial resistant organisms in food products	Medium (0.5)	No relationship (0)	Strongest relationship (1)

[1]The weight of the relationships represents the level of the correlation between the different drivers (components) of antimicrobial resistance in the Swedish food system context exist (from component 1 to component 2). The weights can take on a value between [-1,1] and was divided into 16 categories to represent the different levels: none (0), very low (+/-0.13), low (+/-0.25), medium-low (+/-0.38), medium (+/-0.5), medium-high (+/-0.63), high (+/-0.75), very high (+/-0.88) in which negative values represent a negative correlation. The initial weights were informed by expert opinion and a literature review. The sensitivity analysis changed the weights to the lowest possible value (0) and the highest possible values (+/-1).

Table D2: The changes in the level and associated activation values (AV[1]) of the components to represent three severities of the nine scenarios that were assessed (chosen *a priori*) in a fuzzy cognitive map of the emergence and transmission of antimicrobial resistance in a Swedish food system for their ability to reduce antimicrobial resistance and other negative impacts associated with antimicrobial resistance. These scenarios represent four interventions under current conditions (scenario 1-4) and under climate change conditions (scenario 6-9) and the climate change scenario (scenario 5).

Scenario 1 and 6: Increased infection prevention and control measures				
Component	**Baseline (AV[1])**	**Low intensity (AV[1])**	**Medium intensity (AV[1])**	**High intensity (AV[1])**
Non-antimicrobial disease prevention and control in health and social care	Medium (0.5)	Medium-high (0.63)	High (0.75)	Very high (0.88)
Non-antimicrobial disease prevention and control in food-producing animal agriculture	Medium (0.5)	Medium-high (0.63)	High (0.75)	Very high (0.88)
	Scenario 2 and 7: Educational campaigns and antimicrobial awareness			
Component	**Baseline (AV[1])**	**Low intensity (AV[1])**	**Medium intensity (AV[1])**	**High intensity (AV[1])**
Appropriate prescribing	Medium-low (0.38)	Medium (0.5)	Medium-high (0.63)	High (0.75)
Consumer demand for AMs	Medium (0.5)	Medium-high (0.63)	Medium (0.5)	Medium-low (0.38)
Scenario 3 and 8: Educational campaigns and Increased infection prevention and control				
Component	**Baseline (AV[1])**	**Low intensity (AV[1])**	**Medium intensity (AV[1])**	**High intensity (AV[1])**
Non-AM disease prevention and control in health and social care	Medium (0.5)	Medium-high (0.63)	High (0.75)	Very high (0.88)
Non-AM disease prevention and control in food-producing animal agriculture	Medium (0.5)	Medium-high (0.63)	High (0.75)	Very high (0.88)
Appropriate prescribing	Medium-low (0.38)	Medium (0.5)	Medium-high (0.63)	High (0.75)
Consumer demand for AMs	Medium (0.5)	Medium-high (0.63)	Medium (0.5)	Medium-low (0.38)
Scenario 4 and 9: Increased trade regulations				
Component	**Baseline (AV[1])**	**Low intensity (AV[1])**	**Medium intensity (AV[1])**	**High intensity (AV[1])**
Domestic and international trade	High (0.75)	Medium (0.5)	Very high (0.88)	Highest (1.00)

Scenario 5: Climate change conditions				
Component	**Baseline (AV[1])**	**Best case (AV[1])**	**Medium case (AV[1])**	**Worst case (AV[1])**
Disease in plant agriculture	Low (0.25)	Medium-low (0.38)	Medium (0.5)	Medium-high (0.63)
Food-producing animal illness	Low (0.25)	Medium-low (0.38)	Medium (0.5)	Medium-high (0.63)
Illness in humans	Low (0.25)	Medium-low (0.38)	Medium (0.5)	Medium-high (0.63)
Chronic illness in humans	Medium (0.5)	Medium-high (0.63)	High (0.75)	Very high (0.88)
On-farm production of conventional crops	Medium-low (0.38)	Medium (0.5)	Medium-high (0.63)	High (0.75)
On-farm production of conventional animal-based food products	Medium-low (0.38)	Medium (0.5)	Medium-low (0.38)	Low (0.25)
On-farm production of organic food	Very low (0.13)	Very low (0.13)	Very low (0.13)	None (0.00)
Movement of people	Medium (0.5)	Medium-high (0.63)	High (0.75)	Very high (0.88)

[1]AV - Activation values represents the level at which the different drivers (components) of antimicrobial resistance in the Swedish food system context exist. The activation value can take on a value between [0,1] and was divided into eight categories to represent the different levels: none (0), very low (0.13), low (0.25), medium-low (0.38), medium (0.5), medium-high (0.63), high (0.75), very high (0.88). The initial AVs (baseline scenario) were informed by expert opinion and a literature review. The AV were increased or decreased to reflect the intervention by three levels to reflect the three intensities of the intervention (low, medium, and high intensity).

Table D3: The changes in level and association activation values (AV[1]) of the components to represent the high centrality and high outdegree test scenarios that were assessed in a fuzzy cognitive map of the emergence and transmission of antimicrobial resistance in a Swedish food system for their ability to reduce antimicrobial resistance and other negative impacts associated with antimicrobial resistance.

High centrality scenario		
Component	**Level in baseline (AV[1])**	**Level in scenario (AV[1])**
Animal welfare	Medium-low (0.38)	Highest (1)
Retail cost of food	High (0.75)	None (0)
Appropriate prescribing	Medium-low (0.38)	Highest (1)
Understanding and awareness	Medium (0.5)	Highest (1)
Type of production system	High (0.75)	Highest (1)
Development of alternatives to antimicrobials	Low (0.25)	Highest (1)
Amount of imported product	High (0.75)	None (0)
Development of new antimicrobials	Low (0.25)	Highest (1)
Production costs	Medium (0.5)	None (0)
Population vulnerabilities	Low (0.25)	None (0)
High outdegree scenario		
Component	**Level in baseline (AV[1])**	**Level in scenario (AV[1])**
Type of production system	High (0.75)	Highest (1)
Understanding and awareness	Medium (0.5)	Highest (1)
Development of alternatives to antimicrobials	Low (0.25)	Highest (1)
Domestic and international trade regulations	High (0.75)	Highest (1)
Diagnostics	Medium-low (0.38)	Highest (1)
Retail cost of food	High (0.75)	None (0)
Population vulnerabilities	Low (0.25)	None (0)
Appropriate prescribing	Medium-low (0.38)	Highest (1)
Good farm practices	Medium (0.5)	Highest (1)
Development of new antimicrobials	Low (0.25)	Highest (1)

[1]AV - Activation values represents the level at which the different drivers (components) of antimicrobial resistance in the Swedish food system context exist. The activation value can take on a value between [0,1] and was divided into eight categories to represent the different levels: none (0), very low (0.13), low (0.25), medium-low (0.38), medium (0.5), medium-high (0.63), high (0.75), very high (0.88). The initial AVs (baseline scenario) were informed by expert opinion and a literature review. The AV were increased or decreased to their highest (1) or lowest (0) possible value.

Table D4: The changes in the weights[1] of the relationships to represent three severities of the eight scenarios that were assessed (chosen *a posteriori*) in a fuzzy cognitive map of the emergence and transmission of antimicrobial resistance in a Swedish food system for their ability to reduce antimicrobial resistance and other negative impacts associated with antimicrobial resistance. These scenarios represent four interventions under current conditions (scenario 10-13) and under climate change conditions (scenario 14-17).

Scenario 10 and 14: Reducing cost as a barrier					
Component 1	**Component 2**	**Baseline (weight[1])**	**Low intensity (weight[1])**	**Medium intensity (weight[1])**	**High intensity (weight[1])**
Animal welfare	Production costs	Medium (0.5)	Medium-weak (0.38)	Weak (0.25)	Very weak (0.13)
Animal welfare	Retail cost of food	Strong (0.75)	Medium-strong (0.63)	Medium (0.5)	Medium-weak (0.38)
Type of production system	Production costs	0.75	Medium (0.5)	Medium-weak (0.38)	Weak (0.25)
Type of production system	Retail cost of food	Medium (0.5)	Medium-weak (0.38)	Weak (0.25)	Very weak (0.13)
Retail cost of food	Nutritional quality of food	Medium (-0.5)	-0.38	Weak (-0.25)	-0.13
Retail cost of food	Consumer demand for organic products	Medium-strong (-0.63)	Medium (-0.5)	Medium-weak (-0.38)	Weak (-0.25)
Retail cost of food	Consumer demand for animal welfare friendly products	Medium (-0.5)	Medium-weak (-0.38)	Weak (-0.25)	Very weak (-0.13)
Retail cost of food	Consumer demand for imported food products	Medium (0.5)	Medium-weak (0.38)	Weak (0.25)	Very weak (0.13)
Scenario 11 and 15: Increasing trade regulations					
Component 1	**Component 2**	**Baseline (weight[1])**	**Low intensity (weight[1])**	**Medium intensity (weight[1])**	**High intensity (weight[1])**
Domestic and international trade regulations	Antimicrobial use in terrestrial food producing animals	Medium (-0.5)	Medium-strong (-0.63)	Strong (-0.75)	Very strong (-0.88)
Domestic and international trade regulations	Antimicrobial use in aquaculture	Medium (-0.5)	Medium-strong (-0.63)	Strong (-0.75)	Very strong (-0.88)
Domestic and international trade regulations	Antimicrobial use in plant agriculture	Medium (-0.5)	Medium-strong (-0.63)	Strong (-0.75)	Very strong (-0.88)
Domestic and international trade regulations	Exposure to antimicrobial resistant organisms from imported food products	Medium (-0.5)	Medium-strong (-0.63)	Strong (-0.75)	Very strong (-0.88)

Scenario 12 and 16: Increasing technological advancements and innovation in healthcare					
Component 1	**Component 2**	**Baseline (weight[1])**	**Low intensity (weight[1])**	**Medium intensity (weight[1])**	**High intensity (weight[1])**
Diagnostics	Appropriate prescribing	Strong (0.75)	Very strong (0.88)	Strongest (1)	Strongest (1)
Development of alternatives to antimicrobials	Antimicrobial use in humans	Weak (-0.25)	Medium-weak (-0.38)	Medium (-0.5)	Medium-strong (-0.63)
Development of alternatives to antimicrobials	Antimicrobial use in terrestrial food producing animals	Medium (-0.5)	Medium-strong (-0.63)	Strong (-0.75)	Very strong (-0.88)
Development of alternatives to antimicrobials	Antimicrobial use in aquaculture	Medium (-0.5)	Medium-strong (-0.63)	Strong (-0.75)	Very strong (-0.88)
Development of alternatives to antimicrobials	Antimicrobial use in plant agriculture	Medium (-0.5)	Medium-strong (-0.63)	Strong (-0.75)	Very strong (-0.88)
Scenario 13 and 17: Addressing social inequalities and poverty					
Component 1	**Component 2**	**Baseline (weight[1])**	**Low intensity (weight[1])**	**Medium intensity (weight[1])**	**High intensity (weight[1])**
Population vulnerabilities	Nutritional quality of diet	Medium (-0.5)	Medium-weak (-0.38)	Weak (-0.25)	Very weak (-0.13)
Population vulnerabilities	Illness in humans	Medium (0.5)	Medium-weak (0.38)	Weak (0.25)	Very weak (0.13)
Population vulnerabilities	Chronic and non-communicable illness in humans	Medium (0.5)	Medium-weak (0.38)	Weak (0.25)	Very weak (0.13)
Population vulnerabilities	Psychological illness in humans	Medium (0.5)	Medium-weak (0.38)	Weak (0.25)	Very weak (0.13)
Population vulnerabilities	Access to healthcare	Weak (-0.25)	Very weak (-0.13)	No relationship (0)	Very weak (0.13)

[1]The weight of the relationships represents the level of the correlation between the different drivers (components) of antimicrobial resistance in the Swedish food system context exist (from component 1 to component 2). The weights can take on a value between [-1,1] and was divided into 16 categories to represent the different levels: none (0), very low (+/-0.13), low (+/-0.25), medium-low (+/-0.38), medium (+/-0.5), medium-high (+/-0.63), high (+/-0.75), very high (+/-0.88) in which negative values represent a negative correlation. The initial weights (baseline scenario) were informed by expert opinion and a literature review. The weights were increased or decreased to reflect the intervention by three levels to reflect the three intensities of the intervention (low, medium, and high intensity).

