Antimicrobial resistance in the United Kingdom: a mixed-methods dissertation on diagnostics, discourse, and decision-making

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Abbreviations

AMR	Antimicrobial Resistance
CCG	Clinical Commissioning Group
CDoH	Commercial Determinants of Health
CRE	Carbapenem Resistant *Enterobacteriaceae*
CRP	C-reactive protein
DHSC	Department of Health and Social Care
GP	General Practitioner
HIV	Human Immunodeficiancy Virus
LSHTM	London School of Hygiene and Tropical Medicine
MALDI-TOF	Matrix Assisted Laser Desorption Ionisation Time-of-Flight
MRSA	Methicillin-resistant *Staphylococcus aureus*
MS	Mass spectrometer
MSSA	Methicillin-sensitive *Staphylococcus aureus*
NAP	National Action Plan
NCD	Non-communicable diseases
NHS	National Health Service
PCR	Polymerase chain reaction
PIRU	Policy Innovation Research Unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
RIT	Rapid Influenza Tests
RDT	Rapid Diagnostic Tests
RSV	Respiratory Syncytial Virus
SDIL	Soft Drink Industry Levy
TB	Tuberculosis
WHO	World Health Organization

Abstract

Background Antimicrobial resistance (AMR) is the focus of ongoing global health policy attention. A key policy lever in the United Kingdom is the wide-scale adoption of rapid diagnostic tests (RDTs) in hospitals, laboratories, and communities. I sought to analyse the evidence for the effectiveness of certainrapid diagnostic tests, health care providers' perceptions thereof, the framing of discourses surrounding AMR, and whether key indicators in combatting AMR such as 'appropriate prescribing' were helpful, or indeed the right outcomes to measure.

Methods I conducted (i) a systematic review and meta-analysis of the evidence underpinningrapid diagnostic tests for bacterial identification and antibiotic susceptibility testing, (ii) qualitative, semi-structured interviews of health care providers and senior managers in six study sites across the UK, underpinned by Diffusion of Innovation Theory (iii) a critical discourse analysis of submissions to the UK Health and Social Care Committee on AMR, and (iv) a secondary analysis of the qualitative interview data, guided by meso-level theory drawn from Strauss and Abbott in order to problematise the concept of 'appropriate' antibiotic prescribing.

Results (i)rapid diagnostic tests for bacterial identification and antibiotic susceptibility testing were not readily amenable to meta-analysis due to a variety of methodological problems in the primary studies. Where it was possible to undertake aggregate effect estimates**,** the meta-analysis showed that the introduction ofrapid diagnostic tests did not significantly reduce in-hospital mortality (RR 0.83, 95% CI 0.60 - 1.15) or length of stay (weighted mean difference = -0.36, 95% CI -1.67 to 0.96) for experimental studies. (ii) The analysis of the 71 qualitative interviews, drawing on Diffusion of Innovation Theory, found that, though there was support for certain types of testing in specific contexts, interviewees had serious concerns about the unintended consequences linked with testing adoption, including the development of superlabs, centralisation, and privatisation. (iii) I identified dominant narratives in the submissions to the UK House of Commons Committee on AMR and found that industries used 'market paradoxical' discursive strategies; on the one hand, asking for subsidies and incentives, but on the other hand explaining that regulation would be detrimental to 'innovation'. (iv) My secondary qualitative analysis found that while some

solutions to the AMR crisis appear value-neutral, such as improving ‘appropriate’ prescribing, they are in fact contributing to a narrative of corporate capture in public health.

Discussion As the dissertation progressed, it became clear thatrapid diagnostic tests for AMR could helpfully be contextualised within the field of the Commercial Determinants of Health (CDoH). This is because corporations and governments alike deploy crisis narratives in order to divert public sector funds to the private sector in a low-regulation environment. Industries in AMR adopt several strategies that are well-known to researchers in CDoH, and this suggests that the definition of CDoH research should be widened beyond an interest in products or commodities that cause only non-communicable diseases. I also consider the material effects of privileging of the private sector in public health, and link my research with the ongoing COVID-19 pandemic response. The thesis concludes with a summary of the main strengths and limitations, and suggestions for further research, including the need for research on the use of evidence by industry; further analysis of industry narratives in public discourse; qualitative research with stakeholders and experts on industry influence in research; and analysis of industry messaging in social media in comparison to that of public health organisations.

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Preface for examiners

I have been reliably informed that the style of this thesis may be unusual!

I therefore wanted to tell you upfront what to expect in the coming pages. I will start each chapter with an introduction, explaining where I was in the research, but also in my thought processes. I will be direct. Then, I will present a paper or thesis chapter, as you might expect, and will end with a statement of research impact. My hope is that you will find the preambles work to tie together the different components of this paper-style thesis. More than that, though, this approach should give you an under-the-bonnet view of my research process, which I hope in turn will give you confidence in my conclusions. Quite the opposite of a black box, I have taken the decision to expose – highlight, even - the uncertainties and questions throughout this thesis.

I look forward to discussing my research with you.

Rebecca

Introduction

Preamble

This dissertation started life very differently in 2017 to how it has ended in 2021. When I began my research, I was convinced that rapid diagnostic tests (RDTs) were the future of antimicrobial resistance (AMR), and I had hoped to improve the extant evidence base for them in order to propel their use into the mainstream. I was working at the time as a research fellow on the evaluation of the implementation of the UK's 2013-2018 AMR strategy, and was not alone in this way of thinking; national guidance, AMR experts, and international bodies all extolled the virtues of diagnostics for AMR, and expressed concern that they were not being rolled out more widely.(1–6) Given the relative paucity of systematic reviews and meta-analyses on the clinical effectiveness of diagnostics, and the ways that diagnostic tests are commissioned in the UK, I considered this to be a two-pronged problem requiring (i) evidence generation and (ii) qualitative interviews with the intended users of such tests – doctors, nurses, pharmacists, and so on – to probe questions of acceptability, feasibility, and barriers to access. This programme of research would, I felt sure, represent a straightforward line from research into practice, and through it I would be feeding into programmes of research in the public health community on how best to adapt and adopt novel technologies across the UK.

The first signs of trouble were visible before the systematic review was even completed. As I read study after study for the screening process, I started to realise with some discomfort that the included studies seemed to be presenting findings that were not definitively demonstrating the case for diagnostic testing. When I conducted the meta-analyses, I was, therefore, not entirely surprised to find that the summary effect estimates did not demonstrate that these particularrapid diagnostic tests were affording any clinical gains for hospitalised patients. To be specific,rapid diagnostic tests were seemingly improving clinical outcomes only when there were important confounders, non-randomised study designs, and there was more than a suggestion of small study effect and publication bias. This had the effect of biasing effect size estimates upward – that is, over-estimating the clinical effectiveness of these tests.

At this point - before finalising my systematic review analyses - I had already started to undertake my semi-structured qualitative interviews with key experts in six case study sites across the UK. I was similarly struck by the ambivalence, or even hostility, I found in some NHS professionals who were intended to be the RDT users. Though my topic guide was open-ended, I had grouped my questions according to themes pertaining to Diffusion of Innovation Theory. There were reasons, I had thought, that the diagnostics were being taken up preferentially – I would in 2017 have said 'successfully' - in some NHS Trusts, but not in others. I had intended to determine what those conditions were so I could develop a series of recommendations for Trusts looking to expand the commissioning of diagnostics. What I found when I coded my interview data was that the respondents who were negative about the prospect ofrapid diagnostic tests entering their practice identified one particular reason why they did not want to adopt the technology: they felt it was simply not good enough.

At this point, I had found (i) that the evidence did not support the adoption of certainrapid diagnostic tests, and that (ii) the intended service users did not want, on the whole, to introduce them either. And yet a new AMR strategy had just been published in early 2019, which yet again highlighted the critical importance of introducingrapid diagnostic tests in the 'fight' against AMR.(7) Here, it must be said, my research definitively changed tack. I wanted to understand why, given (i) and (ii), recommendations for diagnostics were omnipresent in national-level documents and top-down policy mandates. I decided to undertake two new pieces of research: a critical discourse analysis of the submissions to the UK House of Commons Health and Social Care Committee on AMR; and a secondary analysis of my qualitative interview data using a different theoretical lens to unpick the concept of 'appropriate' antibiotic prescribing, which was the stated aim of introducingrapid diagnostic tests. By this point I had become aware of – and had begun to contribute to - wider AMR debates in the social sciences on incentivising pharmaceutical companies to develop novel antibiotics. For example, in 2018/2019 there were serious discussions at the National Institute for Health and Clinical Excellence (NICE), Public Health England (PHE), and DHSC about 'decoupling' antibiotic price from volume sold (in other words, paying pharmaceutical companies for a 'subscription' to a particular antibiotic so they weren't incentivised to sell more units of it).(8,9) The concerns I and others raised about this scheme is that it would be very expensive – specifically that it would require the disbursement of eight-to-nine figures of taxpayer funds to private sector-led projects – and that it would not

actually solve the AMR problem, it would just incentivise the development of one, or perhaps two, new antibiotics, which would in due course also lead to bacteria developing resistance to them.(8,9) I had also started presenting preliminary findings at conferences, and trying to get my systematic review accepted for publication; it was becoming clear by the tenor of conference questions and peer review comments that I received that my findings were deeply unpopular with medical diagnostics companies, and, by extension, the infectious disease journals and peer reviewers funded by them. One leading infectious disease journal editor was actually quite explicit, writing in an email that they would not publish my systematic review and meta-analysis as an academic article as the null findings I generated aboutrapid diagnostic tests' clinical effectiveness were too 'controversial', but instead they would be prepared to publish the piece as one half of a 'debate' series. I declined, of course. I later realised that though the journal is a top infectious disease journal, its funders were some of the medical diagnostics companies included in my list of 'not clinically effective' technologies. Presenting the findings of the first comprehensive systematic review ofrapid diagnostic tests for bacterial identification and antibiotic susceptibility testing as one half of a 'debate' is a form of false balance; my scientific evidence versus what would have been, presumably, an opinion piece on the other side of the aisle.

In the process of submitting another paper for publication I encountered another problem. When looking to publish preliminary findings from my discourse analysis, which highlighted the ways in which industry can deploy the public health community's AMR crisis messaging in order to lobby for the co-optation of public funds in the form of subsidies or deregulation, I was told that the British Medical Journal had to remove the specific companies' names because of a fear of litigation, and also would not publish it as an editorial, but rather as an opinion piece because of the 'controversial' content.(10) Though a minor and common problem, the wider message was that producing and disseminating evidence which challenges the received (corporate-friendly) wisdom onrapid diagnostic tests, pharmaceutical research and development, and AMR more broadly was clearly going to be challenging.

I have let my views aboutrapid diagnostic tests evolve as the evidence I generated in this doctoral thesis increasingly questioned their utility. And, in exploring the foundations ofrapid diagnostic tests in the UK, I have found that I have become part of a wider community; one where researchers critically appraise the Commercial Determinants of Health. My thesis is

that commercial interests operate in the development of AMR strategies in order to privilege policy options that benefit corporate actors such as medical diagnostics companies, even in the absence of a robust evidence base to underpin their products, or local professional support for the products. Central to this process is the framing of the 'problems' and 'solutions' of AMR using crisis and biosecurity lenses, and similarly, the value-neutral pushing ofrapid diagnostic tests as a technocratic solution to AMR, that purports to circumvent or mitigate against the risks of AMR without having to address the wider challenges of the health service.

