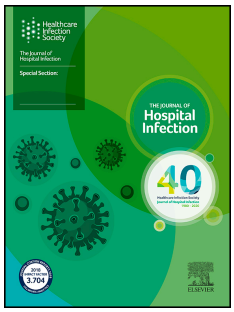
Journal Pre-proof



The use of complexity theory to inform antimicrobial stewardship: a scoping review

Gerry Hughes, Robert Cunney, David Mockler, Alida Fe Talento, Aisling O' Leary, Colm Bergin

PII: S0195-6701(22)00191-8

DOI: https://doi.org/10.1016/j.jhin.2022.06.004

Reference: YJHIN 6683

To appear in: *Journal of Hospital Infection*

Received Date: 2 January 2022

Revised Date: 2 June 2022

Accepted Date: 6 June 2022

Please cite this article as: Hughes G, Cunney R, Mockler D, Talento AF, Leary AO', Bergin C, The use of complexity theory to inform antimicrobial stewardship: a scoping review, *Journal of Hospital Infection*, https://doi.org/10.1016/j.jhin.2022.06.004.

Title Page

Title: The use of complexity theory to inform antimicrobial stewardship: a scoping review

Authors		
Name	**Department**	**Institution**
Gerry Hughes	Infectious diseases School of Medicine	St. James's Hospital Dublin Ireland Trinity College Dublin, Ireland
Robert Cunney	Clinical Microbiology	Children's Health Ireland, Temple Street, Dublin, Ireland Royal College of Surgeons, Dublin, Ireland
David Mockler	School of Medicine	Trinity College Dublin, Ireland
Alida Fe Talento	Clinical Microbiology	Children's Health Ireland, Temple Street, Dublin, Ireland Royal College of Surgeons, Dublin, Ireland
Aisling O' Leary	National Centre for Pharmacoeconomics School of Pharmacy	St. James's Hospital Dublin, Ireland Royal College of Surgeons, Dublin, Ireland
Colm Bergin	Infectious diseases	St. James's Hospital Dublin Ireland

	School of Medicine	Trinity College Dublin, Ireland

Corresponding author details	
Name	Gerry Hughes
Telephone	00353 87 9259678
Email	j.g.hughes@rgu.ac.uk

Short title: Complexity and antimicrobial stewardship: a scoping review

Main document word count:

Abstract

Background: Complexity theory has previously been used as a conceptual lens in human healthcare research. Antimicrobial stewardship (AMS) is an inherently complex healthcare intervention; however, the extent to which complexity has been operationalized in AMS is currently unclear.

Aim: To investigate if, and how, complexity theory has been used to inform AMS in human healthcare.

Methods: Scoping review methodology. Empirical research or policy specifically referencing complexity in relation to AMS were considered in any human healthcare setting and geographical location. Databases searched were: Cinahl, Cochrane Library, Embase, Medline, National Institute for Health and Care Excellence, PsycInfo, Scopus and Web of Science from inception to June 2020. Grey literature and other databases searched: EVIPNet, Google, Mednar, Proquest Theses, and the World Health Organization library of national antimicrobial resistance action plans. Non-English language articles were excluded.

Results: Of 612 records retrieved, 8 articles were included. Heterogeneity in study design and geographical location were noted. Three interventional studies evaluated AMS in hospital (n = 2) and long-term care (n = 1) settings. Remaining studies were non-interventional and proposed AMS strategies conceptualized through complexity theory. The importance of close engagement between researchers or policy administrators and the target population was emphasized in all studies, as a means of ensuring AMS relevance and success.

Conclusions: There is a paucity of AMS research informed by complexity theory, and no policy documents could be located using complexity as a guiding theory. Mixed methods, informed by complexity theory, is a potentially suitable strategy to develop, implement and evaluate AMS as a complex intervention.

Introduction

Complexity theory is a broad concept based on *"…relationships, emerging patterns and interactions."* [1] In its simplest form, complexity is the antithesis to traditional 'cause and effect' models, where the assumption is that addressing a historical event or issue will produce a predictable future response. Examples of this linear thinking can be found in manufacturing facilities. Such processes are arranged in sequence to yield predictable and standardized products, for example an aseptic compounding unit in a hospital pharmacy. Failure of a linear process can usually be addressed by deconstructing it to constituent parts to identify a dysfunctional component. Complex outcomes, on the other hand, are often unpredictable in nature and arise from multiple interactions between components in a non-linear fashion. [1, 2] Examples of everyday complex processes are interactions between air and water to produce weather events or the interaction of plants and animals in an ecological network. [1]