Table D5: The features of each component from the fuzzy cognitive map of antimicrobial resistance in the Swedish food system context, including the indegree, outdegree, centrality and type.

Component	Indegree[1]	Outdegree[1]	Centrality[1]	Type[1]	Component	Indegree[1]	Outdegree[1]	Centrality[1]	Type[1]
Animal density	1	3.88	4.88	ordinary	**Human illness**	8.38	4.38	12.76	ordinary
Access to healthcare	2.75	1.75	4.5	ordinary	**Chronic, non-communicable diseases**	3	5.88	8.88	ordinary
Aquaculture AMU[2]	4.64	4.25	8.89	ordinary	**Psychological illness**	1.88	4.38	6.26	ordinary
AMU[2] in companion animals	2.76	3.5	6.26	ordinary	**Food-producing animal illness**	9	6	15	ordinary
Human AMU[2]	5.47	3.76	9.23	ordinary	**Amount of imported product**	7	4.5	11.5	ordinary
Plant agriculture AMU[2]	4.51	4.75	9.26	ordinary	**Disease in plant agriculture (crops, horticulture)**	1.5	2.25	3.75	ordinary
(Terrestrial) On-farm AMU[2]	6.02	5.25	11.27	ordinary	**Movement of animals: domestic**	3	3	6	ordinary
Access to AMs[3] outside of the system	3.75	0.78	4.53	ordinary	**Movement of animals: international**	2	3.25	5.25	ordinary
Appropriate prescribing, diagnosing, treatment practices	6.88	4.75	11.63	ordinary	**Movement of people**	0.75	4.5	5.25	ordinary
ARO[4] in companion animals	2.5	2	4.5	ordinary	**Market price per production unit: conventional food**	1.75	1.25	3	ordinary
Resistance in wider environment	7.63	2.75	10.38	ordinary	**Market price per production unit: organic food**	1.5	1.5	3	ordinary
AROs[4] in food products	2.25	0.88	3.13	ordinary	**Non-AM disease prevention: food-producing animal farms**	2.25	2.5	4.75	ordinary
AROs[4] in humans	10.85	4.88	15.73	ordinary	**Non-AM disease prevention: health and social-care settings**	1.13	2.75	3.88	ordinary
AROs[4] in imported food	1.5	0.5	2	ordinary	**New and emerging food: GMO[5]**	0.25	4.5	4.75	ordinary
AROs[4] in food-producing animals	8.13	4.5	12.63	ordinary	**New and emerging food: insects**	0.25	3.25	3.5	ordinary
AROs[4] in plant agriculture	3.75	2	5.75	ordinary	**New and emerging food: lab meat/3-D printed food**	0	1.25	1.25	driver

Component	Indegree[1]	Outdegree[1]	Centrality[1]	Type[1]	Component	Indegree[1]	Outdegree[1]	Centrality[1]	Type[1]
AROs[4] in wildlife	1.63	1.88	3.51	ordinary	**New and emerging food: plant-based meat**	0.5	2	2.5	ordinary
Animal welfare (lack of stress)	7.5	4.5	12	ordinary	**Nutritional quality of diet**	4.5	2.5	7	ordinary
Consumer choice, demand, and behaviour: other	1.5	3.75	5.25	ordinary	**Production costs**	6.38	1.25	7.63	ordinary
Consumer choice, demand, and behaviour: AMs[3]	0.75	2.5	3.25	ordinary	**On-farm production level: conventional food animal-based product**	3.25	3	6.25	ordinary
Consumer choice, demand, and behaviour: Health tourism	0	0.25	0.25	driver	**On-farm production level: organic food products**	2.25	2	4.25	ordinary
Consumer choice, demand, and behaviour: Imported food	1.5	1.5	3	ordinary	**On-farm production level: conventional plant-based products**	2.25	1.5	3.75	ordinary
Consumer choice, demand, and behaviour: Meat/egg food products	1	1	2	ordinary	**Pharmaceutical market, public relations, sales**	1.5	1.5	3	ordinary
Consumer choice, demand, and behaviour: New and emerging foods	2	0.5	2.5	ordinary	**Producer profitability**	3.75	0.5	4.25	ordinary
Consumer choice, demand, and behaviour	2.88	3.25	6.13	ordinary	**Type of production systems**	1	9.02	10.02	ordinary
Consumer choice, demand, and behaviour: Organic	1	1	2	ordinary	**Population vulnerabilities**	2	5.38	7.38	ordinary
Consumer choice, demand, and behaviour: Non-meat/egg food products	0.75	0.5	1.25	ordinary	**Retail availability of animal-based food products**	1	0.75	1.75	ordinary
Consumer choice, demand, and behaviour: Animal welfare	1.25	2.75	4	ordinary	**Retail cost of food**	5.75	5.38	11.13	ordinary
Corporate profits from AMs[3]	2.75	2.25	5	ordinary	**Retailer demand for product**	1	1	2	ordinary
Meat/egg consumption	3.25	2.5	5.75	ordinary	**Retailer demand for product: imported food**	1	1.5	2.5	ordinary
Consumption of other (non-meat/egg) foods	2.88	1.13	4.01	ordinary	**Retailer demand: organic**	1	3	4	ordinary
Consumption of seafood	0.75	2.5	3.25	ordinary	**Retailer demand: animal welfare products**	1	1.75	2.75	ordinary

Component	Indegree[1]	Outdegree[1]	Centrality[1]	Type[1]	Component	Indegree[1]	Outdegree[1]	Centrality[1]	Type[1]
Diagnostics	1.5	5.5	7	ordinary	**Science and academia**	0.5	0.5	1	ordinary
Development of alternatives to AMs[2]	3.88	6.5	10.38	ordinary	**Treatment of food productions post-harvest**	0	1	1	driver
Death (Human)	2	0.5	2.5	ordinary	**Treatment of waste and waste-water**	2	3.96	5.96	ordinary
Digital health	0.63	3.75	4.38	ordinary	**Understanding and awareness**	3.63	7.51	11.14	ordinary
Domestic and international trade	2.5	6	8.5	ordinary	**Use for growth promotion**	0.75	0.76	1.51	ordinary
Development of new AMs[2]	4.25	4.75	9	ordinary	**Use for metaphylaxis**	2.5	2	4.5	ordinary
Amount of product in the domestic market	3	1.5	4.5	ordinary	**Use for preventive purposes**	3.25	3	6.25	ordinary
Food and water security	2.5	2.25	4.75	ordinary	**Use for prevention in humans**	1.5	1.26	2.76	ordinary
Good farming practices	2.25	5	7.25	ordinary	**Use for treatment post-procedure**	1.75	0.13	1.88	ordinary
Healthcare costs	5.63	0.75	6.38	ordinary	**Use for treatment**	3	2.75	5.75	ordinary
Healthy host microbiome	4.5	2	6.5	ordinary	**Use for treatment in humans**	2.75	0.83	3.58	ordinary
Healthcare resources	1.5	4.38	5.88	ordinary	**Viability of domestic meat production**	0.5	0.75	1.25	ordinary
Companion animal illness	1.75	1.25	3	ordinary	**Human vaccination**	1.25	1.35	2.6	ordinary

[1]The network metrics used to decscribe the components were indegree (calculated by the number of incoming relationships), the outdegree (the number of outgoing relationships), the centrality (the total number of connections, both ingoing and outgoing), and type which can be: ordinary (has both ingoing and outgoing relationships), driver (only has outgoing relationships), or receiver (only has ingoing relationships).

[2]AMU – Antimicrobial use

[3]AM – Antimicrobial

[4]ARO – Antimicrobial resistant organism

[5]GMO – Genetically modified organism

Appendix E: Scenario Rational and Description – Chapter 4

A priori scenarios

Scenario 1: Increased infection prevention and control (IPC) under current conditions

The first intervention explored was increased (better) infection prevention and control, both on-farm (e.g., biosecurity) and in health and social-care settings. This scenario was operationalized by increasing the activation value of two components: *non-AM infection prevention and control in food-animal agriculture* and *non-AM infection prevention and control in health and social-care*. In the base FCM, these two components had activation values of 0.5 (medium). To assess how increasing infection prevention and control impacted the indicator components, the activation level of these two components were increased by three different levels to reflect different intensities of the intervention (Appendix D, Table D2).

Scenario 2: Educational campaign under current conditions

The second intervention explored was increasing knowledge about AMs and proper AMU through educational campaigns. This was conducted by changing the activation value of two nodes*:* *consumer demand for AMs* and *appropriate prescribing practices*. These two nodes reflect educational campaigns targeted to the general population (consumers) and to prescribers. It was assumed that educational campaigns have the ability to decrease consumer demand for AMs and increase appropriate prescribing. This was reflected by decreasing activation values for *consumer demand for AMs* component and increasing activation values for *appropriate prescribing,* each by three levels to reflect different intensities of the intervention (Appendix D, Table D2).

Scenario 3: Antimicrobial stewardship under current conditions

The third scenario represented increasing antimicrobial stewardship which was a combination of the first two scenarios, increasing infection prevention and control and educational campaigns (Appendix D, Table D2). This scenario was conducted because in complex systems, the effect of combining interventions is not simply the sum of the effect of the two interventions, due to the way the impacts may interact within system (119).