Structure of the thesis

The aim of the dissertation is to explore the evidence base, perceptions, discourse, and policy levers surrounding rapid diagnostic tests for bacterial identification and antibiotic susceptibility testing as they pertain to antibiotic resistance. In order to achieve this aim, this dissertation takes a mixed-methods approach. Because of the mixed methods style chosen for this dissertation, there will be a mixture of paper-style and traditional chapters. This will afford many advantages, including the space and structure required to address each research question separately.

The dissertation is built upon four main studies that each examine different aspects of the AMR RDT agenda. Practically this means that there is a background chapter following this one, and then four chapters (three of which are in paper format and one of which is in a traditional chapter format) in lieu of the traditional background-methods-results monograph. The thesis ends with a discussion which bring the four papers/chapters into conversation with one another, and into conversation with the contemporary context of the COVID-19 pandemic and the Commercial Determinants of Health (CDoH) field. Each chapter starts with a broad introduction in order to situate the enclosed paper within the wider narrative arc and research of the doctoral thesis.

This thesis is also interdisciplinary; the background chapter that follows will therefore take the form of subsections of contextually important information on the topics that will be

engaged with throughout. Additional detail will be included where necessary within each paper/chapter.

Research does not take place in a vacuum. Underpinning all public health research should be the desire to feed into evidence-informed policy and/or practice, and to ultimately improve the health of the population. The PhD is also research training with a view to facilitating a transition into my career of choice, in this case, to continue in academia. Therefore, each chapter will end with an 'impact, engagement, and dissemination' box, explaining how I have begun to position my research in academia and policy circles.

Did I independently complete this research?

I undertook this doctoral research whilst employed as a research fellow with the Policy Innovation and Evaluation Research Unit (PIRU) at the London School of Hygiene and Tropical Medicine (LSHTM). When I began as a researcher in PIRU, the Unit had just been commissioned by the Department of Health to evaluate the implementation of the UK's five-year AMR strategy. There is therefore some agreed overlap between the work I was expected to undertake as a part of my job, and the research I was completing for my doctoral thesis. However, I clearly carved out separate areas where I was responsible for research from beginning to end; the contributions that I and others made are clearly delineated in the forms and prefaces before papers, or in the authorship statements in the submitted papers. I also planned for, and collected, additional data for my dissertation as a part of the PIRU evaluation. Overall, I developed all research questions, undertook all the analysis, and drafted all text that is included in the thesis, with advice, second coding, and edits provided by my advisory committee, co-authors, and colleagues (clearly signposted throughout).

Chapter 1: Background

This is a mixed-methods, interdisciplinary PhD on a wide-ranging, fast-changing topic. This background section will provide some context on my starting points for understanding the scope of my research programme:

1. **Antimicrobial resistance (AMR)**
2. **AMR policy in the UK**
3. **Rapid diagnostic tests (RDTs)**
4. **Situating my research within these topics, disciplines, and methodological traditions**
5. **Mixed methods research**
6. **Undertaking rigorous mixed methods research, and the**
7. **Commercial Determinants of Health (CDOH)**

1. Antimicrobial resistance (AMR)

It has been estimated that the global mortality attributable to antimicrobial resistance (AMR) will exceed 10,000,000 per year by 2050, and AMR's cumulative impact on the world's economic output will exceed USD 100 trillion by the same year (3). Antimicrobial resistance is a catch-all term referring to the situation when a drug that used to treat a bacterial, viral, fungal, or protozoal infection no longer works as well due to the fact that the infecting organism has stopped being vulnerable to it. Practically, in the UK, the primary concern within the wider field of AMR is antibacterial resistance; it is common practice in the National Health Service (NHS) to prescribe antibiotics to treat clinically suspected or diagnosed bacterial infections in patients. However, bacteria can evolve resistance to antibiotic drugs over time so that the first-choice antibiotics are no longer effective. This is antibiotic resistance. People can be infected with resistant bacteria, or bacteria can develop resistance over the course of antibiotic treatment. It is common in the UK to refer to the broader term (AMR) when only antibiotic resistance is being discussed and indeed this is what I have done throughout this dissertation.

Annually, 2,500 patients die from infection by a gram-negative resistant bacterial organism in the United Kingdom (UK) (4). 'Gram-negative' is a way of classifying a group of bacteria that includes *E. coli, Klebsiella, Acinetobacter, Pseudomonas,* and others. These bacteria can cause infections that can be life-threatening, particularly for older or immune-compromised patients, such as bacterial pneumonia, bloodstream infections, surgical site infections, and

urinary tract infections, and are often the cause of opportunistic health care acquired infections.(11)

The number of these infections is increasing every year, as is the number of patients who cannot be treated using normal antibiotic combinations that once worked.

2. *Antimicrobial resistance policy in the UK*

To combat the increased number of resistant infections, the UK has taken an aggressive policy stance over the last 10 years. Considered a world-leader in AMR policy, the UK

Figure 1 Major AMR policy developments in the United Kingdom

government has published a series of influential reports on AMR (Figure 1) and championed the issue of AMR on the global stage. In 2011, Professor Dame Sally Davies chose, as her first report as the newly appointed Chief Medical Officer, to write on the risks of antimicrobial resistance.(12)

The UK Department of Health and Social Care (formerly the UK Department of Health) published the "Five-year antimicrobial resistance strategy to combat the decreasing effectiveness of antibiotics, antivirals, and antifungals, 2013-2018", which, while there were no funds attached, was one of the most comprehensive AMR strategies in the world and set out ambitious targets aimed at decreasing antibiotic prescribing in the community and in hospitals.(1) The strategy was written in collaboration with the governments of the devolved nations, and the Department for Environment, Food, and Rural Affairs (DEFRA). It has three stated key aims:

1. To improve the knowledge and understanding of AMR,
2. To conserve and steward the effectiveness of existing treatments, and
3. To stimulate the development of new antibiotics, diagnostics and novel therapies.

These aims were to be achieved through seven areas of activity: infection prevention and control; prescribing; professional education and public engagement; development of new drugs and diagnostic tools; use of surveillance data; research; and international activity.(1)

In response to these two reports, the then UK Prime Minister David Cameron commissioned an independent review into AMR led by economist Jim O'Neill, which came to be known as the O'Neill Review. It took the form of a series of reports published between 2014 and 2016.(2) In 2018, as the UK Government was 'refreshing' their AMR Strategy, the Health and Social Care Committee of the UK House of Commons sent out a call for written submissions of 'evidence'. They asked respondents to address two main prompts: what results had been delivered by the UK AMR 2013-18 Strategy; and what should be the key actions and priorities for the Government's next AMR strategy.

In 2019, the UK government published two AMR reports. The first was a refresh of the 2013-2018 Strategy, and called the 'UK 5-year action plan for antimicrobial resistance 2019-2024'. Alongside this, the government also published the 'UK 20-year vision for antimicrobial resistance'.(7,13)

Alongside work at the national level, the UK championed the introduction of an AMR resolution at a high-level meeting of the General Assembly of the United Nations (UN) on 21 September 2016. In this resolution (16-16108 (E)), heads of state committed to taking a broad, coordinated approach to addressing the root causes of AMR across multiple sectors, especially human health, animal health and agriculture.(14) This was only the fourth time a health issue has been taken up by the UN General Assembly (the others were on HIV, non-communicable diseases, and Ebola). The UK also brought the topic of AMR to the G20 in Berlin in 2017, and the G20 published in June of the same year a declaration with a stated commitment to helping countries without AMR policies to develop them.(15) In 2017, only 1/3 of countries worldwide had a national action plan to combat AMR. By mid-2018, this was over half.(16)

Of course, writing an action plan is one thing, and implementing it is quite another. Not all measures have been successful. In the UK, many measures have been introduced to try to reduce antibiotic prescribing. In recent years in England, there have been top-up tied payments, called quality premiums, for reducing prescribing in primary care, and increasing the monitoring and evaluation of prescribing practices of outlier GP practices.(17,18) These have had the effect of reducing broad-spectrum antibiotic prescribing in the community by over 18% since 2015, and overall antibiotic prescribing has decreased by 8.2%.(19) This has

been described as a reduction in ‘inappropriate’ prescribing, though in fact very little analysis has been undertaken to support whether the reductions were in ‘appropriate’ or ‘inappropriate’ prescribing.(20–23) Other measures, some of which have been rolled out in Scotland, Northern Ireland, Wales, or UK-wide, have revolved around electronic prescribing system subsidies, rapid diagnostic testing pilots, incentive schemes for multinational pharmaceutical companies, and public awareness campaigns.(21,24,24–27) All of these will be recurrent themes throughout this dissertation.

As is the case with many health policy PhDs, the policy has marched forward before the PhD has been completed. For clarity, all primary data collection and analysis of primary data occurred before the 2019 action plan or the 20-year vision were published. The secondary data collection presented in the discourse analysis did, however, occur after the new AMR strategies were published.

4. Rapid Diagnostic Tests (RDTs)

In the United Kingdom, the standard of care for hospital patients being investigated for a bacterial infection is to take samples, test them in a laboratory to identify the infecting bacteria, and determine the bacteria’s susceptibility to antibiotics. This process supports the choice of the most appropriate antibiotic for any given patient. rapid diagnostic tests for bacterial detection and susceptibility testing may provide same day results, rather than one or more days for older tests. These may improve patient care by confirming that the correct drug has been prescribed, or quickly switching to a more appropriate drug. However, the evidence thatrapid diagnostic tests have a significant beneficial effect on patient outcomes and antibiotic prescriptions is unclear.

It may be helpful to review the basic tenets of classical bacterial identification and antimicrobial sensitivity testing for fast-growing bacteria. Some common sensitivity testing techniques include broth dilution tests, the antimicrobial gradient method, and disk diffusion testing. The commonality between these tests is that they are take a standardised bacterial inoculum, they take at least 16-24 hours in addition to a previous 1-2 day culture of the sample taken from the patient, and they cost between US $1 and $5 per test.(28,29) The time that these tests take can be improved by automation; there are many commercially available

automated processes that optimise the incubation time by measuring colour or light changes (fluorometry, colorimetry, turbidimetry, or photometry) that arise well in advance of a visible culture growth.(30–32) These automated tests often still require samples to be plated and cultured, after which point a swab of the colony that has grown is taken and analysed.(31,33,34) This process, though more rapid than traditional techniques, does not approach the stated criteria of the Nesta Longitude Prize, which was established in the UK in 2014 with the stated aim of incentivising the development of a truly 'rapid' AMR test with a bedside-to-result time of 30 minutes, and operated on the ward rather than in the laboratory.(35) This award, for £10 million, has not yet been collected due to the fact that the quickest near-patient tests currently on the market do not meet these criteria.