Complexity theory can also be applied to systems thinking, where a system can be thought of as an entity with multiple interacting components. [3] A complex adaptive system (CAS), therefore, occurs where the interaction between system components can be unpredictable, random, and not easily modifiable. [1] Plsek and Greenhalgh define a CAS as:

"…a collection of individual agents with freedom to act in ways that are not always totally predictable, and whose actions are interconnected so that one agent's actions changes the context for other agents." [2]

Antimicrobial resistance, a problem propagated from interaction between multiple different factors, within and outside of human healthcare, is inherently complex. [4] Antimicrobial stewardship (AMS) is a strategy aimed at addressing AMR by optimizing antimicrobial use. [5] It is a complex intervention in itself, and relies on the interaction between multiple actors

in various healthcare contexts and settings to ensure safe and effective antimicrobial therapy. [5, 6] Despite the similarities of AMS with principles of complexity, there is a paucity of empirical research on the application of complexity science to rational antimicrobial use. Furthermore, although established action plans and policies to address AMR firmly advocate a One Health approach, there is little or no suggestion that complexity has been applied to the One Health Agenda.

Thompson *et als* scoping review of complexity theory in health services research found a focus on relationships, self-organisation and diversity as aspects of complexity theory. [7] However, none of the articles focused on either AMR or AMS specifically. Notably, Thompson *et al* excluded quality improvement (QI) studies and included articles published up until June 2015. Talkhan *et al* have recently published a systematic review on the use of theory in the development and evaluation of behaviour change interventions to improve antimicrobial prescribing. [8] Their review did not identify the use of complexity as an informative element to behaviour change interventions. However, the authors focused on primary studies and did not search the grey literature.

Aim

The aim of this scoping review was to describe if, and how, complexity theory has been used to inform AMS research or policy and to identify any evidence gaps.

Methods

A preliminary search for registered scoping or systematic reviews or protocols was conducted on the Joanna Briggs Institute (JBI) Evidence Synthesis database, the Cochrane Database of Systematic Reviews and the Prospero database, of which none were found. A scoping review was chosen as the most suitable method for several reasons. The extent to which complexity

science has been used to inform AMS has not previously been explored. Furthermore, scoping reviews are a suitable method to identify if certain concepts are used, not just in research publications, but in policy or practice. Inclusion of such policy documents and sources are usually outside of systematic review parameters. Finally, as no systematic review was found on the use of complexity theory in AMS, a scoping review would determine if such a review is warranted in the future. The review was conducted according to scoping review guidelines from JBI. [9]

Protocol

An a-*priori* protocol (Supplementary material) was developed between study authors in accordance with the JBI scoping review manual. [9]

Inclusion criteria

Participants

AMS research or policy involving clinicians or patients and the public of all ages, in any healthcare setting, as well as those involved in the management of healthcare delivery.

Concept

Explicit use of complexity theory to conceptualise, design, implement or analyse AMS in human healthcare. The framework described in Supplementary File (Table I) was used to conceptualize complexity for this study.

Context

Healthcare settings such as acute hospitals or primary care centres in any geographical or economic setting were included. Larger healthcare contexts, such as governmental organisations, where complexity theory was cited in a published report, guideline or policy document were also included.

Evidence sources

Primary research(for example quantitative, qualitative or mixed methods) were included as well as secondary research such as literature reviews from peer-reviewed journals. Policy or policy-related reports from healthcare organisations concerned with AMR or AMS were also included.

Search strategy

1. Two databases were searched initially (Embase and Medline). Keywords and index terms from relevant publications in this search were used to build the search strategy across all databases. A medical subject librarian constructed the search strategy.
2. Research databases searched: Cinahl, Cochrane Library, Embase, Medline, National Institute for Health and Care Excellence, PsycInfo, Scopus and Web of Science from the date of archive inception to June 2020.
3. Grey literature and other databases searched: EVIPNet, Google, Mednar, Proquest Theses, and the WHO library of national AMR action plans.
4. Additional searching of reference lists of included publications.
5. Authors of included studies were contacted to enquire if they are aware of any relevant additional or unpublished data.

The search strategy is described in detail in Supplementary File (Table II).

Data extraction, analysis and presentation

Articles returned from searches were exported to Microsoft Excel ® where titles and abstracts were independently screened by two authors. Articles that met the inclusion criteria underwent a full text review. A third reviewer was available to resolve disagreements where

necessary, through discussion with the other authors. Data were charted on summary tables in Microsoft Word ® and reported descriptively.