Scenario 4: Increased trade regulations under current conditions

The fourth scenario represented increasing trade regulations. This was based on France's 2022 decision to ban the importation of all animal-based food products from animals that have received growth promoters (72). The component *domestic and international trade* represents the strength of trade restrictions for food being imported into Sweden and is focused on restrictions around AMU and the presence of AM residues and AROs in imported food. Therefore, increasing the activation value of the *domestic and international trade* node would represent stronger restrictions being implemented and was assessed at two levels higher (stronger) and one level lower (weaker) to assess how this component impacts the indicator components. This was because two levels higher was the highest possible level, therefore, we decided to test one lower to total three intensities. The activation values that were inputted for this scenario are found in Appendix D, Table D2.

Scenario 5: Climate change conditions

This scenario represents the system under climate change conditions. Climate change conditions were based on predicted impacts due to a changing climate presented in a scenario planning workshop conducted in Sweden by Lambraki et al. (70). This workshop explored two interventions under an alternative future (climate change conditions). Experts were presented with a description of the world in 2050 which included a representation of how the changing climate had altered many aspects of the food system (70). These were reflected in the FCM by altering eight components: *disease in plant agriculture, food-producing animal illness, illness in humans, chronic illness in humans, on-farm production of conventional crops, on-farm production of conventional animal-based food products, on-farm production of organic food,* and *movement of people.* Changes in climate are predicted to increase disease in crops, humans, and animals due to extreme weather, heat stress, and the introduction of new pathogens (e.g., vector-borne disease agents). Chronic illnesses such as lung cancer and asthma are also predicted to increase due to poor air quality resulting from pollution and wildfires. The changing weather patterns are also predicted to decrease production of animal-based foods (both terrestrial and aquatic) due to increased stress, decreased immune system function, decreased reproductive health, and destruction of habitat. However, since the temperatures are predicted to increase in Sweden, climate change also allows for longer growing seasons and expanding production areas of crops such as winter wheat, thus increasing overall production of plant-based foods. Finally, extreme weather within Sweden and globally is expected to increase migration and immigration which will increase the movement of people into and around Sweden. These components were all changed by three levels from their initial value to reflect three levels of severity of the climate change scenario: best-, medium-, and worst-case climate change conditions (Appendix E, Table E2).

Scenario 6: Increased infection prevention and control (IPC) under climate change conditions

The fifth scenario assessed the first intervention (increased IPC) under climate change conditions (Appendix D, Table D2).

Scenario 7: Educational campaign under climate change conditions

The sixth scenario assessed the second intervention (educational campaigns) under climate change conditions (Appendix D, Table D2).

Scenario 8: Antimicrobial stewardship under climate change conditions

The seventh scenario assessed was the third intervention (antimicrobial stewardship) under climate change conditions (Appendix D, Table D2).

Scenario 9: Increased trade regulations under climate change conditions

The eighth scenario assessed was the fourth intervention (increased trade regulations) under climate change conditions (Appendix D, Table D2).

A posteriori scenarios:

Scenario 10: Reducing cost as a barrier for access to nutritious food and sustainable agriculture under current conditions

This intervention aimed to address two of the SDG: The second SDG (Zero hunger), and the twelfth SDG (Responsible consumption and production; 72). It was mentioned within the scenario planning workshops that cost was a major barrier for addressing both of these SDG (60). Access to nutritious and sustainable food requires money, which makes it unavailable to some populations. In this model, sustainable food could be represented by organic and other non-conventional production systems and animal welfare-friendly food. Therefore, if national budgets were used to provide subsidies to farmers to convert their farms to these more sustainable production systems, and to reduce the extra production costs that are associated with raising animals and growing crops under these systems, we could shift more farmers to adopt alternative and potentially better farming practices. These subsidies could also be used to reduce the end costs to consumers, thus reducing cost as a barrier for consumers to buy foods grown under more sustainable conditions. Therefore, this intervention was modelled by altering eight relationships at three different intensities to reflect the success and strength of the intervention. The subsidies would be targeted at reducing the impact that animal welfare friendly farms and organic production systems has on production costs, reducing the impact of these food systems on the retail costs of the food, and reducing the impact that cost has on demand for these products (Appendix D, Table D4).

Scenario 11: Increased international trade regulations and implementation under current conditions

Increased trade regulations and implementation addressed the seventeenth SDG (Partnerships for the goals), which aims to strengthen implementation and revitalize global partnerships for sustainable development (72). This intervention is similar to the previously outline trade intervention (Scenarios 4 and 9) but is more targeted at implementation and enforcement. Therefore, instead of simply increasing the strength of the regulations globally around AMU in agriculture and AROs in food being imported, we wanted to see how increasing the influence that these regulations have on agricultural AMU and AROs in imported food can affect the indicator components. We assumed that if new international guidelines and restrictions (on AMU and AROs from imported food) were implemented such as the new EU trade restrictions (72), that this would have a stronger impact on changing use practices on farm in the exporting country and that there would be more screening for AROs in foods being imported into the country (Appendix D, Table D4).

Scenario 12: Technological advancements and innovation under current conditions

The twelfth intervention, technological advancement and innovation, aimed to address the ninth SDG (Industry, innovation, and infrastructure) (72). It was mentioned within our scenario planning workshops that technological advancements could have the power to change the system, especially when focused on reducing AMU (60). One major technological advancement that was mentioned was the enhancement of rapid diagnostic technology to be able to detect organisms and inform prescribing decisions (60). Therefore, we wanted to assess if better diagnostics have a more positive influence on appropriate prescribing and thus could reduce AMU and AMR. Alternatives to AMs is another innovation that could have an impact on AMR. If alternatives to AMs become as good or better at killing organisms, this could have a large impact on reducing AMU in humans and agriculture. Therefore, we wanted to assess if the development of better alternatives to AMs could reduce AMR and alter our other indicator components for the better (Appendix D, Table D4).

Scenario 13: Addressing social inequalities and poverty under current conditions

Addressing social inequalities and poverty aimed to address the first SDG (No poverty) and the tenth SDG (Reduced inequalities) (72). During the scenario planning workshops the experts highlighted that addressing social inequalities was a major factor in reducing illness and some of the major drivers of AMU and AMR (60). Vulnerable populations are at a disadvantage in terms of access to healthcare and nutritious food, and are at higher risk of illness. Addressing the socioeconomic factors that lead to poverty and vulnerable populations is a difficult task. However, if social supports could be enacted to help reduce some of the negative impacts that vulnerable populations endure, this could be a starting point. Therefore, our intervention aimed to reduce the impact that population vulnerability has on access to nutritious food and healthcare (thus increasing access to nutritious food and healthcare to these populations), and reduce the impact that population vulnerability has on negative health outcomes (communicable, non-communicable, and psychological health issues) (Appendix D, Table D4).

Scenario 14: Reducing cost as a barrier for access to nutritious food and sustainable agriculture under climate change conditions

The fourteenth scenario was the intervention for reducing cost as a barrier for access to nutritious food and sustainable agriculture under climate change conditions (Appendix D, Table D4).

Scenario 15: Increased trade regulations in the European Union under climate change conditions

The fifteenth scenario was the Increased international trade regulations and implementation intervention under current conditions (Appendix D, Table D4).

Scenario 16: Technological advancements and innovation under climate change conditions

The sixteenth scenario was the technological advancements and innovation intervention under current conditions under climate change conditions (Appendix D, Table D4).

Scenario 17: Addressing social inequalities and poverty under climate change conditions

The seventeenth scenario was the addressing social inequalities and poverty intervention under climate change conditions (Appendix D, Table D4).

Scenario 18: The Hail Mary scenario

After analyzing the *a posteriori* scenarios it was evident that the interventions had impacts on many of the indicator variables, but they were not overly impactful at reducing AMR in any of the sectors (human, animal, plants, or the environment). Therefore, we decided to test all of the *a posteriori* interventions simultaneously to see if they could reduce AMR (Appendix D, Table D4).

Appendix F: Additional Figures – Chapter 4

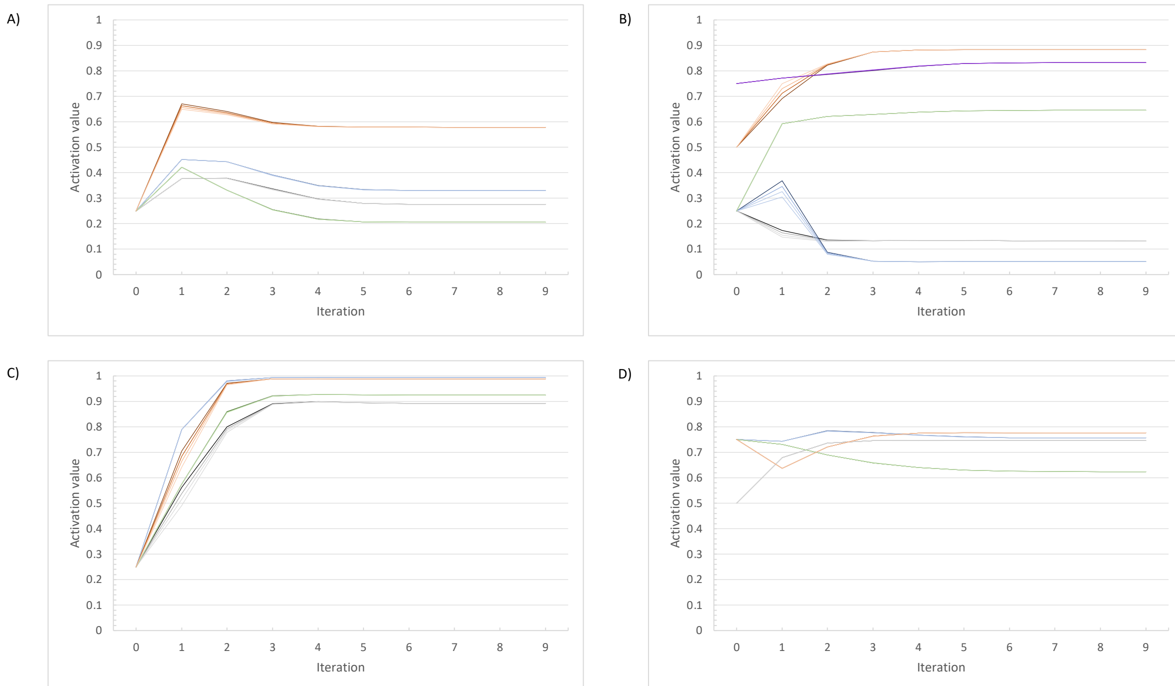

Figure F1: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 1 which represents the intervention increasing infection prevention and control measures at three varying intensities under current conditions. The darkest line of each colour represents the baseline scenario and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