In spite of this, in the last five years there have been advances in molecular diagnostic tests that allow physicians to know whether the patient is infected, and with what – and the sensitivity/resistant profile of the infectious pathogen – using syndromic panels, matrix assisted laser desorption ionisation time-of-flight mass spectrometers (MALDI-TOF MS), and next generation sequencing. These latter tests are based on a myriad of technologies: nucleic acid-based diagnostics, microarrays, mass spectrometry, fluorescent *in situ* hybridisation, and sequencing, *inter alia*.(36–40) These technologies approach high levels of complexity, with investment and interest being drawn from the fields of chemistry, physics, software engineering, and engineering experts.

There has been interest inrapid diagnostic tests for AMR for some time. For example, in a similar field, recent advances in tuberculosis (TB)rapid diagnostic tests that detect resistance to rifampin and isoniazid – first line antibiotics used to treat the disease – have long been seen as a solution to patient retention and improving the treatment cascade.(41–43)
However, even where there is evidence thatrapid diagnostic tests can improve diagnosis, and get patients started on appropriate therapy earlier, there is uncertainty about the tests' effects on clinical outcomes.(44)
With respect to the priority areas of fast-growing gram-positive and gram-negative bacteria - which are distinct from TB because of both the time it takes to detect a clinically important infection in laboratory and the natural history of the diseases - there is a growing body of evidence documenting the decrease in turnaround time, or lab processing time, ofrapid diagnostic tests for hospital patients, including literature evaluating test performance in the

laboratory, and reports on outcomes including turnaround time, positive and negative predictive values, sensitivity and specificity.(45–51) These papers describe, review, and in some cases trial, technological innovations. However there has been no systematic review assessing the clinical impact ofrapid diagnostic tests for fast-growing bacteria, like there has been for TB diagnostics. This represents a clear gap in the evidence base forrapid diagnostic tests for the detection of resistance in fast-growing bacterial pathogens and one that I aim to address in the next chapter.

5. *Situating my research within these topics, disciplines, and methodological traditions*

My research sits among several academic traditions (Table 1).

Table 1 A description of the studies, methods, and theoretical perspectives explored

STUDY	METHODS ADOPTED	THEORETICAL UNDERPINNING
1	Systematic review and meta-analysis	Evidence-based medicine Cochrane reviews
2	Qualitative semi-structured interviews and thematic analysis	Diffusion of innovation Greenhalgh's NASSS framework
3	Critical discourse analysis	Fairclough Foucault Entman Bacchi
4	Qualitative semi-structured interviews and thematic analysis	Abbott and Strauss

While each paper/chapter describes its methods and theoretical underpinning, my dissertation may face a critique that this is not, in fact, mixed methods research, but rather simply different theories and methods included in the same document. I therefore spend some time below reviewing the definitions and academic research on mixed methods research and contextualising my approach within – and separate from - this realm.

6. *Mixed methods*

Mixed methods research is a field that is developing quickly. It has been called the third major research paradigm following on from qualitative and quantitative approaches.(52) However, both the boundaries of methods research, and the accepted practices of how such research is undertaken, remain fuzzy. The overarching goal in such research is, broadly, to

integrate qualitative and quantitative research in some way in order to generate a more complete or nuanced view of a particular topic.

This process could be said to have begun with cultural anthropology or sociology in the 1920s and 30s, though was formalised much later.(52) Campbell and Fiske described the idea of 'triangulation' in their 1959 article (without using the actual term; triangulation is now understood to be one of the central tenets of some types of mixed methods research, where validation is a desired endpoint).(52) Webb, Campbell, Schwartz, and Sechrest (1966) extended Campbell and Fiske's work to define 'multiple operationalism' as measures that 'are hypothesized to share in the theoretically relevant components but have different patterns of irrelevant components' and categorising 'triangulation' as one type of evidence coming from divergent research methods that is more persuasive than those individual types.(52)

Denzin developed methods for how to triangulate findings generated from different methodologies in 1978, developing four types of triangulation: data triangulation, investigator triangulation, theory triangulation, and methodological triangulation. Denzin also realised that there was scope for 'within-methods triangulation', and 'between-methods triangulation', arguing that the results from the latter were more robust, because 'the bias inherent in any particular data source, investigators, and particularly method will be cancelled out when used in conjunction with other data sources, investigators, and methods […] the result will be a convergence upon the truth about some social phenomenon.'(52) This understanding of truth as static would be unlikely to be considered best practice by researchers today, but the concepts were echoed by Jick (1979), who noted that mixed methods research can allow researchers to be more confident in the interpretation of their results, and can lead to 'thicker, richer data', allow for divergence, and help to determine which of competing theories is more suited (or where there is scope for theoretical development).(53)

Many early proponents of mixed methods research focused on the concept of triangulation. Rossman and Wilson (1985) listed it as one of their three main reasons for combining qualitative and quantitative data (along with richer data and being able to use paradoxes in data to develop ways of thinking).(54) Greene, Caracelli, and Graham listed triangulation as the first in their five rationales for undertaking mixed methodological studies (alongside complementarity, development initiation, and expansion).(55) Sechrest and Sidana listed

triangulation (or ‘verification’) as the first of their four reasons for using multiple methods (alongside estimating error, easier data monitoring, and to ‘probe a dataset’).(56)

In recent years, the focus on triangulation as an endpoint has waned somewhat. Collins, Onwuegbuzie, and Sutton (2006) list four rationales for mixed methods research: participant enrichment, instrument fidelity, treatment integrity, and significance enhancement – this last could be said to comprise both the concept of ‘thicker richer data’ from Jick, and also the benefits of triangulation.(53,57)

There have been, as qualitative researchers will be aware, academic debates about mixed methods research. Schwandt refers to ‘paradigm’ wars, and took a radical position in his 2000 and 2006 papers, which was that the distinction between qualitative and quantitative inquiries was neither meaningful nor helpful.(58–60) Johnson concurs, and in 2007 described the divisions between these worlds as fuzzy and unproductive.(52)

Currently, mixed methods research goes by a number of names: ‘blended research’, ‘integrative research’, ‘multimethod research’, and so on.(52,61–63) Mixed methods research, however, is not the same as a *mixed methods study*. Provision is made for this distinction by Creswell in the table of definitions published by Johnson in 2007, who writes that ‘mixed methods research is a research design (or methodology) in which the researcher collects, analyses, and mixes (integrates or connects) both quantitative and qualitative data in a single study or a multiphase program of inquiry’.(52) Furthermore, the definition of mixed methods research as requiring quantitative and qualitative research is somewhat out of date. Formosa acknowledges this, and does not specific the methodological tradition of the methods, opting instead for a broader definition: ‘mixed methods research is the utilization of two or more different methods to meet the aims of a research project as best as one can’.(52) Greene’s definition concurs: ‘mixed method inquiry is an approach to investigating the social world that ideally involves more than one methodological tradition, and thus more than one way of knowing, along with more than one kind of technique for gathering, analysing, and representing human phenomena, all for the purpose of better understanding’.(52) The Johnson and Onwuegbuzie definition, however, requires the mixing or combination of ‘quantitative and qualitative research techniques, methods, approaches, concepts, or language into a single study or set of related studies’.(62)

There is also debate about where the mixing has to occur. Does the planning, data collection, and data analysis all need to involve mixing? Some definitions of mixed methods research seem to think so, however others take the view that any mixing anywhere makes for a mixed methods research programme or study. And with respect to the question of 'bottom-up' vs 'top-down' rationale for conducting a mixed methods study – whether the research question, or the researcher, is pushing for mixed-methods research – I take the view of Tashakkori who asserted that this is necessarily a continuum rather than a binary proposition, and unlikely to be helpful when viewed as a discrete choice.(64,65)

In my case, my individual studies were themselves single-method (with the exception of the systematic review, which had made provision for being a mixed methods review, but which did not uncover any papers who reported on both qualitative and quantitative data). Some mixing will occur in the discussion of this thesis; multiple perspectives on my research questions will be integrated into an interpretation of what we know about rapid diagnostic testing for bacterial infections and antimicrobial resistance; and what we know about diagnostics in the health service more broadly.

Of course, mixed-methods researchers have further classified types of mixed-methods research as qualitative dominant, quantitative dominant, and 'pure' mixed methods (a term with which I take great exception and am not particularly sure is helpful for advancing the field). The work I have undertaken would, if situated within the Johnson definitions, be considered to be qualitative dominant (QUAL + quan, using their terminology) because it relies on a 'qualitative, constructivist-poststructuralist-critical view of the research process, while concurrently recognizing that the addition of quantitative data and approaches are likely to benefit most research projects'.(52) While I take issue with the final part of Johnson's definition, in my case the introduction of quantitative analysis to answer my research questions has been helpful and indeed necessary. Others have discussed the requirements for meeting the definition of mixed methods research; Pluye et al required three components for the definition of mixed methods research to be satisfied: (i) at least one qualitative and quantitative method are used, (ii) each method is rigorous, and (iii) some part of data collection/analysis/result is integrated.(66)

There are plenty of issues in the practical undertaking of mixed methods research, many of which I have considered but not all of which I have addressed. There are concerns about what philosophy or philosophies of science one ought to espouse for mixed methods research – constructivism, post structuralism, post-positivism, or others. While these are by no means trivial – and while I would certainly agree that a post-structuralist and constructivist *a priori* fits my research model, I enjoyed – and espoused - Johnson's notion that 'pragmatism' is actually the most important position to take in mixed methods research. (52)

Concerns have centred around the extent to which mixed methods researchers actually integrate the strands of diverse methodologies. The analysis of whether studies are sufficiently 'mixed' is itself plagued by the same issues as the studies themselves. Greene et al reported that only 44% of the 57 so-called 'mixed methods' studies that they included in an analysis actually integrated the quantitative and qualitative data.(55) When trying to understand the barriers to integrating quantitative and qualitative research, Bryman undertook interviews with 20 social researchers in the UK – of course, a qualitative undertaking.(67)

The main concerns that Bryman described are that researchers were not integrating the qualitative and quantitative data at the analysis phase, or that one strand of data were reported, but not analysed. This is similar to what Greene et al identfied. But this alleged problem for some – that each study's analysis is undertaken separately– is actually part of the solution for others. Bryman's respondent 6 says that '*it's very difficult to intertwine [the qual and quant data]. I am – in some ways, what I've done in my research to overcome this problem of comparing one against the other is to analyse them separately and to represent them separately in any writing up'*.(68) Respondent 16 agreed, saying that '*there is a tendency to do, what I own up myself, I've said I've been guilty of sometimes and it is that, you know, in name you appear to be doing mixing methods but in practice – in terms of the analysis and writing up that, mixing doesn't always come through in the way the data's analyzed*'.(68)

If the researchers who critique mixed methods research cannot escape the same criticisms as they point out in that same work, then it seems only right to acknowledge that mixed methods research will suffer inescapably from a set of biases and limitations, and simply to be as

transparent as possible about where the mixing or integration occurred, how analyses were conducted, and so on.