Results

Database searches yielded 612 initial records. After removing duplicates, titles and abstracts or executive summaries of 561 publications were screened, of which 528 were excluded. Full text review was conducted on 33 articles, of which 25 were excluded, leaving 8 articles included in the review [10-17] (Figure 1).

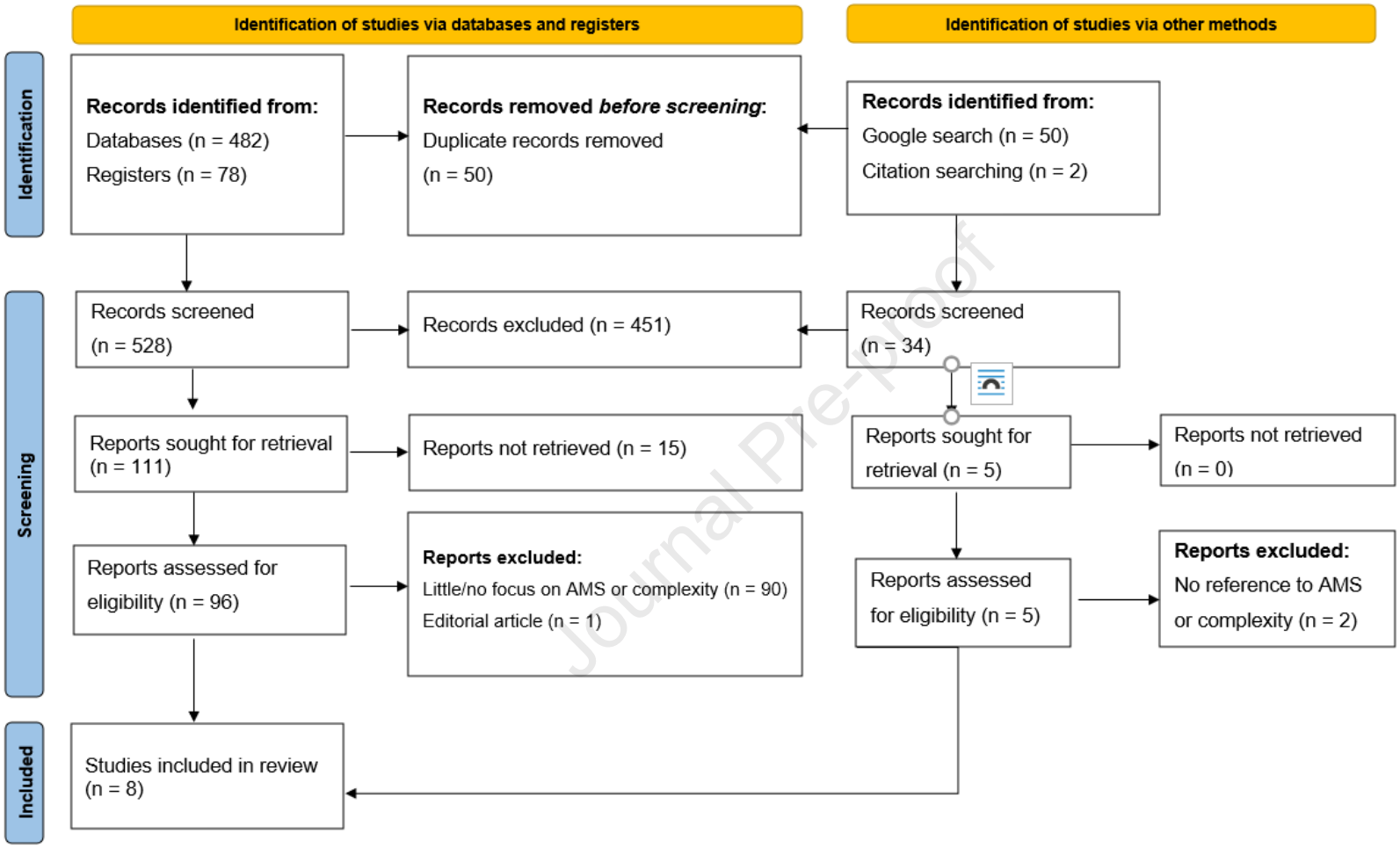


Figure 1: PRISMA flow chart, adapted from Page *et al* (2021) **[18]**. Automation tools were not used to assist data collection or analysis; AMS = antimicrobial stewardship