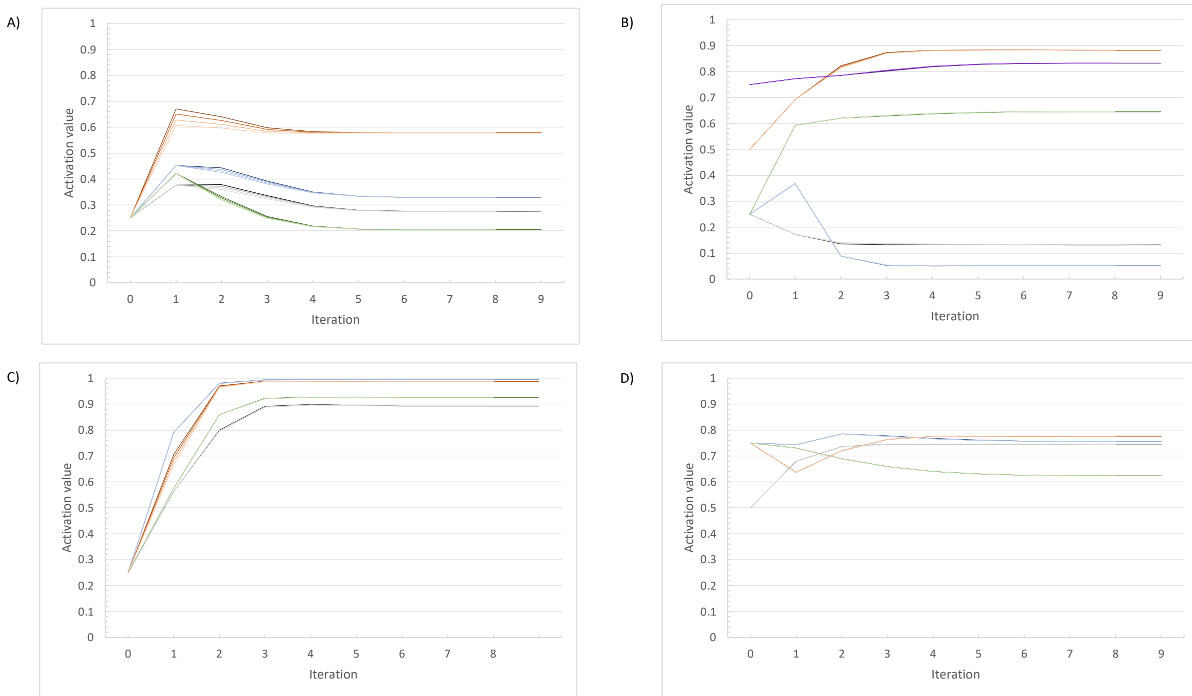

Figure F2: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 2 which represents educational campaigns about appropriate antimicrobial use at three levels of intensity under current conditions. The darkest line of each colour represents the baseline scenario and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

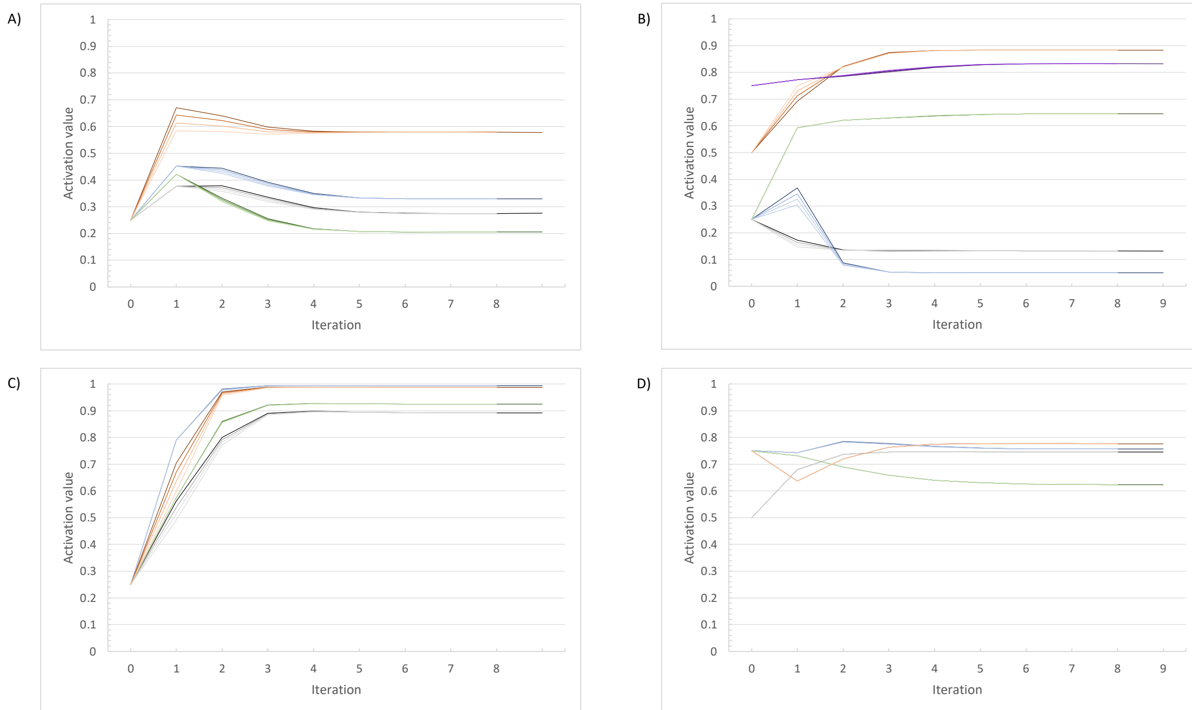

Figure F3: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 3 which represents antimicrobial stewardship at three levels of intensity under current conditions. The darkest line of each colour represents the baseline scenario and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

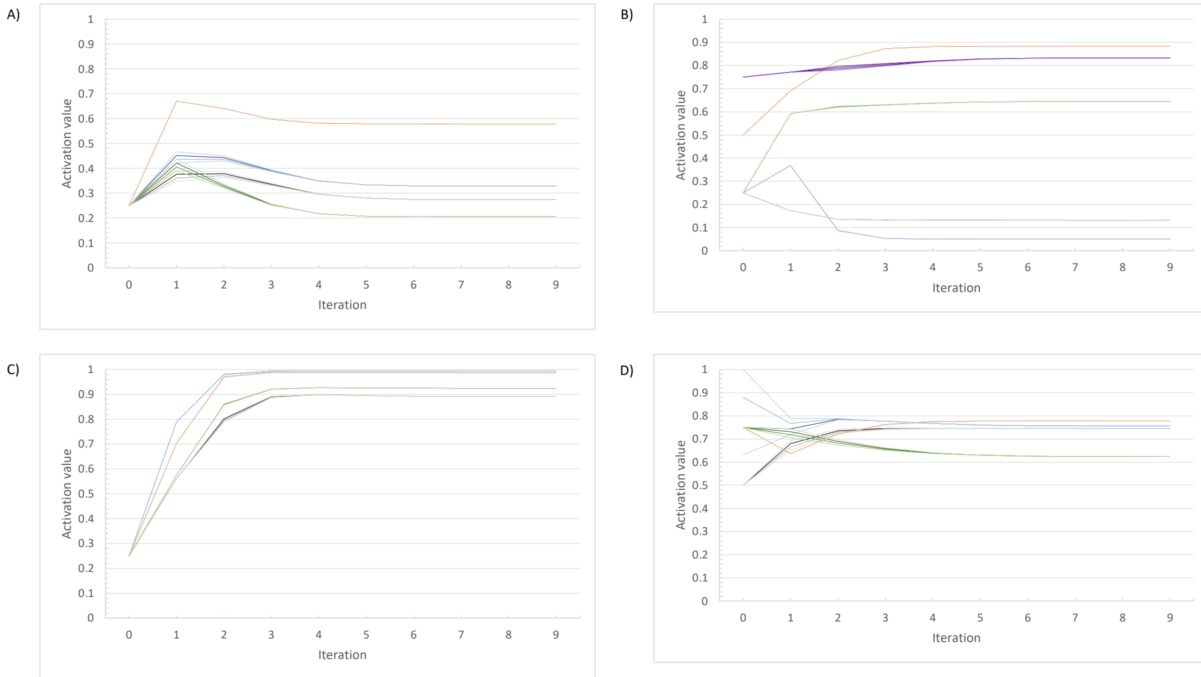

Figure F4: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 4 which represents increased trade regulations at three levels of intensity under current conditions. The darkest line of each colour represents the baseline scenario and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

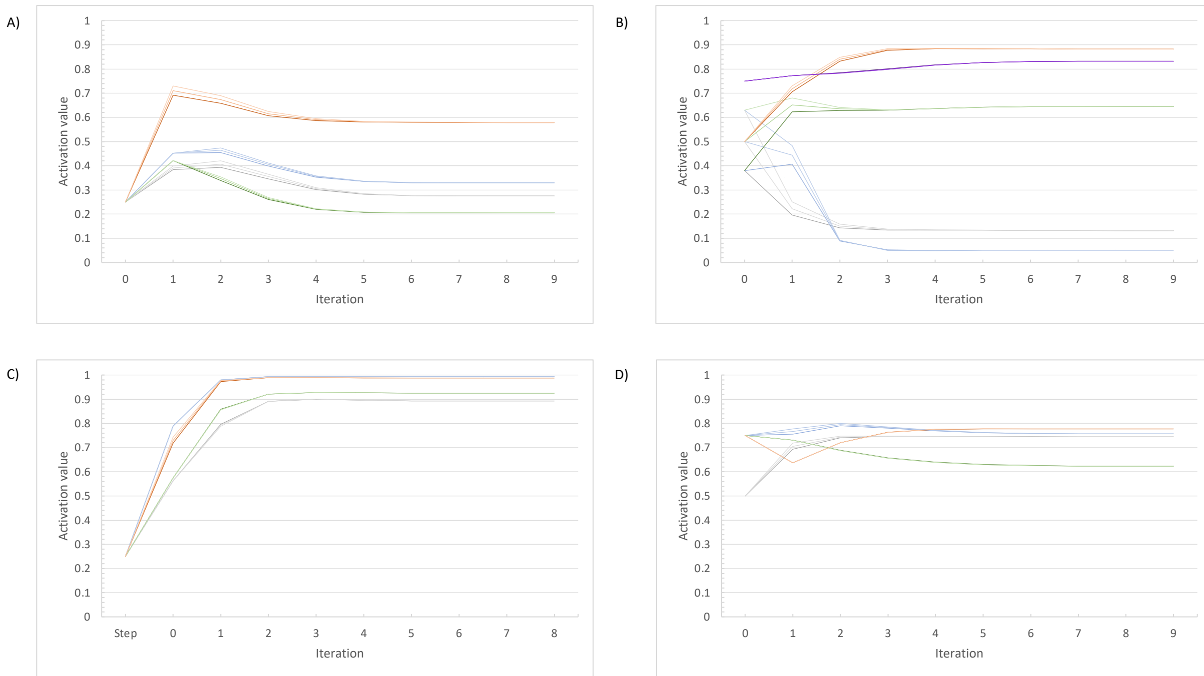

Figure F5: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 5 which represents increasing infection prevention and control measures climate change conditions at three levels of intensity under climate change conditions. The dotted line represents the baseline scenario, the darkest line of each colour represents the baseline scenario under climate change and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