The main concern focused on in the literature is that of the 'writing up' phase – research has to be written up for an intended audience. When this happens, a choice has to be made about which nouns they choose, which literature they engage with, and which journals they will be writing *for*. Bryman writes that mixed methods researchers can end up writing up for different audiences. This was certainly true when submitting papers from my dissertation. Four papers have been submitted to journals belonging to different academic traditions on the basis of the work that follows in this thesis (Table 2).

Table 2 PhD papers and their current status at journals

Paper	**Thesis chapter**	**Journal**	**Status when thesis was submitted**
Systematic Review and meta-analysis	Chapter 2	Journal of Clinical Epidemiology	Under Review
Critical Discourse Analysis	Chapter 4	Critical Public Health	Under Review
Qualitative analysis of semi-structured interviews	Chapter 5	Critical Public Health	Submitted
Commercial Determinants of Health /publication bias	Chapter 6	British Medical Journal	Under Review

Nevertheless, there are attempts to formalise how best to integrate qualitative and quantitative research. These depend on the timelines of research, the priority, the purpose of mixing (triangulation, explanation, or exploration), where the research mixes, and whether it is within one study or among several.(52,55,65,67,69) Curry explains that there are four main formats for mixed methods study design: sequential explanatory, sequential exploratory, convergent parallel, and concurrent embedded.(69) Sequential exploratory is similar to the format of the work I have undertaken, as it involves the quantitative component being followed by qualitative research that aims to improve the explanation of the quantitative results. However, my research also draws on convergent parallel approaches, or in other

words, where the quantitative and qualitative data collection is concurrent. The definition for convergent parallel used by Curry also stipulates that for research to be truly ‘convergent parallel’, the quantitative and qualitative research should be given equal weight, but the concept of ‘equal weight’ is difficult to measure in qualitative research, and perhaps even limiting, or unhelpful.(69) In the case of my programme of PhD research, some of the qualitative work (the primary data collection in interviews) was planned and undertaken contemporaneously with the systematic review and meta-analysis. However, the critical discourse analysis and the meso-level analysis of ‘appropriate’ antibiotic prescribing occurred after the first qualitative and quantitative components were complete. This is common in many studies; the typologies that Curry described are similar to the typology of qualitative/quantitative dominance as broken down by Johnson in that, practically, mixed methods research rarely stays rigidly within these temporal boundaries. Where adherence is more important, however, is in rigorous methodology. Mixed methods research requires consideration of the standards that would be required to be met in each of the strands of research. For the systematic review and meta-analysis, this would mean that PRISMA guidelines would be expected to be followed, and wherever possible, guidance taken from texts on how to conduct a proper review.(70–72) For each of the three qualitative strands, similar levels of attention must be given to qualitative methodologies and theories from which I have built my analyses in order that the qualitative results be accepted by academics in these fields.(73–78)

Some disciplines and subject matters have taken more quickly to mixed methods research. Health services research and public health are two of those. My research therefore fits within a tradition of mixed methods research. There is some tension in definitions about whether this is a mixed methods thesis even within my own advisory committee due to the lack of mixing within each paper, but I will endeavour to meet the constituent requirements of mixed methods research throughout this thesis while also being transparent about where and how mixing occurs. More importantly, though, the PhD is also a chance to undertake research training and I have tried to train in multiple methods, multiple topics, and multiple disciplines. I think, though it has been difficult at times, this will make me a better researcher.

In the next chapter, I will begin with the epidemiological story. I will start by explaining the methodological decisions I took to evaluate certainrapid diagnostic tests for bacterial

identification and antimicrobial susceptibility testing, and I will present the submitted systematic review and meta-analysis paper. Over the remainder of the dissertation, I will weave in the narrative of where and why I changed research questions and methods, and how the direction of research was influenced by early findings in my first two studies.

7. Commercial determinants of health

Over time, I came to realise that the literature underpinning the field of the Commercial Determinants of Health (CDoH), while predominantly situated in non-communicable diseases (NCDs), was particularly relevant to the questions I was asking in my research.

Commercial determinants of health (CDoH) research has defined itself as relevant to corporate behaviours that can be linked epidemiologically to physiological or psychological non-communicable diseases (NCDs).(79) CDoH research was in large part influenced by scientific research being undertaken on tobacco industry practices, which in many ways has acted as the archetype for the discipline. The tobacco industry's playbook was vast, but included, over half a century: litigation against scientists, the co-optation of scientific and epidemiological jargon, the use of logical fallacies, financial lobbying of governments around the world, funding experts to contradict mainstream science, employing and deploying a coterie of corporate lawyers to defend against individual and government lawsuits, and marketing tactics (often to children and other growth markets including expansion into LMICs).(80–82) Often, research into the methods the tobacco industry used systematically to undermine regulation and scientific consensus in this field was described as investigating 'financial conflicts of interest'; this was also how the pharmaceutical industry sales and marketing practices of providing gifts, samples, continuous professional development opportunities, and other incentives were described.(83,84)

In the pharmaceutical field, it is well understood in behavioural sciences that the gifts distributed to clinicians by pharmaceutical companies – a common tactic around the globe – can influence a clinician's prescriptions of products and drugs sold by those companies.(84,85) But more than that, in order to indirectly influence volumes of prescriptions sold, multinational pharmaceutical companies are known to fund studies and scientists; heavily lobby governments; hide financial conflicts of interests through corporate diversification; discredit science and scientists who dispute the effectiveness of their

products; and, where legal, market drugs directly to patients and the general public.(84–90) A recent high-profile example of this is Purdue Pharmaceuticals' material contribution to the opioid epidemic by: understating the addictiveness of the opioid OxyContin; marketing this drug to treat chronic pain to physicians; suppressing science and scientists that tried to reveal the scale of the problem; and developing naloxone, an OxyContin overdose cure – patenting the ability to profit from patients when they are 'coming and going'.(88,91,92) Meanwhile, corporate diversification practices mean that Purdue Pharmaceuticals has filed for bankruptcy in the United States (due to continued, successful legal action brought by multiple US states against the company due to their role in the public health epidemic), but meanwhile, the international arm of the company, Mundipharma, continues to market to doctors in Europe, infiltrate scientific conferences, and work towards casting doubt on European countries' government guidelines urging caution about opioid prescribing.(92,93) These practices mirror those in the tobacco and other industries' playbook, without even beginning to catalogue other corporate practices in the pharmaceutical industries that harm health, such as lobbying for long patent protections for novel drugs, legal challenges to antibiotic and antiretroviral generic manufacturing, even in LMICs, 'disease mongering' – convincing healthy people that they are sick - and orphan drug pricing, such as in recent examples with insulin pricing.(94,95)

Similar tactics were being deployed throughout the latter half of the twentieth century and into the twenty-first in the food, alcohol, and gambling industries. The food industry has been extracting value out of cheap sugars and grains by marketing to children, lobbying governments to avoid or reduce regulations, discrediting nutrition science and personally attacking scientists, linking regulation to 'nanny-statism', and even changing the official government dietary advice, all while pushing alternate non-evidence-based solutions to the obesity crisis such as the 'personal responsibility' narrative.(96,97) Epidemiological research establishing the links between marketing or consumption of foodstuffs and ill health exists and is necessary but not sufficient when advocating for policy responses and public health regulations, therefore research on the food industry's tactics has grown over recent years.(97–99) In the UK, there is also a growing body of qualitative and mixed-methods research on understanding the links, arguments, and mechanisms of influence among corporate actors, and how they are deployed in the contexts of specific policy debates. Experts have used stakeholder qualitative analysis, content analysis, citation analysis, and discourse network

analysis, and in the public debates on policy interventions, such as the soft drinks industry levy (SDIL) and sugar tax.(100–102)

Alcohol is another product that has been known to cause and exacerbate morbidity and mortality through a variety of acute and chronic mechanisms, including: worsening individual physiological health; increasing the risks of numerous cancers, heart disease, and diabetes, increasing addiction; worsening mental health; increasing road traffic accidents; and others.(103–106) Public interventions such as taxation, restrictions on marketing activities, and other price policies have been demonstrated to reduce consumption and concomitant ill health.(105,107,108) The alcohol industry has also been demonstrated to target – and benefit from - marketing to youth and growth groups, while misrepresenting the serious risks of alcohol consumption, heavily lobbying public health authorities, and funding charities and academics to distort the science, while using corporate social responsibility (CSR) activities as white-washing for these activities.(109–114)

Gambling has also been understood to be an addictive behaviour that can cause serious health harms to an individual and their family.(115–118) Like tobacco, unhealthy foods, and alcohol, gambling harms accrue inequitably, with the highest burden placed on the worst-off in societies. The international gambling industry has been demonstrated to: target their marketing to problem gamblers, the most vulnerable in society, and children; gamify gambling and associate it with all tiers of sport to make it more addictive and make it a part of normal life; and work to associate gambling with other unhealthy commodities such as alcohol.(119–122)

In recent years, experts have sought to (i) demonstrate how these tactics are similar across health fields, and (ii) develop methods to catalogue and analyse how, where, and when, discursively, the industry playbook is deployed in particular policy debates.(79,100,102,123). Companies operating across multiple sectors – including fossil fuels, pesticides, asbestos, mining, - have been found to have adopted the same playbook as tobacco companies. The extraction and consumption of fossil fuels, for example, contributes to ill health by decreasing air quality and consequently morbidity and mortality.(124–126) There is also private sector investment lobbying for influence in the development of systems – like roads – that privilege fossil fuel users and erect barriers to consumers easily making a different

lifestyle choice, and investment in denying and manipulating climate science while misinforming the public about the risks of fossil fuels.(127–129)

Both the characteristics of Commercial Determinants of Health research, and the boundaries of the discipline are amorphous, but in recent years there have been attempts to track the development of the field and circumscribe some *a priori* conditions for CDoH research. The term 'corporate determinants of health' was coined by Millar in 2013, in relation to the food and beverage industries.(130) Kickbusch described the 'Commercial Determinants of Health' in a 2016 Lancet Global Health commentary on non-communicable diseases (NCDs).(131) The concept of vested interests, conflicts-of-interest, and the industry playbook existed long before the dual CDoH terms developed, as the tobacco, alcohol, and pharmaceutical research demonstrates. However, since the Kickbusch 2016 comment, there has been an increasing disciplinary understanding among the various fields and experts in CDoH that it is primarily an avenue of inquiry related to corporations whose products link to morbidity and mortality caused by *non-communicable diseases*. This is evidenced in recent systematic reviews on the nascent field.(132,133) However, the industry tactics described therein match some of those which I identify in the discourse analysis I undertake, and are aligned with larger discussions surrounding neoliberalism in government and personal responsibility narratives that I have myself engaged with in the AMR academic community whilst in the process of writing up this dissertation.(8,10,134)

My experiences, reflections on potential biases in the literature, and consideration of the relevance of CDoH led me eventually to considerrapid diagnostic tests within a CDoH framing. This means a more explicit consideration of the epidemiological, political, and health ramifications of advocating for, and adopting,rapid diagnostic tests and other private-sector led and government-facilitated solutions to the AMR response in the UK. This will help to determine better (i) whether CDoH is a suitable label for the AMR response, and (ii) whether, if similar tactics are used, what can be learned about them and how to deal with them from analysis alongside the playbooks and tactics of other industries. The responses to these questions will govern the likely tactics, the fallacies at play, and the strategies that may be most effective in public health research and practice.