Study characteristics

Included studies were heterogenous in terms of study design, healthcare context and geographical location. There were three interventional studies, [11, 12, 15] one cross-sectional survey, [16] two case studies, [14, 17] one literature review [13] and one short article describing a case vignette. [10] The contexts of these studies were varied: primary care, [10, 16] acute care, [12, 15] ambulatory care, [17] long term care [11] and the remaining two from regional or national policy perspectives. [13, 14] Geographical locations were also diverse with two studies from western Europe, [12, 15] one from the US, [11] two from Africa, [16, 17] one from China, [14] one focusing on low/middle income countries (LMICs) [13] and one not specified. [10] Using the complexity theory characteristics previously described by Plsek and Greenhalgh [2] (Supplementary File Table I), included articles were searched for incorporation of these characteristics to the studies. A summary of the findings is available in the Table I.

Study findings

The interventional studies used complexity as a guiding theory and included study participants as a co-design strategy. The non-interventional studies used complexity theory to propose potential interventions to guide antimicrobial prescribing behaviour change (Table II). However, there was variation in the extent to which complexity theory was operationalised in the studies. For example, Merrett *et al* [13] and Wang *et al* [14] refer to CAS in general terms and integrate it to their studies in a relatively unstructured format. Conversely, Adamu *et al* specifically used complexity theory as a framework to analyse their data. This approach enabled the construction of causal loop diagrams to illustrate feedback mechanisms within their system of antimicrobial use in primary care. The heterogenous

nature of the studies proposed a challenge to perform synthesis on the data. However, two specific themes were notable: the importance of considered communication in the conduct of AMS and the utility of mixed methods as an AMS research strategy.

Table I: Use of complexity theory in included article

Importance of tailored communication strategies in AMS

Sturmberg argued that merely educating doctors on prudent prescribing practices does not address other issues such as patient beliefs and perceptions of a satisfactory consultation. Instead, a focus on this communication is required to break the reinforcement of antibiotic prescribing. [10] This was exemplified by other studies where, for example, providing clinicians with prescribing feedback led to improvements in antimicrobial prescribing quality. [11, 12, 15] Cunney *et al* [15] found that feedback was best delivered to junior doctors during scheduled ward rounds, while McLellan *et al* [12] provided additional time and space for participants to reflect on their prescribing practice.

As part of considerate communication approaches, Zimmerman *et al* [11] and Lanham *et al* identified the importance of close communication and regular exchanges between those seeking to optimise antimicrobial use, and the study population . [17] For example, when Zimmerman *et al* [11] realised that healthcare providers were not engaging with online education sessions, they quickly switched to face-to-face sessions to increase impact and a team leader was nominated within the study population.

Use of mixed methods

The QI studies used mixed methods approaches to study antimicrobial prescribing and modify their interventions in real time, based on participant feedback. [11, 15, 17] McLellan *et al* used a more rigid approach of qualitative methods nested within an RCT to provide antimicrobial prescribing feedback to junior doctors and generate an interventional theory to inform future studies. [12] .

Table II: Summary of study characteristics and results

Discussion

In an explicit way, complexity theory has not been extensively used to inform AMS in human healthcare, despite previous calls for complexity-driven approaches to healthcare interventions. [2, 19] The relatively low number of articles included in this review and their heterogenous nature suggests a fragmented and disparate application of complexity theory to AMS. Indeed, this posed a challenge to synthesise the evidence for this review. However, this could also be considered as a strength of complexity theory, in that it has been integrated as a conceptual framework in a variety of research methods and contexts. Papoutsi and Greenhalgh have previously highlighted this point, that complexity offers "…*a flexible and emergent approach…"* to conducting healthcare research. [19]

One of the potential challenges of capturing the integration of complexity theory and AMS is how this is reported in the literature. In our review, Adamu *et al,* [16] Merrett *et al* [13] and Wang *et al* [14] discussed the unexpected impact of financial incentives and disincentives on rational antimicrobial prescribing. However, this has previously been termed a *"squeezing the balloon"* effect, where introducing a restrictive measure may result in an adaptive, compensatory response. [20] This effect has recently been reported in aUK primary care, where a financial incentive resulted in a sustained reduction in antimicrobial prescribing for uncomplicated respiratory tract infections, but with an unpredictable reduction in appropriate prescribing for lower respiratory tract infections. [21] These two studies describe one facet of complexity theory (unexpected occurrences), but neither of these studies specifically reference complexity. Therefore, the apparent lack of complexity theory integration to AMS research as an informative framework to AMS may be due to semantics. This is likely also true of policy and policy-related publications. A 2014 Department of Health (England) publication on factors influencing AMR describes multifactorial problems as *"messy,*

complex situations" [22] An detailed systems map in this report elegantly describes the myriad influences on antimicrobial prescribing in the style of a causal loop diagram but, again, without specifically mentioning complexity as an overarching theory.