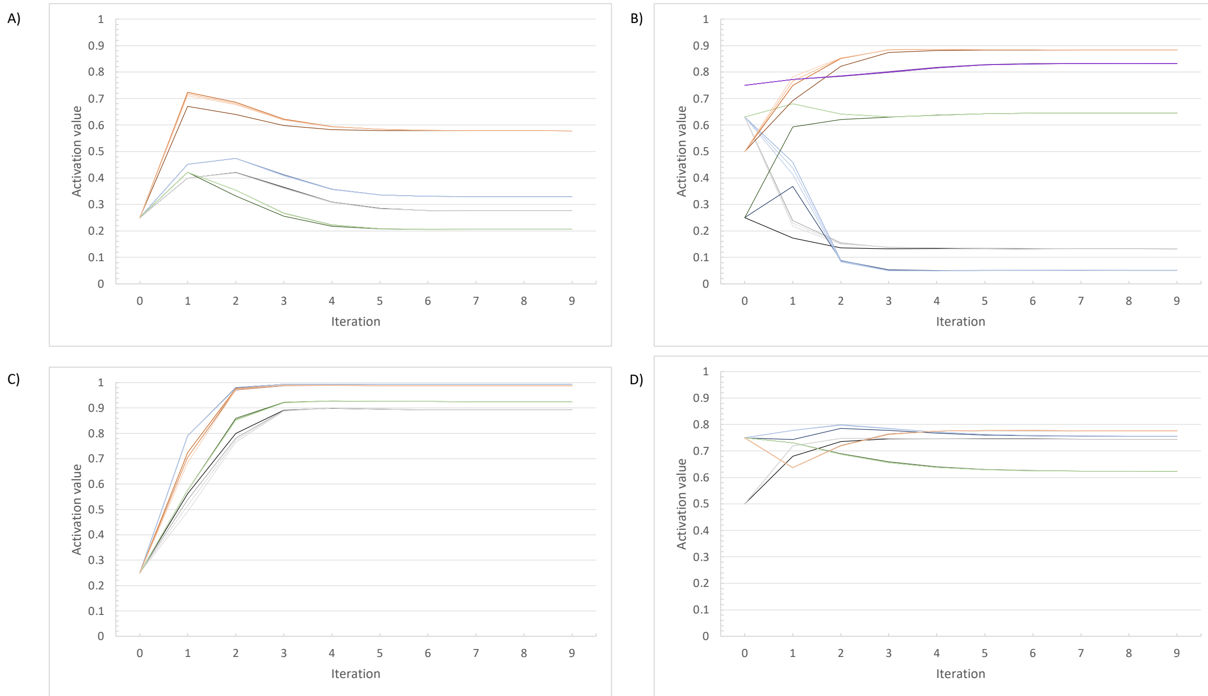

Figure F6: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 6 which represents increased infection and prevention measures at three levels of intensity under climate change conditions. The dotted line represents the baseline scenario, the darkest line of each colour represents the baseline scenario under climate change and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

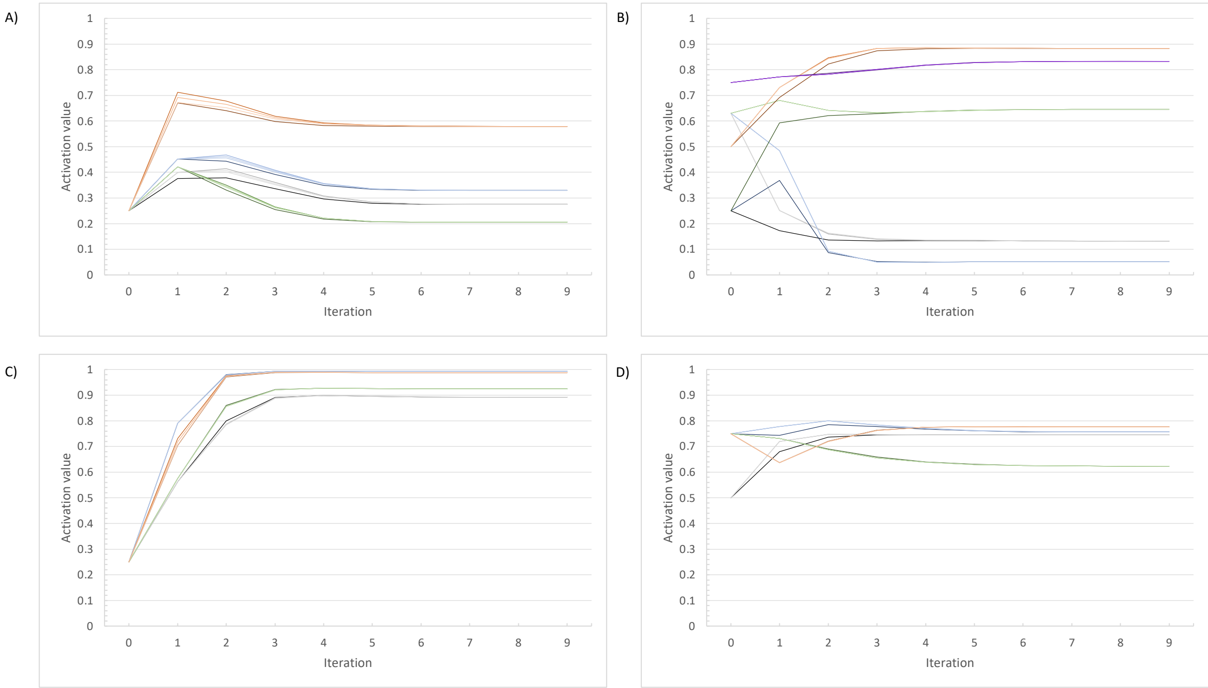

Figure F7: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 7 which represents educational campaigns at three levels of intensity under climate change conditions. The dotted line represents the baseline scenario, the darkest line of each colour represents the baseline scenario under climate change and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

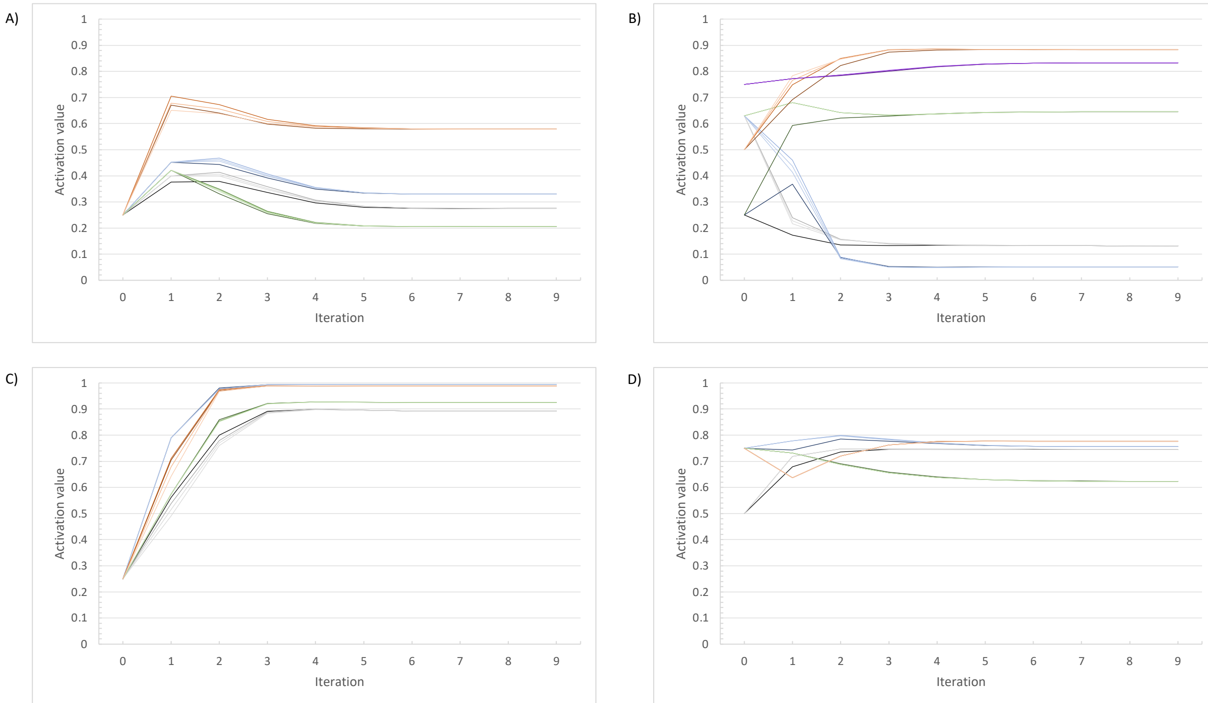

Figure F8: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 8 which represents antimicrobial stewardship at three levels of intensity under climate change conditions. The dotted line represents the baseline scenario, the darkest line of each colour represents the baseline scenario under climate change and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

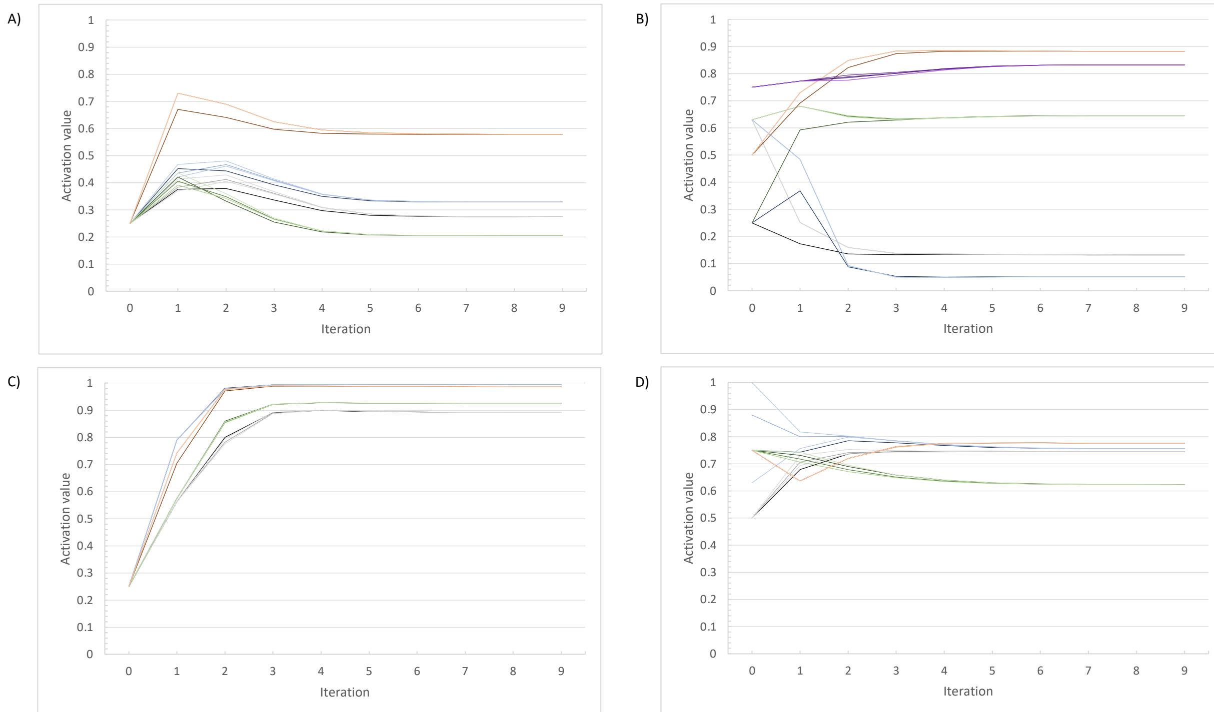

Figure F9: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 9 which represents increased trade regulations at three levels of intensity under climate change conditions The dotted line represents the baseline scenario, the darkest line of each colour represents the baseline scenario under climate change and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