Impact, engagement, and dissemination

I presented this framing of the PhD work, within the context of mixed methods research, CDoH, and Diffusion of Innovation Theory, in two different presentations.

First, I gave an invited lecture at the PHE public health registrar training day (27 February 2020) on CDoH, and participated in a panel discussion on the day.

Second, I was an invited seminar speaker at LSHTM's AMR Centre. I gave a one-hour lecture on 2 November 2020 on the story interlinking this research. This lecture also functioned as my pre-viva seminar.

Chapter 2: Systematic Review and Meta-Analysis methodology

Preface

The systematic review and meta-analysis that I present below was the first part of my dissertation. I developed the protocol and began the search when I was convinced that the key to increased uptake of diagnostic technology was to conduct a systematic review and meta-analysis that could find a way to capture and disseminate the benefits of diagnostic technology.

Though several systematic reviews of diagnostic tests exist,(44,135–139) I noted an evidence gap in the diagnostic tests for bacterial identification and antibiotic susceptibility testing, so I developed my review question around this gap. I wanted to assess know what the evidence was for the clinical impact of implementing rapid diagnostic tests for bacterial identification and antibiotic susceptibility testing. Ultimately the process of undertaking this multi-year review, and screening over 20,000 papers, made me start to question my *a priori* assumptions about the innate benefits of such technologies.

In the chapter below, I first describe the methodological decisions I undertook in the development of the systematic review in some detail– and then I present the academic paper reporting the results of the systematic review and meta-analysis.

Introduction

Systematic reviews and meta-analysis are both tools that aim to formally review and synthesise the evidence in relation to a specific research question; when used appropriately, effects in *a priori* subgroups can be investigated, and the effects of methodological and other biases on study findings can be assessed.(140) Systematic reviews and meta-analyses can add to 'traditional' narrative reviews in terms of reliability, transparency, and impact. They can help to inform, or critique, practice guidelines, and can also identify gaps in the evidence base.(140) Their use mitigates against the limitations of single studies by objectively assessing the whole evidence base, and they are considered highly-valued decision-making tools by academics, health professionals, policy-makers, and others in the health fields.(71,140–143) Using systematic review and meta-analysis methods, I aimed to answer the following research question: Dorapid diagnostic tests for antimicrobial resistance change clinical outcomes or antibiotic prescribing for high-risk patient subgroups, compared to non-RDT best practice?

It is often assumed that the meta-analysis of studies of effectiveness tends to be restricted to randomised controlled trials (RCTs) due to a belief that these represent the 'gold standard' for effectiveness research.(144) Of course, many research questions cannot be answered using RCTs, because: randomisation may be impossible (e.g. in the case of many large scale structural and policy interventions); randomisation would be ethically inappropriate in the absence of equipoise; or randomisation may simply be too expensive.(71,145–147) Thus, it is not uncommon to find systematic reviews of observational studies of interventions.(148) However, there is limited guidance on how and whether to aggregate non-randomised studies in meta-analyses.(148,149) What is certain is that study design should be included in factors that are investigated as causing variation in any summary effect estimates. In areas where there is a paucity of RCTs, and where public health guidelines are being developed, it seems appropriate to move toward the thoughtful use of existing observational evidence, in combination with careful interpretation, rather than waiting until a hypothetical critical mass of RCTs is produced (which in public health may be never). I have therefore taken the following approach in my systematic review: I have incorporated both experimental and observational studies in my meta-analyses, though they remain disaggregated in the statistical synthesis. I have mitigated the potential for bias associated with systematic reviews of observational studies by including information asymmetry analyses, sensitivity analyses, and

subgroup analyses, and have been cautious not to over-interpret summary effect estimates. This decision has been taken in the context of another important debate in systematic review methodology, namely the division between ‘lumping’ and ‘splitting’ the literature.

Lumping versus splitting

There is a body of literature devoted to ‘lumping versus splitting’ in the world of clinical trials, systematic reviews, and meta-analyses.(150–152) This refers to the approach taken when defining outcome categories. For example, a ‘lumper’ would report that intervention X improved patient outcomes, even if in 2 out of 6 studies there was no statistically significant effect (provided that the effect was significant overall).(153) However, a ‘splitter’ would subdivide and report by subgroup of patients, perhaps even in a different review. This is common in drug trials or pharmaceutical studies, which aim to assess a narrow outcome, and the ‘lumping’ approach is the one favoured by the BMJ, among others. (153) More broadly, conceptual lumpers may feel that broad categories can group things together which are more similar than they are different, and is a concept that expands far beyond systematic reviewing, and into any discipline. In systematic reviewing in particular, the arguments for lumping and splitting are summarised in Table 3, adapted from Weir et al.

Table 3 Adapted from Weir et al. (153) Arguments for lumping and splitting

Why lump?	Why split?
Greater potential to reduce chance findings	Feasibility
Generalisability/consistency of research findings across settings, populations, and behaviours	More specific research question and targeted to area of interest
Ability to test *a priori* ideas of subgroup effects	Increased homogeneity of included studies

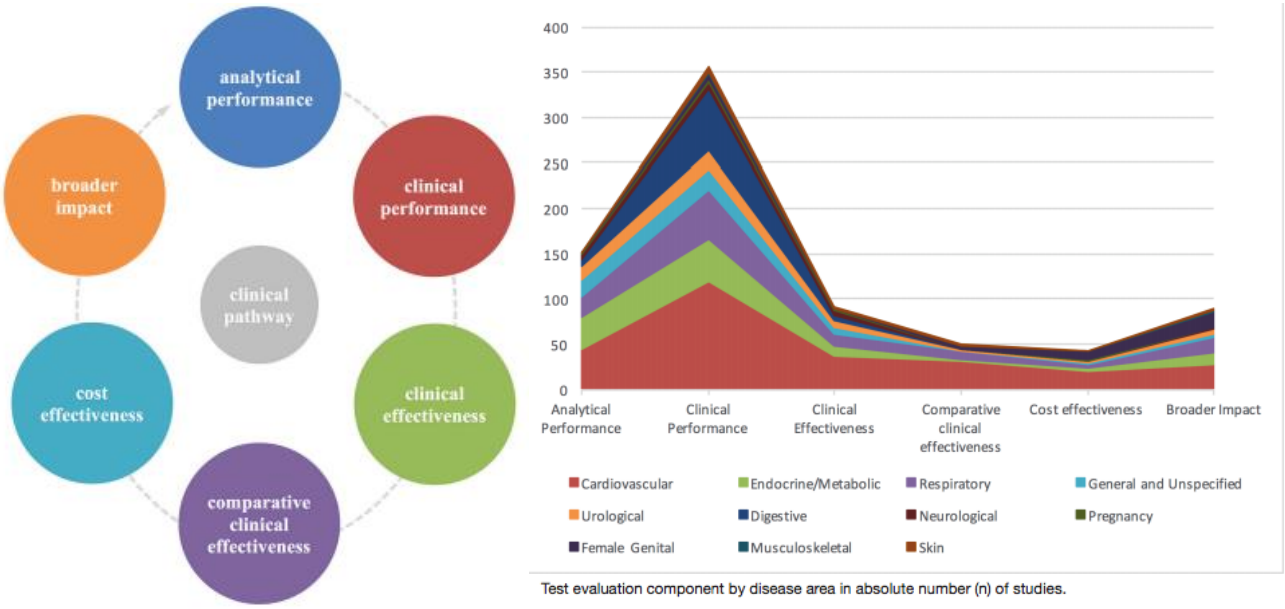
Methodologically, lumping is a choice derived from the principle that a broader approach allows for greater generalisability, and to mitigate against concerns of (external) heterogeneity, it is possible to perform an *a priori* specified subgroup analysis (154). Moreover, lumping follows from the assumption that it is right to combine results if two conditions are satisfied: 1) that small differences in methodology should not, according to the logic model, change the outcomes, and 2) that the intervention should not have opposing

effects (142). This contrasts with splitting, which is in effect a subgroup analysis, and has the same power and statistical problems of any small study (155).

In the case of public health interventions, the complexities of interventions mean that very often the answers to 1) and 2) are unclear. In fact, complexity can result from interactions between components of an intervention; non-standardisation of implementation; feedback loops; phase transitions; multiple outcomes; effects at different levels; and the moderating effects of context, as has been shown elsewhere.(145) The methodological consequences are that systematic reviewers need to find ways of addressing this. Lumpers may try to address this by grouping studies of complex interventions even when the study designs, types of outcome, and populations are somewhat different. I have taken this approach in my systematic review – grouping different types of proprietary diagnostics and different study designs into this review, then making provision for subgroup analyses as necessary.

The popularity of lumping and splitting methodologies varies by the intervention in question, and the evidence base underpinning it. Squires et al suggest taking a lumping approach wherever possible, due to the decreased risk of bias and chance results. (142) However, when discussing treatments for conditions that have heterogeneous outcomes based on genetics or strongly determined by individual patient characteristics, lumping may not be appropriate. (156)

Figure 2 (L) Horvath's cycle for diagnostic test evidence (R) Hayward et al's figure of the evidence generated by the Oxford Diagnostics Unit, by type of evidence



In the case of the review of diagnostic tests, splitting is more common in the evidence base.

More specifically, splitting by diagnostic technique is almost always the case, and splitting by proprietary technology is also very common.(157) Moreover, in the case of diagnostic tests, the vast majority of evidence is concentrated in their accuracy (Figure 2).(158) This is when diagnostic tests are evaluated against their ability to accurately detect a target condition, often with set panels of samples, or rule out that same condition. Systematic reviews of diagnostics face particular challenges; one paper estimated the likelihood of completing a Cochrane review on diagnostic test accuracy within two years was less than 10%.(158) Systematic reviews of diagnostic tests' clinical effectiveness are far rarer still than those reviewing questions of accuracy. The Oxford Diagnostics Horizon Scan Programme, established in 2008 by the National Institute Assessment Programme and the National Institute for Health and Clinical excellence (NICE) adapted Horvath's cyclical model for diagnostic tests (Figure 2) and demonstrated that out of the 40 reports they had generated in the first 10 years of their existence, very few were focussed on the clinical effectiveness or comparative clinical effectiveness of the diagnostic technologies (Figure 2).(3,136) The importance of the distinction between clinical performance and clinical effectiveness or comparative clinical effectiveness cannot be overstated; their definitions can be found in Table 4.

Table 4 Adapted from Verbackel et al and Hayward et al - differences between the clinical components of the diagnostics evidence cycle (3,136)

Clinical performance	Does the test detect the condition of interest in patients?
Clinical effectiveness	Does the test improve the health of patients?
Comparative clinical effectiveness	Does one test improve the health of patients more than another?