The recently updated Medical Research Council guidelines on developing and evaluating complex interventions advocates considering intervention development in a system context, where the intervention itself interacts with the local environment an emergent, unpredictable fashion. As AMS is, by definition from the MRC, a complex intervention, frequently deployed in complex settings such as acute hospitals, future AMS endeavours will likely benefit from using complexity science as a guiding theory. [23]

Strengths and limitations

This review adds to the literature on theory-informed AMS research. The search strategy widened the explorative scope in comparison to previous reviews. Although the number of included articles was relatively small, they transcended across different contexts and settings and provided recommendations for AMS interventions applicable to these settings. In keeping with scoping review methodology, this review did not appraise the quality of the included articles. However, it is clear from the limited and heterogenous publications available, a systematic review on the application of complexity theory to AMS in human healthcare is not currently warranted.

Conclusions and future work

Antimicrobial prescribing and consumption behaviours are part of an overall complex network of behaviours within healthcare settings. While there is extant literature on this subject, little has been conducted from a complexity theory perspective.

Understanding the drivers and reinforcements of these behaviours is important for healthcare systems to foster cultures of prudent antimicrobial use. Complexity theory is a practical and useful way to conceptualise and design AMS interventions in human healthcare. It is unclear whether those concerned with addressing AMR are unaware of complexity as a practical theory to inform AMS, whether they have not embraced it as an informative concept or whether aspects of complexity are being utilized but just not explicitly. Future research on the design, implementation and evaluation of AMS interventions in healthcare should consider complexity as an informative theory to guide study designs. Equally, policy makers and regulators concerned with prudent antimicrobial use should consider complexity in the administration and monitoring of their programmes.

Conflicts of Interest

None to declare

Funding

This research did not receive any specific grant funding from agencies in the public, commercial or not for profit sectors.

References

[1] The Health Foundation. Evidence scan: Complex adaptive systems. 2010. Available from: https://www.health.org.uk/publications/complex-adaptive-systems#:~:text=This%20evidence%20scan%20collates%20more,or%20development%20in%20this%20area.
[2] Plsek PE, Greenhalgh T. Complexity science: The challenge of complexity in health care. *BMJ* 2001; 323: (625-8).
[3] Peters DH. The application of systems thinking in health: why use systems thinking? *Health Research Policy and Systems* 2014; 12: (51).
[4] Holmes AH, Moore LS, Sundsfjord A*, et al.* Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 2016; 387: (176-87).
[5] Dellit TH, Owens RC, McGowan JEJ*, et al.* Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; 44: (159-77).
[6] Health Protection Surveillance Centre. Guidelines for antimicrobial stewardship in hospitals in Ireland. 2009. Available from: https://www.hpsc.ie/a-z/microbiologyantimicrobialresistance/infectioncontrolandhai/guidelines/File,4116,en.pdf.
[7] Thompson DS, Fazio X, Kustra E*, et al.* Scoping review of complexity theory in health services research. *BMC Health Serv Res* 2016; 16: (87).
[8] Talkhan H, Stewart D, Mcintosh T*, et al.* The use of theory in the development and evaluation of behaviour change interventions to improve antimicrobial prescribing: a systematic review. *J Antimicrob Chemother* 2020; 75: (2394-410).
[9] Peters MDJ, Godfrey C, McInerney P*, et al.* Chapter 11: Scoping reviews (2020 Version). 2020. In: Joanna Briggs Institute Reviewer's Manual [Internet]. The Joanna Briggs Institute. Available from: https://reviewersmanual.joannabriggs.org/.
[10] Sturmberg J. Systems and complexity thinking in general practice. Part 2: application in primary care research. *Aust Fam Physician* 2007; 36 4: (273-5).
[11] Strategies to reduce potentially inappropriate antibiotic prescribing in assisted living and nursing homes [Internet]. 2014 [cited 20/02/2020]. Available from: https://www.ahrq.gov/hai/patient-safety-resources/advances-in-hai/hai-article8.html.
[12] McLellan L, Dornan T, Newton P*, et al.* Pharmacist-led feedback workshops increase appropriate prescribing of antimicrobials. *J Antimicrob Chemother* 2016; 71: (1415-25).
[13] Merrett GL, Bloom G, Wilkinson A*, et al.* Towards the just and sustainable use of antibiotics. *J Pharm Policy Pract* 2016; 9: (31).
[14] Wang L, Zhang X, Liang X*, et al.* Addressing antimicrobial resistance in China: policy implementation in a complex context. *Global Health* 2016; 12: (30).
[15] Cunney R, Kirrane-Scott M, Rafferty A*, et al.* 'Start smart': using front-line ownership to improve the quality of empiric antibiotic prescribing in a paediatric hospital. *BMJ Open Qual* 2019; 8: (e000445).
[16] Adamu AA, Gadanya MA, Jalo RI*, et al.* Factors influencing non-prescription sales of antibiotics among patent and proprietary medicine vendors in Kano, Nigeria: a cross-sectional study. *Health Policy Plan* 2020; 35: (819-28).
[17] Lanham HJ, Leykum LK, Taylor BS*, et al.* How complexity science can inform scale-up and spread in health care: Understanding the role of self-organization in variation across local contexts. *Soc Sci Med* 2013; 93: (194-202).