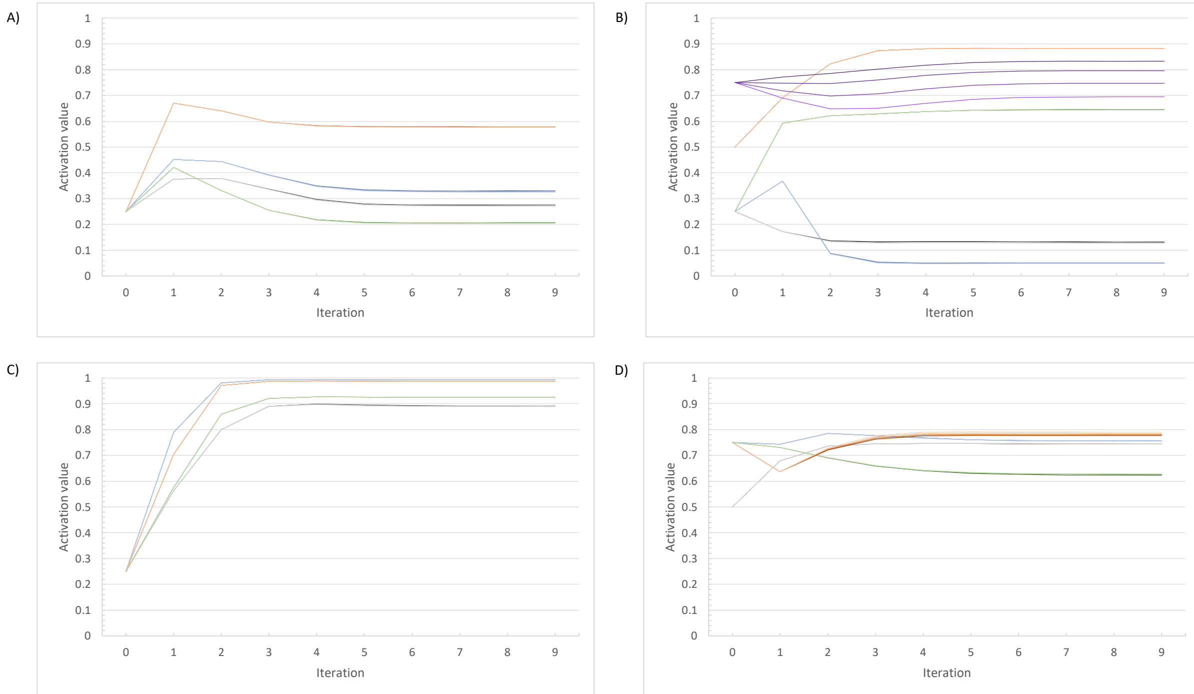

Figure F10: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 10 which represents reducing cost as a barrier to sustainable and nutritious food at three levels of intensity under current conditions. The darkest line of each colour represents the baseline scenario and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

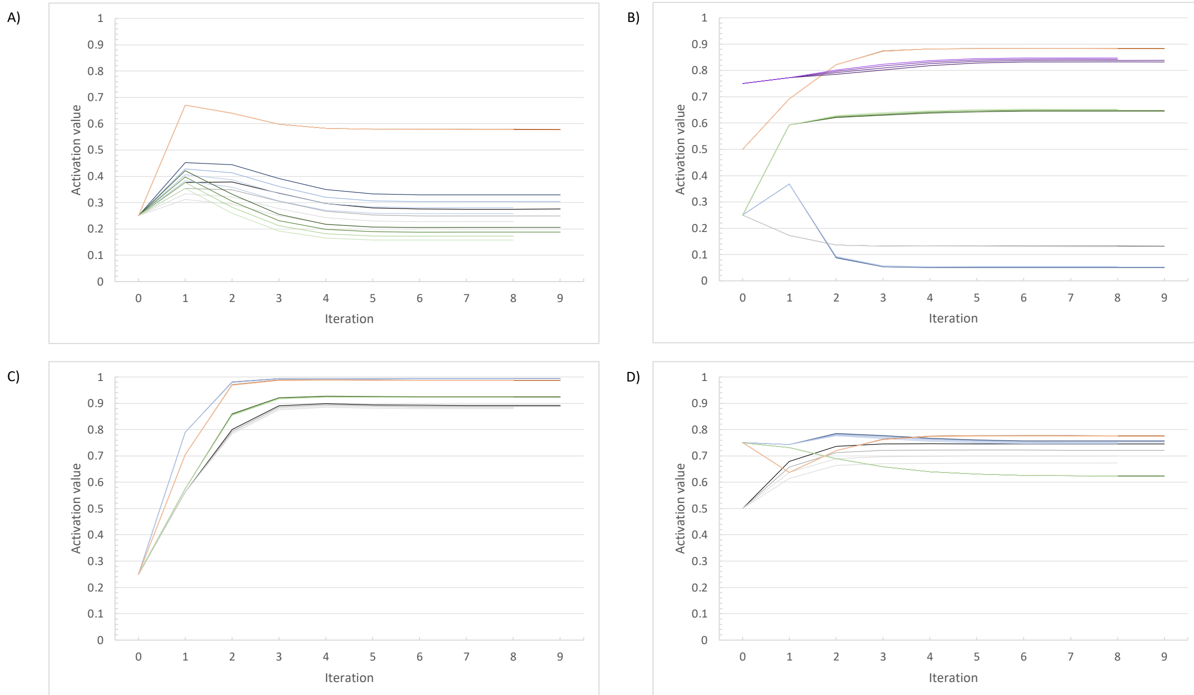

Figure F11: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 11 which represents increased international trade regulations and implementation at three levels of intensity under current conditions. The darkest line of each colour represents the baseline scenario and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

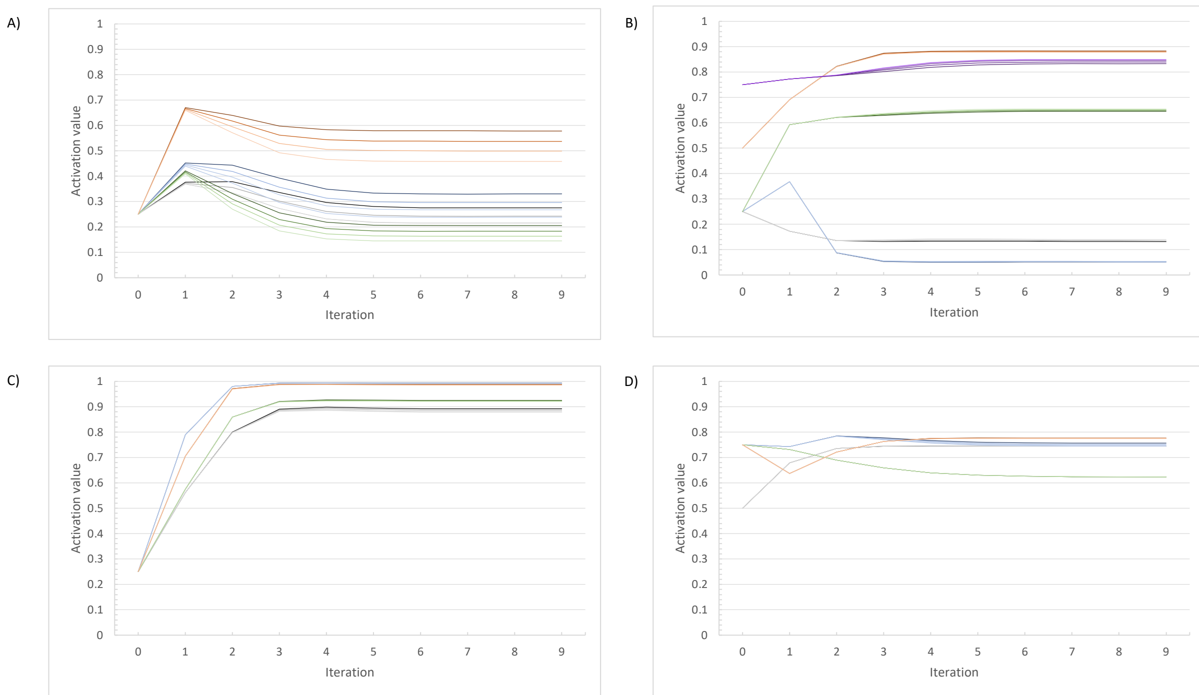

Figure F12: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 12 which represents technological advancements and innovation at three levels of intensity under current conditions. The darkest line of each colour represents the baseline scenario and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

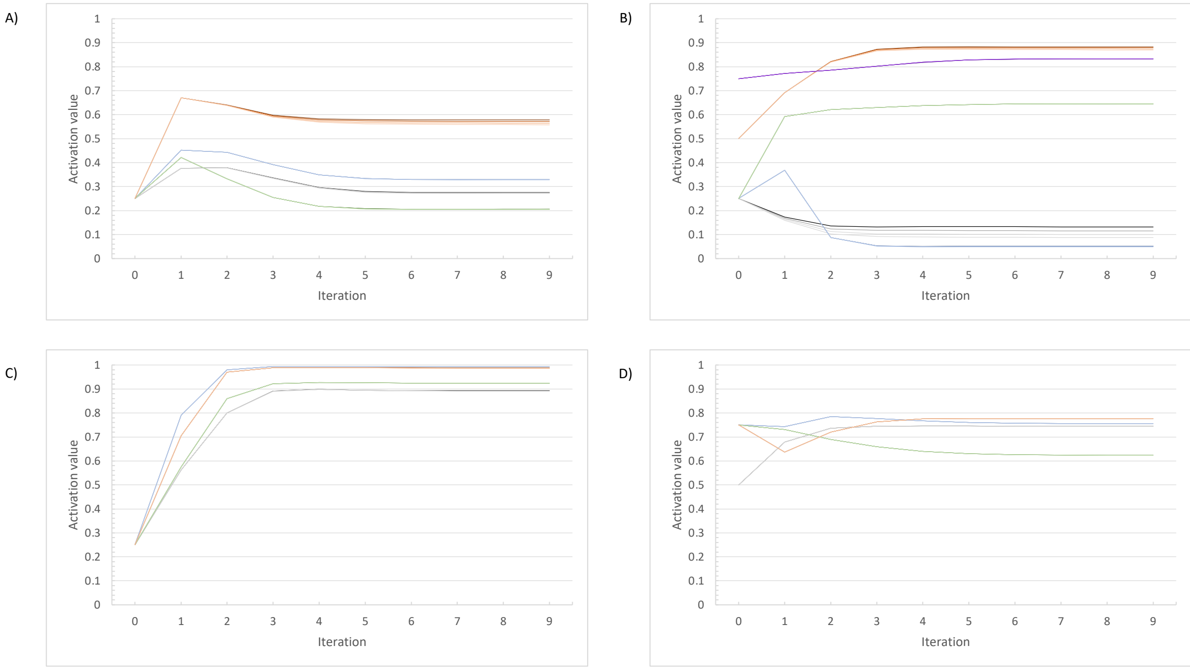

Figure F13: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 13 which represents addressing poverty and social inequalities at three levels of intensity under current conditions. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