Systematic reviews of clinical effectiveness also tend to be *complex.* This is because they meet several criteria for complexity in public health interventions, including that studies measuring effectiveness of diagnostics are rarely randomised, are rarely measuring the same outcomes, or are measuring multiple outcomes that could be impacting on one another.(145)

Conducting my systematic review

I conducted a systematic review between May 2016 and March 2019 to examine the impact of rapid diagnostic tests for bacterial identification and antibiotic susceptibility testing on clinical and antibiotic prescribing outcomes of interest. I registered a protocol on

PROSPERO (Appendix: Document 1) in April 2018, and the paper describing the methods, results, and analysis is included at the end of this chapter. However, publishing a final output like a paper is only one – relatively small – part of the systematic review process. I therefore describe my decision-making process over the course of the review below as a way of highlighting and justifying the methodological decisions that were taken. Some methodological choices, with the benefit of hindsight, were not perfect, however, this chapter should help to answer questions about the rationale underpinning key components of this systematic review. A retrospective analysis of these decisions is not merely an academic exercise; each decision taken through the lifespan of a systematic review has the capacity to change which studies were included, the nature of the analysis, and ultimately the final interpretation, conclusions, and implications of the review. Transparency at this stage should help not only to contextualise the interpretation of the review's findings, but should help the reader to assess the extent to which the risk of introducing bias has been mitigated.

I am presenting an abstract of the paper, to familiarise the reader with the relevant processes, results, and interpretation, all of which will be discussed throughout this methodology chapter. If you would prefer to read the systematic review paper before the chapter on review methodology, then this can be found on page **66**.

Background Antibiotic resistance is a serious problem worldwide, hampering appropriate antibiotic therapy. Rapid diagnostic tests (RDTs) for bacterial identification and antibiotic susceptibility testing are promoted as a possible solution to this problem, though their clinical effectiveness in practice has been questioned. Assessing the evidence is also difficult because of the use of multiple inconsistent endpoints in the primary studies. We synthesized the evidence on the impact ofrapid diagnostic tests for bacterial identification and antibiotic susceptibility testing on clinical and antibiotic stewardship outcomes compared with standard practice in hospitals, and used a Sankey diagram to help present the findings and illustrate study heterogeneity.

Methods We conducted a systematic review of experimental and observational studies which included at least one prescribing or clinical outcome ofrapid diagnostic tests in hospital in-patients. Sub-group analysis and meta-analysis were used to synthesise the results, including exploration of heterogeneity in summary effect estimates. A Sankey diagram was then used to show the flow of evidence through the review.

Results 58 studies from 14 countries were eligible for inclusion. The introduction ofrapid diagnostic tests did not significantly reduce in-hospital mortality (RR 0.83, 95% CI 0.60 - 1.15) or length of stay (weighted mean difference for experimental studies = -0.36, 95% CI -1.67 to 0.96). There was high heterogeneity in antibiotic stewardship outcomes, prescribing outcomes and the definitions of turnaround time used in study reports.

Discussion Currently, there is no evidence that the routine use ofrapid diagnostic tests for bacterial identification and antibiotic susceptibility testing improves clinical outcomes. The lack of standard definitions such as turnaround time precludes full use of the evidence, as the Sankey diagram showed. Sankey diagrams may be a useful adjunct to the PRISMA diagram in complex systematic reviews where evidence is heterogeneous and not easily amenable to meta-analysis.

Review Methodology

The process of undertaking systematic reviews is still something of a black box; there are very few papers which describe the fact that, as well as following a systematic process, decisions throughout the process are also judgement-based, and reflect the experience of those making the decision, and the norms in their fields, even though measures are taken to limit subjective influences such as personal biases. I felt it worthwhile, therefore, to spend a chapter describing the set of decisions I took throughout the process, and their justifications across the major decision points within a systematic review.

1. Developing the research question(s)
2. Writing and registering the review protocol
3. Developing the search strings(s) for database searching
4. Screening the found articles

5. Extracting data from the included articles
6. Data analysis
7. Methodological Innovation
8. Interpretation
9. Writing the review
10. Facing potential criticism of grouping diagnostic technologies

1. Developing the research questions

A series of three systematic reviews were commissioned by the Department of Health (now the Department of Health and Social Care) in 2016 from the policy research unit of which I am a member. However, apart from the steer from DHSC that the reviews ought to be relevant to the current state of the UK's Five-Year AMR strategy, no further guidance was given with respect to the scope of the reviews. It seemed to me important first to determine the state was of the evidence underpinning the Strategy. I therefore decided to first subject the AMR Strategy to a detailed gap analysis in order to determine what previous evidence existed – and what did not – in relation to the AMR strategy.(159) I dissected the AMR strategies' seven Key Areas into sub-actions. In order to determine whether the numerous recommendations were based in evidence, I broke down every sentence in the policy document with multiple proposed actions into constituent clauses so that each proposed action was separate and evaluable (Appendix: Document 2). Once each action was separated, I and two other research fellows identified the target population (human/animal) to which each sub-action was referring. The research fellows, myself included, then conducted a pragmatic review of reviews to determine whether we could find at least one high-quality, recent, systematic review evidence with evidence underpinning the proposed action. The intention of this work was to determine which recommendations were being made with insufficient or contradictory evidence bases underpinning them. In this task, we consulted key experts, as we did not purport to cover the breadth of literature at this stage; this was a presence or absence exercise, in that the presence of one relevant review halted search efforts in a category.

I focused this work on three of the seven Key Areas of the AMR strategy. These were (i) infection prevention and control practices, (iv) development of new drugs, treatments, and diagnostics, and (vi) identification and prioritisation of AMR research needs.
I then devised four categories and classified the actions into: at least one recent systematic review with supporting evidence found; tangential or inconclusive evidence found; not appropriate for systematic review; and no evidence found on first rapid search.
I also highlighted the sub-actions that would not benefit from evaluation. For example, one sub-action was to 'fund a health protection research unit'; it is unlikely that a systematic review on this action exists, or is needed. Moreover, the action had already been completed by central government.

After removing the sub-actions unlikely to be able to be underpinned by evidence, I conducted a rapid scan of databases, and consulted experts to determine whether there was at least one systematic review underpinning each of the remaining sub-actions. Where a systematic review could not be identified, I looked for other types of evidence (including NICE diagnostics guidances, or WHO bulletins). The studies identified were inputted into the chart, and the strength of the evidence was annotated. Sub-actions were colour-coded green, yellow, orange, and white to connote strong and recent evidence, tangential or patchy evidence, areas not suitable for evaluation, and areas outside PIRU's expertise, respectively (Appendix: Document 2).

This chart was distributed at group meeting, where consensus discussions took place to determine where the group agreed or disagreed with each colour classification, and to identify evaluable gaps in the evidence base underpinning the UK AMR Strategy's mechanisms of change. This was all preparatory work which led to the systematic review. I led on both the preparatory work and also the systematic review.

In developing new drugs, treatments, and diagnostics – one key action was 'encouraging innovation and providing an impetus for improved collaborative action to develop rapid diagnostics and new treatments and vaccines'. I first examined the clause of 'encouraging innovation and providing an impetus for improved collaborative action to develop rapid diagnostics'. In the first rapid review of the literature, I found a 2007 Health Technology Assessment (HTA) by Abubakar et al. that stated that, while there was strong evidence to

support the sensitivity of rapid PCR-based technologies for the detection of faecal and food-based pathogens such as Campylobacter, E. coli O157, and Salmonella, there was insufficient evidence to determine the effect of rapid technology on clinical outcomes.(138) Moreover, there was some evidence to suggest that rapid PCR-based testing was unlikely to be cost-effective in conjunction with routine culture.(138) Further research found articles on the sensitivity and specificity of rapid diagnostics, but very little on the impact that diagnostics were having on clinical outcomes for patients, or indeed on the Strategy's goal, antibiotic resistance (or its more capturable proxy indicator, antibiotic prescribing).(160–162)

There was also what I believed to an uneasy elision between the types of rapid diagnostics used to *diagnose* –rapid diagnostic tests for malaria, HIV, TB, flu, etc. – and tests used to *detect resistance*. There was an increase in the evidence base for the former, but the latter was lagging well behind in terms of demonstrating impact, improvement in patient outcomes, a reduction in antibiotic prescribing, an improvement in appropriate prescribing, or any number of indicators. This was particularly true in a hospital setting, where more costly molecular diagnostics are increasingly being concentrated.(50,51,163–167) In fact, there were several papers that I read in this first part of the scoping study that reported on clinical outcomes, but found that these were the outcomes in their studies that had shown no demonstrable improvement following the introduction of molecular diagnostic tests.(45,138,168) There were two diagnostic guidance reports from NICE on very specific tests (including procalcitonin testing to direct antibiotic treatment in hospital, and LightCycler Septifast and Septitest for the same aim), both of which again were highly specific targeted reviews.(169,170) In these diagnostic guidance reports, there were similar concerns that these tests seemed not to improve clinical outcomes in the existing literature. I felt it important to develop a new systematic review question on this theme. I took this to the PIRU team, who agreed. I then developed my primary research question and secondary research questions:

Primary. Dorapid diagnostic tests for antimicrobial resistance change clinical outcomes or antibiotic prescribing rates, compared to non-RDT best practice? (Quantitative)

Secondary

- Dorapid diagnostic tests for antimicrobial resistance change clinical outcomes or antibiotic prescribing for high-risk patient subgroups, compared to non-RDT best practice? (Quantitative)
- What is the acceptability of usingrapid diagnostic tests for AMR detection in hospitals among hospital staff? (Qualitative)
- What is the acceptability of usingrapid diagnostic tests for AMR detection in hospitals among patients? (Qualitative)
- What are the barriers to implementingrapid diagnostic tests for AMR detection in hospitals and their laboratories? (Qualitative)

I had assumed that there would be a qualitative evidence base which could be reviewed to answer the questions on acceptability, feasibility, and barriers to implementation. I also assumed that there would be surveys that could answer these questions, and that these qualitative and quantitative forms of evidence would appear in mixed methods studies. I had scoped the review in such a way that I would be able to capture a subset of existing studies that included surveys and/or other mixed methods approaches. I wanted to capture those studies that would be included in my full text screened studies, but the subset of those that included surveys of acceptability, feasibility and barriers to implementation of these diagnostics. I was advised by experts in the field that these studies would exist. However, what I found was that, in those trials or studies that reported on one of my primary clinical or prescribing outcomes of interest, none of them also reported qualitative data. This is important for my learning in the field, and also a reflection on the field itself – it is relevant that studies discussing clinical outcomes of interest do not find it important or relevant to include user (patient or provider) acceptability metrics.

I mitigated the loss of this hypothesised data by relying on my complementary qualitative data analyses in subsequent chapters.

One hypothesis about the absence of qualitative data may be that previous researchers have assumed that the intervention in question (the adoption ofrapid diagnostic tests) is not, in fact, complex enough to warrant a study design taking a mixed methods approach to account for complexity. However, I would argue that this is not the case, particularly for the observational or pre-post quasi-experimental studies being undertaken. Sources of complexity

include phase transitions, multiple outcomes, effects at different levels, and non-standardisation of implementation.(145) All of these sources of complexity arise in, for example, a pre-post quasi-experimental study of RDT adoption, as follows.