[18] Page MJ, Moher D, Bossuyt PM*, et al.* PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021; 372: (n160).
[19] Greenhalgh T, Papoutsi C. Studying complexity in health services research: desperately seeking an overdue paradigm shift. *BMC Med* 2018; 16: (95).
[20] Burke JP. Antibiotic resistance-squeezing the balloon? *JAMA* 1998; 280: (1270-1).
[21] Bou-Antoun S, Costelloe C, Honeyford K*, et al.* Age-related decline in antibiotic prescribing for uncomplicated respiratory tract infections in primary care in England following the introduction of a national financial incentive (the Quality Premium) for health commissioners to reduce use of antibiotics in the community: an interrupted time series analysis. *J Antimicrob Chemother* 2018; 73: (2883-92).
[22] UK Department of Health. Antimicrobial resistance (AMR) systems map. 2014. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/387746/Microbial_Maps.pdf.
[23] Shahsavari H, Matourypour P, Ghiyasvandian S*, et al.* Medical Research Council framework for development and evaluation of complex interventions: A comprehensive guidance. *J Educ Health Promot* 2020; 9: (88).

Table I: Use of complexity theory in included articles

Author	Elements of complexity theory discussed
Sturmberg [10]	Identification of internalised patient and doctor rules which drive antibiotic use for sore throat Non-linearity identified through reinforcing feedback loops which drive doctor and patient behaviour Paradoxically, doctors may choose antibiotic prescription for sore throat (although not evidence based) as there is less workload involved than avoiding prescription
Lanham *et al* [17]	Self-organisation was intentionally supported and encouraged in the original RCT The mobile phone intervention supported existing interactional behaviour to produce new emergent behaviours Intervention effects spread outside the intervention group to the control group which was an unexpected occurrence
Zimmerman *et al* [11]	Unexpected behaviour occurred in variable adoption of intervention components across study settings Physicians were identified as behaviour attractors in nursing homes

Author	Elements of complexity theory discussed
McLellan *et al* [12]	Feedback workshops facilitated optimal antimicrobial prescribing behaviour by junior doctors
	Proposition that junior doctors could foster prudent antimicrobial prescribing in hospital settings
	Prescribing behaviour emerges from interactions between junior doctors' individual (e.g. knowledge) and social (e.g. workplace culture) variables
Merrett *et al* [13]	Identification of influencing factors, individuals and organisations which drive AMR and the interactions between these elements
	Fluid boundaries, such as those between public and private healthcare sectors, facilitates access to antibiotics
	Continuous evaluation of health systems required to observe intervention impact and identify unexpected consequences
	Tension, for example between mass antimicrobial administration campaigns and the potential for development of AMR
	Potential for inappropriate antimicrobial use to become the normal pattern within a healthcare system

Author	Elements of complexity theory discussed
Wang *et al* [14]	Mapped the emergent behaviour of multiple actors within the healthcare system as adaptive responses to antibiotic regulation
	Described overall pattern of antibiotic prescription and consumption based on this adaptive behaviour
	Highlighted unexpected outcomes from antibiotic regulation and policy such as reduced impact of regulation to decrease overall antibiotic consumption
	Tension between regulators ensuring financial health of hospital systems but also controlling antibiotic use
	Internalised rules held by patients and prescribers drive inappropriate antibiotic use
	Fluid boundaries between antibiotic access routes
Cunney *et al* [15]	Leveraged attractors within the hospital system to co-design intervention
	Preference of participants for written vs electronic feedback, rejection of reminder cards attached to reference material and rebuffing education opportunities were unexpected occurrences