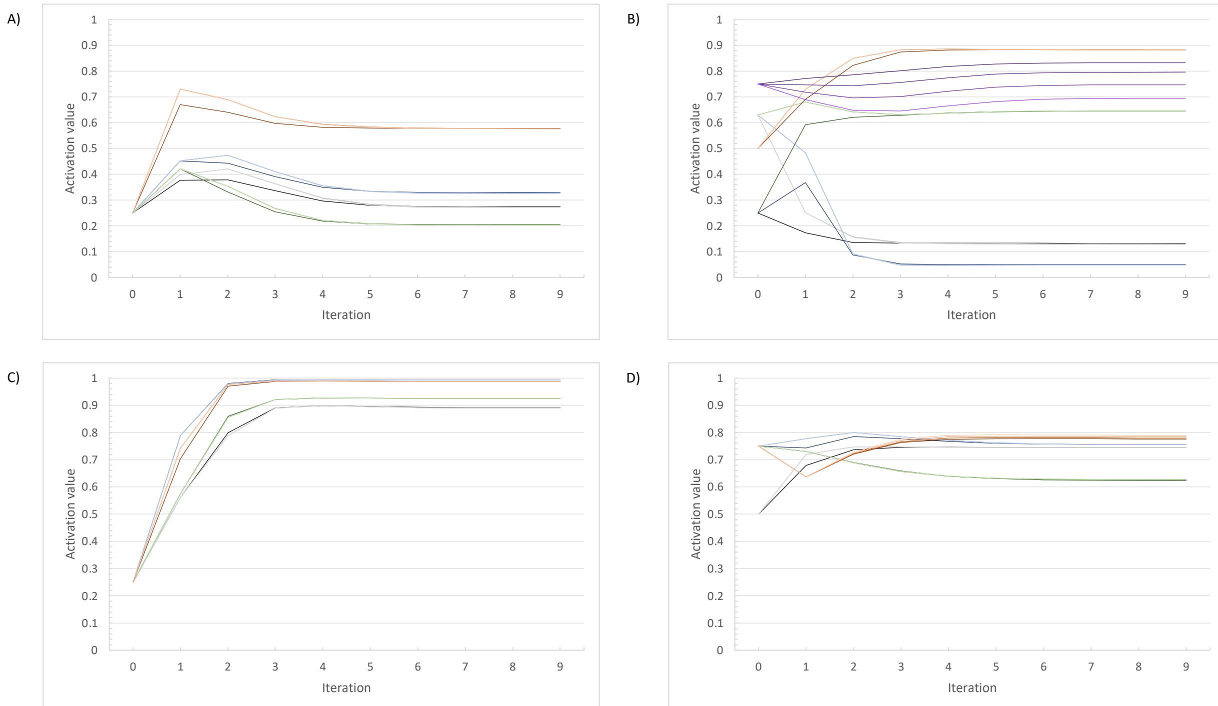

Figure F14: The activation values for the indicator variables over the nine iterations of the inference process for Scenarios 14 which represents reducing cost as a barrier to nutritious food and sustainable agricultural practices at three levels of intensity under climate change conditions. The dotted line represents the baseline scenario, the darkest line of each colour represents the baseline scenario under climate change and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

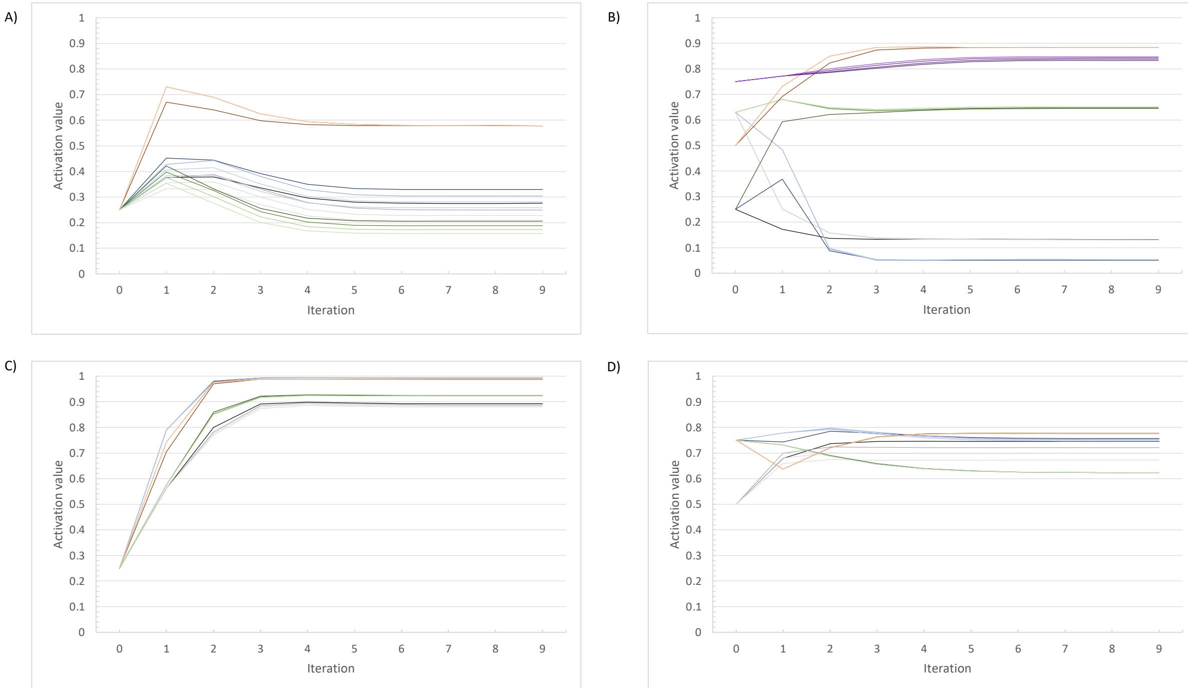

Figure F15: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 15 which represents increased international trade regulations and implementation at three levels of intensity under climate change conditions. The dotted line represents the baseline scenario, the darkest line of each colour represents the baseline scenario under climate change and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

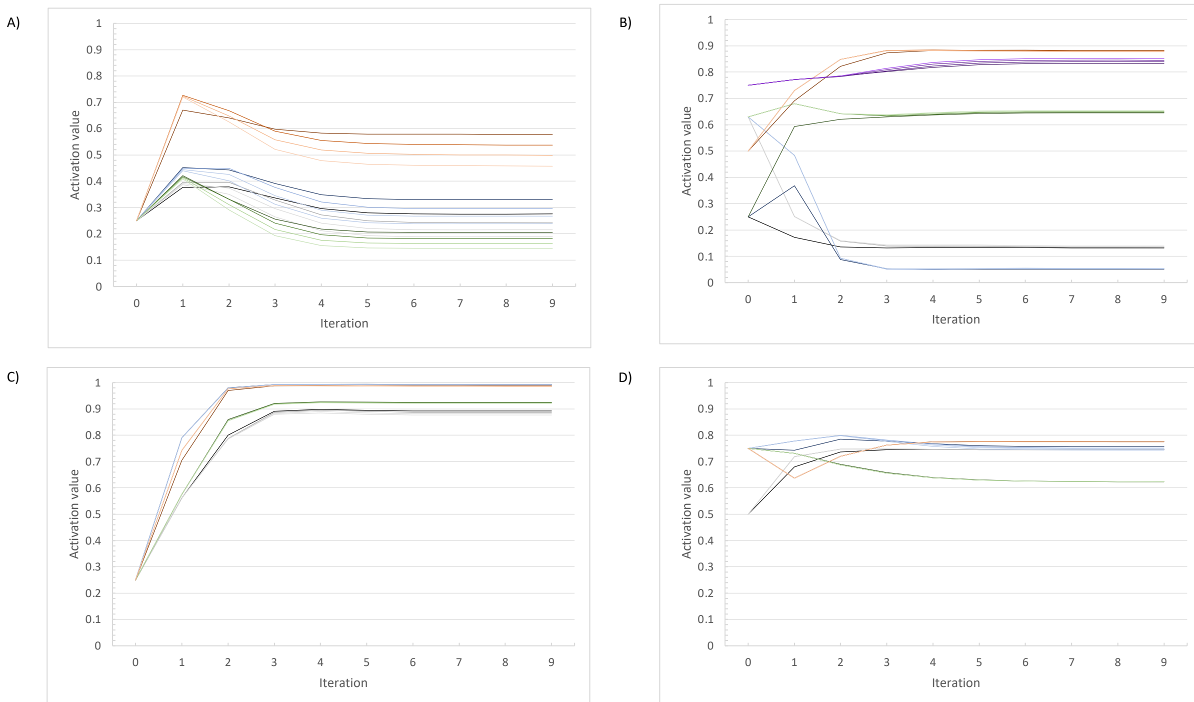

Figure F16: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 16 which represents technological advancements and innovation at three levels of intensity under climate change conditions. The dotted line represents the baseline scenario, the darkest line of each colour represents the baseline scenario under climate change and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