Phase transitions – this is taken to mean that longitudinal data may demonstrate changes in direction or size of effect over time. This can be observed, in particular, with interrupted time series studies. However, in cases where interrupted time series data could have been used, the included studies opted instead for a pre-and post-implementation period figure (i.e. an aggregated statistic describing length of stay and mortality, rather than weekly dots). This would have been particularly relevant in those studies that included an antibiotic stewardship component in their implementation 'bundle'.

Multiple outcomes – The main criticism that was levied at this review was that it did not aggregate the evidence underpinning the impact ofrapid diagnostic tests on antibiotic prescribing or stewardship outcomes. This is because, in 58 studies, there were 17 antibiotic stewardship outcomes reported of different types, including reduction of inappropriate antibiotics by class or specific antibiotics, time to appropriate antibiotic therapy, time to scaling up or scaling down antibiotic therapy by mechanism (i.e. IV vs oral antibiotics) and time to moving the patient (i.e. out of, or into, isolation). This was in addition to the relevant clinical outcomes that were narratively described but not aggregated, and the bed management, costs, and potential intra-hospital infections averted, and provider time saved (both in the lab, and on the ward). Qualitative companion results or analysis could have helped to demonstrate the range or direction of effects.(145)

Effects at different levels – This is a particularly important problem in the field of AMR, since in many cases the beneficial effect of optimising prescribing is unlikely to be confined to the patient alone. Instead, the organisation can reap the benefits of reduced intra-hospital transmission, and/or reduced closures of wards to disinfect/decontaminate following an outbreak of resistant bacteria, which can be costly and have consequences for achieving quality premiums. In this case, synthesizing the views of stakeholders can be important when determining the impact at the relevant individual, ward, hospital, trust, and country-level.

Non-standardisation of update/implementation – This is of particular concern when the pre-post studies are reporting a six-month pre/post implementation of RDT figure. Is the effect estimate masking intra-period heterogeneity? What are the practical concerns, if any, with the new diagnostic? Is it being used consistently? Is it being used out-of-hours? How have doctors used the new information? Have they found it difficult to adjust to out-of-hours antibiotic sensitivity information being made available (if it is)? Are the rates of antibiotic courses being switched the same at night as during the day? What about by grade of hospital doctor who sees the patients? Implementation data, including survey data and qualitative interviews, and ethnographies could have been used to great effect in many of these studies that purported to elaborate on the switch to RDT in many of these sites. In this way the evaluation ofrapid diagnostic tests fulfils a number of key criteria for complexity.

2. *Writing and registering the review protocol*

It is considered best practice to register a systematic review protocol on a system like PROSPERO so that *post hoc* 'fishing' through data can be avoided, and *a priori* hypotheses are formalised, like with other methodologically rigorous studies. As such, the protocol writing process can be slow, and in some ways it can be more difficult than the execution of the review, since decisions must be made at this stage in a state of uncertainty, both of what types of evidence will later be found, and what data may be available in that evidence base. Amendments to a registered protocol are permissible by PROSPERO, but only until right before data extraction begins.

When I was scoping this review protocol, I relied heavily on the Centre for Evidence-Based Medicine's position paper onrapid diagnostic tests.(4) Heneghan's team at Oxford reviewed many rapid diagnostic tests, and grouped them into categories. Based on that categorisation, and based on my own rapid review, I determined that tests for bacterial identification and antibiotic susceptibility testing was the area with the largest gap in the evidence. However, even within that category, there were technologically distinctrapid diagnostic tests that covered a number of different parts of the clinical care pathway, and while I was happy to group many proprietary technologies based on what they replaced in the laboratory, I did not want to include tests whose primary purpose was to provide a diagnosis, or that rapidly distinguished between bacterial and viral diagnostic technologies. This was for two reasons. First, the number of technologies multiplied by the number of types of test was overwhelming. And second, there were previous systematic reviews on bacterial versus viral

diagnostic tests.(136,137) When I summarised the Heneghan paper I decided to focus on the tests that identified bacteria and also aimed to identify bacterial resistance, and were considered to be molecular, rather than automated, or mechanical. In practice, this ended up including all types of polymerase chain reaction (PCR) tests (including real-time, quantitative, and multiplex), MALDI-TOF, and procalcitonin testing, for a variety of different bacterial targets (a mixture of gram-negative and gram-positive fast-growing bacteria), and clinical conditions (bloodstream infections, MRSA/SA, CRE screening). I decided to adopt a health services approach. Rather than a direct test-to-test siloed approach, I made the decision to lump tests together if their study comparators were similar. Therefore, if the primary clinical outcomes of interest were the same, and being compared to culture or automated culture, I concluded that they were occupying the same clinical space in the bacteriology care pathway, and could therefore be compared.

I was aware that this decision would increase external heterogeneity and might have two consequences: (i) requiring the prior specification of a range of subgroup analyses, and (ii) reducing the perceived validity of any calculated summary effect estimates. However, since there have been no meta-analyses in this area, and only one systematic review – likely due to this problem – I felt that the gains I would make outweighed these limitations, namely (i) increasing the population and power available for meta-analysis, (ii) producing the first clinical summary effect estimates in this field, and (iii) contributing to methodological advances in the rapidly moving field of diagnostics.

To summarise, in the case of this systematic review, it makes more sense to ‘lump’ than to ‘split’. Similarly, I felt it best, in the absence of a large number of studies in this area, to include experimental and observational methodologies and then treat them with care in subsequent subgroup analysis rather than to exclude observational and quasi-experimental work at an early stage, as is done by many other clinically focussed systematic reviews.

Throughout the drafting process of this review protocol, I relied on methodological and subject matter experts for consultation and sense checking. I asked for comments on my protocol from three sources: my PhD supervisory team; my internal colleagues in PIRU, and Professors Mike Sharland (St. George’s), Dr. Richard Stabler (LSHTM) and Mark Wilcox (Leeds) for external expert comment with respect to diagnostic testing. These comments

demonstrably changed the draft protocol. For example, I had originally included all molecular diagnostic tests for all bacterial infections. However, Professors Sharland and Wilcox both suggested that the inclusion of tuberculosis with other gram-negative infections added complexities to the review, since the rate of growth of mycobacterial infections in the lab is far longer than other, fast-growing infections.

Moreover, perhaps because of this material difference, and because of efforts to staunch the transmission of TB in low- and middle-income countries (LMICs) there already existed a burgeoning evidence base on the existing molecular diagnostics in this area. At the time of planning my review, there were several other systematic reviews registered on PROSPERO on Xpert MTB/Rif currently in progress on cost-effectiveness, patient outcomes, and test implementation. (44,135) There is also a relatively large published literature on the cost, test, and clinical effectiveness of the test, along with a healthy debate about the failure of eight trials to demonstrate improvements in clinical outcomes.(41,168,171–184) This academic interest is partially because, while the Xpert MTB/Rif test measures, among other things, resistance to rifampin, a first-line treatment for tuberculosis, it is first and foremost a diagnostic test and as such, is used for people with suspected tuberculosis.

In many ways, the successes with TB diagnostics were being used to propel molecular diagnostics in AMR. However, TB can take up to six weeks to grow in a laboratory, whereas so-called 'fast-growing' bacteria takes 24-36 hours on an agar plate, and 16-24 hours in the automated systems that were introduced in the late 20th and early 21st centuries. As such, the marginal gains available to guide clinical care, even if the test time was reduced to 2-6 hours, were vastly smaller than in TB. This is partly why, I theorised, the extant studies had struggled to show impact on clinical outcomes. it was also why I felt it reasonable to exclude TB from my review.

I registered the systematic review protocol on PROSPERO on 1 April 2017 (Appendix: Document 2), and conducted the searches in all databases on 09 May 2017, and again on 4 April 2018.

3. *Developing the search strings for database searching*

I searched many databases (reported in the paper, below). As this was my first systematic review, I drafted a search string, and asked for advice from the expert systematic review librarian at LSHTM, Jane Falconer. Once this was complete, I used this as my master search string and modified it according to the search requirements in each database.

I aimed for a highly sensitive search strategy, and named individual antibiotics, rather than simply searching for 'antibiotic', or even antibiotic classes, such as 'penicillins'. Similarly, I included relevant diagnostic technologies in the search string. For example, 'PCR', 'MALDI-TOF', and 'procalcitonin' were all included. When I added the name of specific diagnostic technologies, and the named antibiotics and antibiotic classes, I more than doubled the number of returned results. This, of course, extended the timelines of the screening component of the work. However, because this is the first such review in this area, and because of the relative paucity of studies in this area, I made this decision because I felt missing one seminal paper in the field would compromise the legitimacy of the review. I further mitigated the risk at the end of the screening process by turning over the list of included papers my external advisors, who reviewed it for me, and felt it was appropriate. I triangulated the included papers list with the extant diagnostic guidance onrapid diagnostic tests and the other systematic review in this area (see section iv, below).

One limitation of my search string is that, even though I trialled it before conducting my 'official' search in April 2017, I had not remembered to exclude papers that referenced tuberculosis. Over 1,100 search terms included the term tuberculosis out of the c 20,500 papers returned. To avoid having to screen 1,100 extra articles with my second screener, I unilaterally deleted these 1,100 papers (identified by keyword search in titles only) in Endnote before turning over the final list to the second systematic review screener for independent checking.

4. Screening the found articles

Screening titles then abstracts consecutively

I chose to screen titles first, and then abstracts. This was for two reasons. First, there were pragmatic reasons for this choice. There were over 20,500 included titles. It is important to be cognizant of the role pragmatism plays in any systematic review. As with primary data

collection, systematic reviews are dictated by cost and time constraints. It is important to be transparent about these, and about the ways in which the risk of this decision was mitigated. In this case, I approached title screening in a highly sensitive way. If the title did not report on the primary relevant information (type of RDT, clinical outcomes, hospital-based, for example) it was included and the abstract was screened. As much as possible, adopting a cautious screening attitude can go some way to mitigating the choose to screen titles and abstracts consecutively. This tendency toward inclusion was adopted in the abstract and full-text screening rounds as well.

Information management system

Many people choose to manage their systematic reviews in a systematic review-specific software. I decided not to do this, choosing instead to export my citations to Excel.(185) I then hid the non-screening information from sight for both my second screener and me, preferring instead to have visible only the unique study ID, the screening data (i.e. title or abstract), and then an include/exclude/unsure column, which was a drop-down menu populated with validated text.

There is a literature on the impact of information management systems on interrater reliability and speed of screening.(186,187) It seems clear from the literature available that there are material accuracy and time gains won by adopting an electronic system in comparison to a paper-based systematic review. However, beyond that, any gains in a system like RevMan seem relatively marginal, though more important when using more than two, or rotating, screeners. In my case, the screeners were consistent throughout, and never numbered more than two. Furthermore, the benefit of Excel is that it required me to manage my data in a way that RevMan does not. It required that I check and validate my PRISMA diagram, account for missing data, and justify when and where studies were falling away. This constant checking of the data meant that I was in contact with the process, and had to have a better understanding of why I was taking certain decisions, and how my data were being managed. While I would want to use RevMan or similar software in a future review to streamline some of this work, this process has afforded me an understanding of the processual problems and decisions that arise throughout a review, while simultaneously capturing the accuracy and time gains of using a dedicated system.