Author	Elements of complexity theory discussed
	Participants identified simple rules to achieve study objectives Emergent behaviour occurred when junior doctors exiting their rotation informed incoming junior doctors of the principles of prudent antimicrobial prescribing, which sustained the intervention
Adamu *et al* [16]	Attractors/influencing factors on antibiotic consumption identified through causal loop diagrams

AMR: antimicrobial resistance; RCT: randomised controlled trial

Table II: Summary of included articles

Author	**Setting**	**Aim(s)**	**Study population/sample size**	**Methods**	**Intervention**	**Outcomes and key findings**
Sturmberg *et al* [10]	Primary care	To gain contextual understanding of known problems in primary care	N/A	Narrative conceptualization of a sore throat vignette through CAS	N/A	Highlighted decision-making processes in prescribing antimicrobials for sore throat. Complexity science is a useful tool to inform AMS in primary care
Lanham *et al* [17]	Ambulatory care in Kenya	To examine the role of self-	538 ambulatory	Re-analysis of a previously published RCT	N/A	Importance of integrating intervention with local organisational infrastructure

Author	Setting	Aim(s)	Study population/sample size	Methods	Intervention	Outcomes and key findings
		organisation in the scale up and spread of an antiretroviral adherence intervention	care HIV patients			Close contact between investigators and participants key for intervention adoption Interventions are shaped by their environments and outcomes may spread outside study population
Zimmerman *et al* [11]	US LTCS	To optimise antimicrobial	Healthcare professionals, residents/	QI methodology	Antibiotic prescriber, resident/residen	Suboptimal antimicrobial use decreased in nursing

Author	Setting	Aim(s)	Study population/sample size	Methods	Intervention	Outcomes and key findings
		prescribing in LTCS	resident families		t family education Communication form for healthcare staff to report infection Feedback to stakeholders	homes, to a lesser extent in residential care Resident/family education did not result in change Use of CAS provided observations and guidance for further QI projects

Author	Setting	Aim(s)	Study population/sample size	Methods	Intervention	Outcomes and key findings
McLellan et al [12]	UK acute care hospital	To investigate if providing feedback to junior doctors optimized antimicrobial prescribing	35 junior doctors	Mixed methods nested in an RCT	Pharmacist-led antimicrobial prescribing feedback to doctors	Lower suboptimal prescribing in intervention group Knowledge and awareness of suboptimal antimicrobial prescribing important to drive appropriate prescribing habits Mechanism for change suggested by placing junior doctors as positive

Author	Setting	Aim(s)	Study population/sample size	Methods	Intervention	Outcomes and key findings
						influencers of antimicrobial prescribing
Merrett *et al* [13]	Governmental/policy level of LMICs	Identify interventions to optimize antimicrobial access	Citizens of LMICs	Literature review	N/A	Interventions need to account for the complex system in which antibiotic use occurs Synergies between multiple interventions (e.g. access to diagnostics, ensuring drug quality) are needed

Author	Setting	Aim(s)	Study population/sample size	Methods	Intervention	Outcomes and key findings
Wang *et al* [14]	Governmental/policy level in China	To investigate the implementation of regulations and strategies to control antimicrobial use in China	Chinese citizens	Case study	N/A	Review identified routes to reverse the unexpected rise in Chinese antimicrobial use, despite regulations Heterogeneity of actors in the system need to be accounted for Complicated incentive schemes should be simplified

Author	Setting	Aim(s)	Study population/sample size	Methods	Intervention	Outcomes and key findings
Cunney *et al* [15]	Irish paediatric hospital	To improve documentation and compliance with local antimicrobial prescribing policy	Emergency department doctors	QI methodology	Feedback sessions and plan, do, study, act cycles	Maintained 100% compliance rate with agent choice and documentation at 18 months follow up Antimicrobial consumption decreased Improvement in antimicrobial use quality indicator measurements

Author	Setting	Aim(s)	Study population/sample size	Methods	Intervention	Outcomes and key findings
						Participant co-design helped foster frontline ownership of the project Goal setting and action planning identified as key components
Adamu *et al* [16]	Primary care in Nigeria	To describe the volume of non-prescription antibiotic sales and	453 'medication retailers'	Cross-sectional survey	N/A	Construction of causal loop diagrams to explain behavioural factors