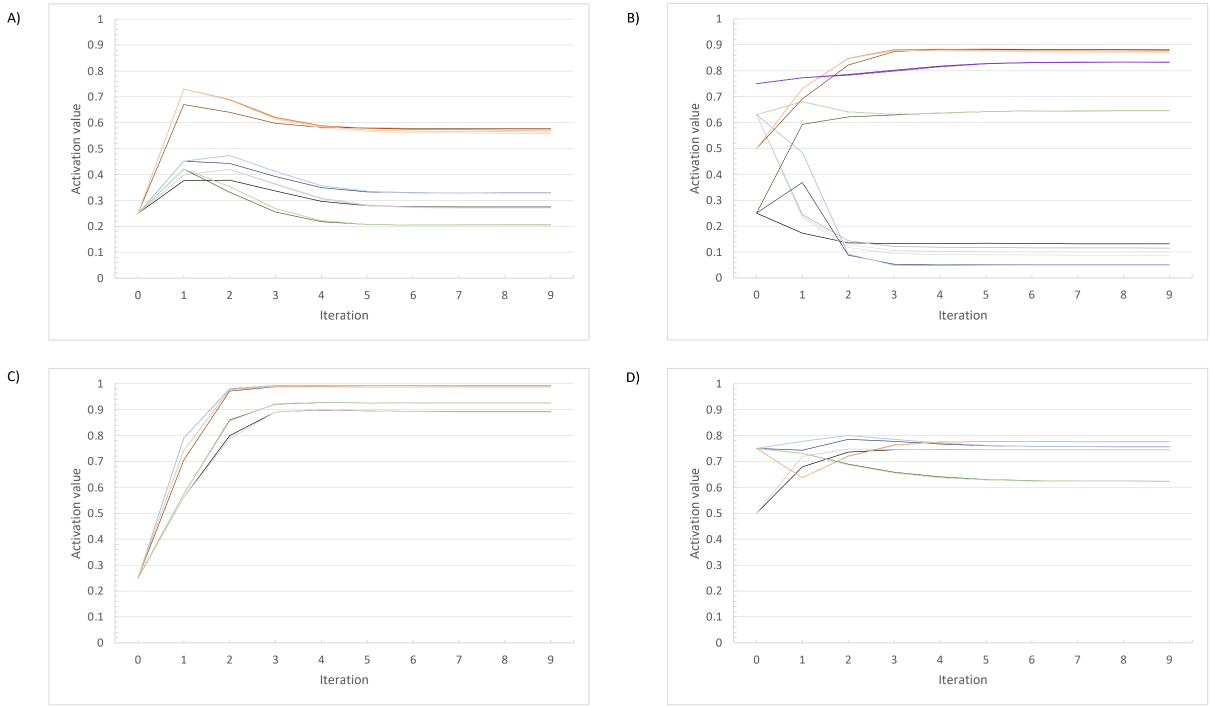

Figure F17: The activation values for the indicator variables over the nine iterations of the inference process for Scenario 17 which represents addressing poverty and social inequalities at three levels of intensity under climate change conditions. The dotted line represents the baseline scenario, the darkest line of each colour represents the baseline scenario under climate change and the lightest line represents the highest intensity of the intervention. **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

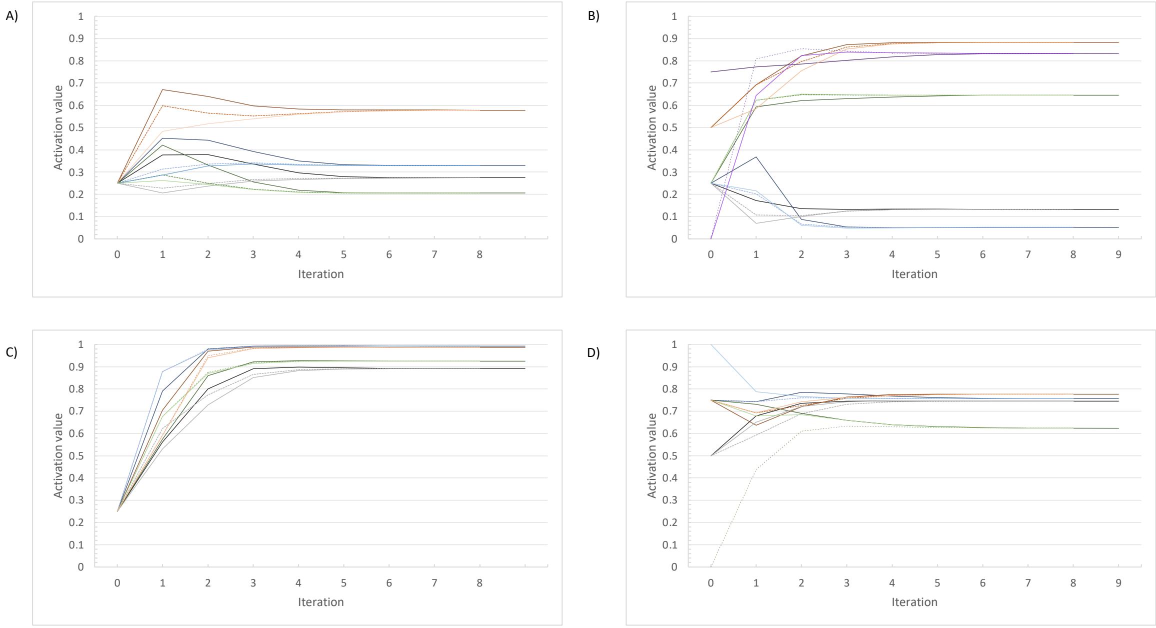

Figure F18: The activation values for the indicator variables over the nine iterations of the inference process for the high centrality scenario (dotted line) and the high outdegree scenario (light solid line) compared to the baseline (dark solid line). **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

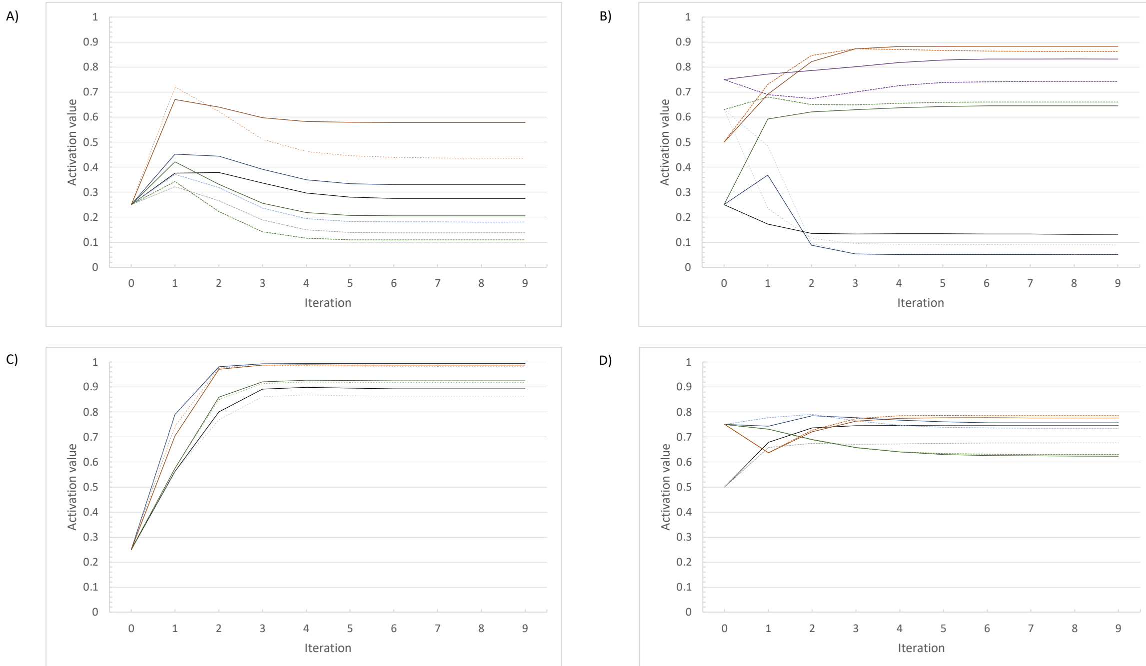

Figure F19: The activation values for the indicator variables over the nine iterations of the inference process for the "Hail Mary" scenario (dotted line), which was a combination of Scenario 10-13, compared to the baseline (solid line). **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).

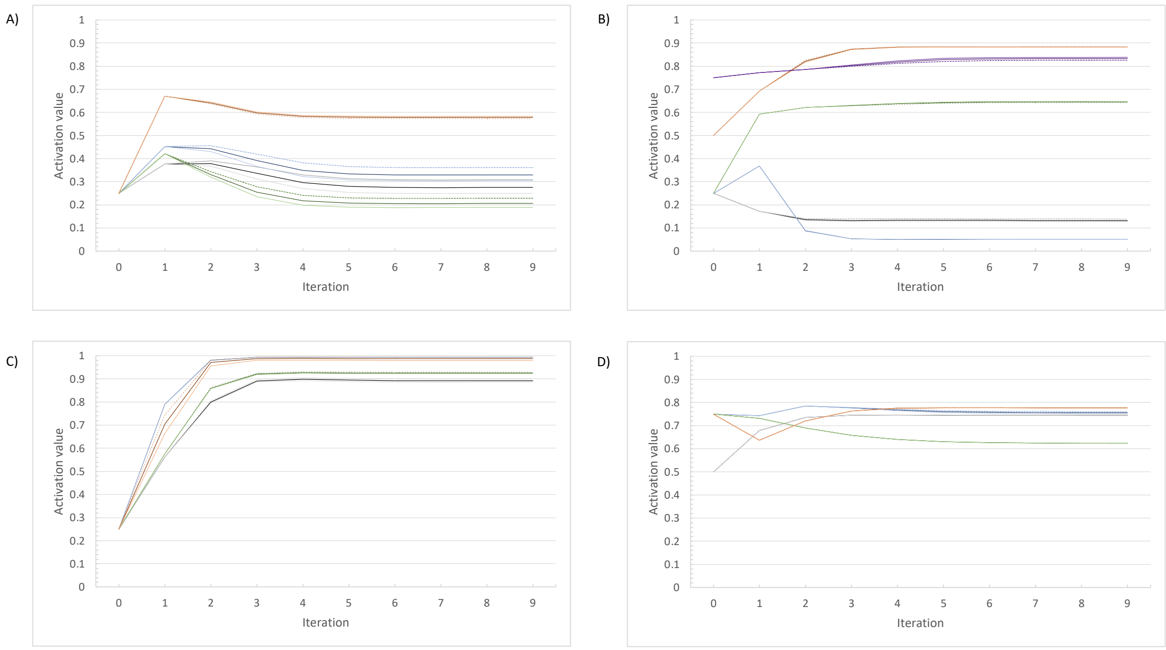

Figure F20: The activation values for the indicator variables over the nine iterations of the inference process for the sensitivity analysis with the relationships tested at the lowest possible value (dotted line) and highest possible value (light solid line) compared to the baseline (dark solid line). **(a)** The activation values for: antimicrobial use in terrestrial food-producing animal agriculture (black lines), antimicrobial use in aquaculture (blue lines), antimicrobial use in plant agriculture (green lines), and antimicrobial use in humans (orange lines). **(b)** The activation values for illness in humans (black lines), illness in food-producing animals (blue lines), illness in plant agriculture (green lines), healthcare costs (orange lines), and retail cost of food (purple lines). **(c)** The activation values for: resistance in food-producing animals (black lines), resistance in the wider environment (blue lines), resistance in plant agriculture (green lines), and resistance in humans (orange lines). **(d)** The activation values for: resistance from imported food products (black lines), domestic and international trade (blue lines), amount of imported food (green lines), and food security (orange lines).