Author	Setting	Aim(s)	Study population/sample size	Methods	Intervention	Outcomes and key findings
		associated behavioural factors				66.67% of participants sold antibiotics without a prescription Provider training decreased the likelihood of selling antibiotics without a prescription

AMS: antimicrobial stewardship; CAS: complex adaptive system; LMIC: low/middle income country; LTCS: long term care setting; QI: quality improvement; RCT: randomized controlled trial; UK: United Kingdom; US: United States

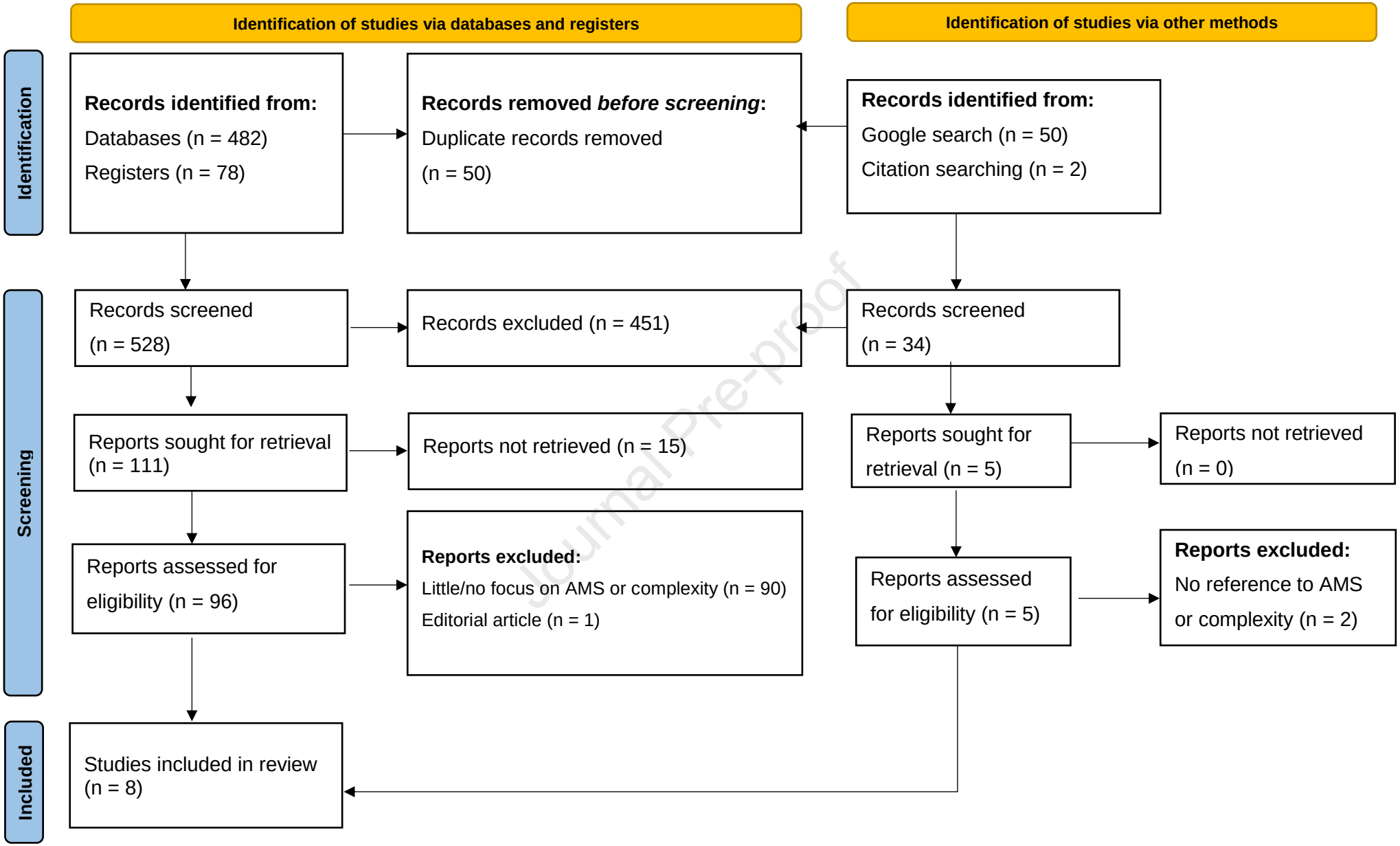


Figure 1: PRISMA Flow Chart, adapted from Page *et al* 2021. Automation tools were not used to assist data collection or analysis; AMS = antimicrobial stewardship