Kappa statistics

As this review was part of a package of work evaluating the UK's five-year AMR strategy, there was provision for a second reviewer. As such, I worked with the same second screener, Dr. Mustafa Al-Haboubi, for the duration of this review. This provided us with consistency. and aided the inter-rater reliability of our decision-making. This can be seen by the Kappa statistic reported in the paper. When one is reporting the Kappa statistic for a paper, this is typically a global figure that rolls all inter-rater decisions into one calculation. However, I was interested in how raters work together throughout a project. I did not know whether inherent rating decisions and appetite for risk were static or modifiable.

I therefore calculated the Kappa statistic at the end of each screening stage. I found that our Kappa statistic increased at each screening stage (titles, abstracts, and full text). This could be due to a variety of factors. First, I was responsible for creating and conducting training for Dr. Al-Haboubi before every stage. While, before title screening, I felt that I had been comprehensive, I used the feedback of the post-title screening Kappa statistic in order to tighten my training programme before abstract screening. For example, after conducting the abstract training, Dr. Al-Haboubi and I both provisionally screened 100 abstracts. Instead of simply looking through the agreement and feeding back my summary to the second reviewer, we did this step together, and discussed in real-time why we had included or excluded the abstract. This way, I could interrogate misunderstandings (including my own) in real-time, and both of us could move to the second phase of screening with a better understanding of the requirements and indeed a better grasp on the inclusion and exclusion criteria.

I would recommend that a step-wise Kappa statistic be reported in systematic reviews in future. Not only does it aid transparency in reporting, it also demonstrates the levels of risk with respect to sensitivity/specificity of included studies at each step in the screening process. For example, if inter-rater reliability is very high in the initial, high-volume stages of screening, but very low when reviewing the relatively few full text articles, the high initial denominator could mask a lack of clarity in the inclusion and exclusion criteria or uncertainty at the final stage, and there could therefore be a case for an audit of the excluded articles at this final screening step.

5. *Extracting data from the included articles*

For data extraction, I created and piloted a chart in Excel 2016 with fields for all the pre-specified clinical and prescribing outcomes, and supplementary fields for the original secondary outcomes of interest that I had proposed to evaluate in the protocol.(185) These were fields such as hospital costs. However, perhaps due to the fact that I had prespecified that a study had to have real-world data reported on at least one clinical outcome to be included, very few studies included economic modelling. Those studies fell away because they would tend to specify test sensitivities or specificities, and then model the likely cost-effectiveness impact for a particular hospital. Positive and negative predictive values (PPV and NPV) were also prespecified potential secondary outcomes that were ultimately not collected. Studies reporting PPV and NPV of diagnostic tests were not going on to report real-world clinical setting data. Instead, these studies were validating the tests on a selection of known samples from a reference laboratory, rather than real-time patient samples.

However, on the whole, the data extraction table worked well for both reviewers when it came to extracting the relevant data, in spite of these data's relatively high heterogeneity (different tests, different technologies, different study populations, and often different clinical outcomes of interest). An unexpected challenge (and limitation) of the data extraction is that I did not train the second reviewer on identifying the type of epidemiological study. For those studies that did not list their exact study design, the second reviewer's decisions were often not correct, since the second reviewer did not have epidemiology training. This meant that I relied solely on my data extraction for study design. As such, I did not catch an error in the first draft, where I had miscategorised one study as an RCT, which it was not. This paper was relevant for meta-analysis and was included, misclassified, in many summary effect estimate calculations. This error was caught in the writing up/data validation process for the paper, but highlights the methodological importance of using two reviewers throughout the systematic review process.

Risk of bias assessment

Due to the fact that I included experimental and observational studies in my analysis, risk of bias assessment was a serious concern. Should I use different risk of bias metrics for each study design? This is an area with a vast literature base, and while many risk of bias assessment systems are validated for particular study designs, the choice of particular system remains, to a high degree, a matter of reviewer preference. While in my study design I had made provision for particular risk of bias assessment strategies according to the study design,

I took expert advice throughout the process and ultimately chose to use the Effective Public Health Practice Project (EPHPP) for all studies because of previous research that demonstrated its consistency, internal validity, and excellent inter-rater reliability, discussed below.(188)

- Given the wide variation in study designs, and the fact that even the experimental studies were not able to conduct any form of meaningful blinding or randomising, I felt that these studies were similar in study design to pre-post quasi-experimental and the prospective observational studies that were conducted on the impact of RDT adoption in secondary care.
- The challenges of comparing between studies that were rated on different scales meant that I was wary of attributing studies to the correct subgroups in subsequent analysis. EPHPP divides studies into only three categories. I judged that these would be able to act as broad 'bins' in which to divide studies, allowing me to attribute all studies according to the same risk of bias metric.
- Unfortunately, it was not possible to have a second reviewer conduct the risk of bias analysis, and so this represents a 'known unknown' when it comes to bias classifications. This is another reason why I chose the EPHPP. There is a literature underpinning this rating system showing that one of its strengths is the fair inter-rater concordance rate.(188,189) As such, in the absence of a second rater for this (and only this) section of my review, I felt that using such a rating system would help to mitigate the risk of incorrect, or divergent, classification.

6. Data analysis

<u>Data transformation for length of stay</u>

Length of stay is a variable that is skewed for hospital admission data.(190,191) For some patient populations, it is more or less skewed. Length of stay for bacteraemias, to take a relevant example, tend to be particularly right-skewed**.**(190) In such cases, length of stay tends to be reported as median and range, or median and interquartile range, rather than mean and standard deviation.(192) This is certainly an appropriate reporting choice in the literature. However, the rate of skewness is rarely reported in the original paper; we are meant, therefore, to infer that the skew was sufficient to warrant that choice for data reporting.

It is understood not to be statistically appropriate to conduct a meta-analysis on median and range data because the likely reason why median and range data are reported in the first place is because they are skewed.(193,194) There is some debate about the acceptability of transforming median and range data into means and standard deviations.(192,194–196) However, the choice is not between a statistically 'good' or statistically 'poor' option; but rather, where one wants to introduce one's own bias. By not aggregating data that has been provided as medians and IQRs, I would be neglecting a plurality of the data. If I transform those data, I am introducing bias in my estimation of the mean and variance. This has been explained elsewhere.(193)

There are, however, statistical papers that provide guidance for those meta-analysts who want to transform these data into mean and standard deviation data in order to aggregate more data., depending on whether the meta-analyst can access median and IQR or median and range, there are papers that provide validated equations to facilitate that transformation.

I used an online calculator based on data from one such paper.(197) On balance, therefore, I felt it appropriate to conduct the analysis, and then report the limitations, as I have done in the submitted paper.

Meta-analysis and meta-regression

I had always made provision for meta-analysis of any clinical or prescribing outcomes of interest reported sufficiently frequently in the literature, but did not realistically believe that this was going to be either an eventuality or a possibility. I was surprised when length of stay, 30-day mortality, and all-cause in-hospital mortality were suitable targets for meta-analysis.

I ran all meta-analyses in STATA 15.1.(198) I considered the studies, in different countries, with different technologies, too disparate for a fixed effect model, so in all cases, I used random effects models. This is in accordance with meta-analysis guidance.(140,145,199,200) For length of stay (a continuous variable), I chose not to standardise my data**.** I did, however, weight according to the size of the study and the standard deviations reported around the effect estimates. This weighting was the one embedded in the *metan* command in STATA.(140) My modifications of this command were only these (*random nostandard)* because I judged the other embedded assumptions in metan to be appropriate for my data. These include: the assumption of continuous data when six variables are entered; adding effect size (ES) to the dataset, estimating standard error for the ES, and estimating lower and upper confidence limits for the ES.(198)

The only arena where I felt it was possible to conduct a meta-regression was for the ten non-RCT papers in the length of stay analysis. For the other meta-analyses, there were too few papers to meaningfully understand the impact of multiple factors. The main concern that I had about that particular analysis was the moderate-to-high heterogeneity, which I felt warranted investigation. As such, I examined the impact of three binary variables (using *metareg univariate* and *permute* due to the small number of studies). These three variables were (i) the presence/absence of other antibiotic stewardship improvements alongside the adoption of therapid diagnostic tests, (ii) whether a laboratory was processing samples 24 hours a day or not, and (iii) whether the type of test had any bearing on the summary effect estimate. Of these three, the only one with a statistically significant, unadjusted p-value (p=0.008) was the variable which indicated whether there was an ASP bundled into the introduction ofrapid diagnostic tests. As expected, those who had an ASP attached had a greater reduction in length of stay than those who did not. However, when adjusted, this did not reach statistical significance at p=0.05, the pre-specified level. However, given the small number of studies, this is a relevant avenue for future research.

Funnel plot analysis

This theme of underpowered further investigation continues into the funnel plot analysis. While I had planned on conducting a funnel plot analysis in order to determine whether there was likely to be a small study effect, information asymmetry (i.e. publication or other biases), the Cochrane handbook recommends not conducting an Egger's test or other statistical analysis with fewer than 10 papers (and to consider that the test is likely underpowered until there are 20 or more included papers).(140,196) I therefore did not report on these, but would recommend Egger's tests for small study effect in future reviews.

This is an area where the adoption of a mixed-methods research design has proven useful; in the qualitative research presented in Chapter 3, there is data from a clinical microbiologist at a large teaching trust, where they confirm that they conducted an internal study of the clinical impact of introducing the MALDI-TOF to their teaching hospital. The microbiologist described that there was no demonstrable effect on either length of stay or mortality for the in-patients. the paper was shelved, and has not yet been published. This fits with the theory of publication bias, which is that the negative studies aren't simply missing, but delayed, or lagging behind the publication of the positive studies, for many reasons, including the

perception of the researchers that negative results will be harder to publish, therefore perpetuating the publication bias that they decry.(201)

Sensitivity analysis

Egger et al urge sensitivity analyses should always be presented.(140) However, there are many ways to accomplish this task. As with data analysis above, sensitivity analysis is difficult when there are very few studies, since each of three or four studies can have a substantial impact on the summary effect estimate. I did conduct a sensitivity analysis on the ten studies included in the length of stay non-RCT group. I did explore the impact of removing each one of these ten studies and rerunning the meta-analysis on the remaining nine – this type of analysis is provided in the STATA command *metaninf*. However, this type of sensitivity analysis runs the risk of post hoc rationalisation, or 'fishing', for the impact of a particular type of study, population, or other divergent factor.(140) A more thoughtful approach to sensitivity analysis could involve conducting sub-group analysis according to stratifications based on study quality, length of follow-up, or type of statistical model. In my case, fixed effects would not have been appropriate due to the heterogeneous contexts of the studies, and length of follow-up was not included in the studies, since all studies included patients' whole hospitalisation episode, but I did examine the impact of the study quality where possible, on the ten non-RCT papers reporting length of stay, as follows.

Moderate vs weak risk of bias

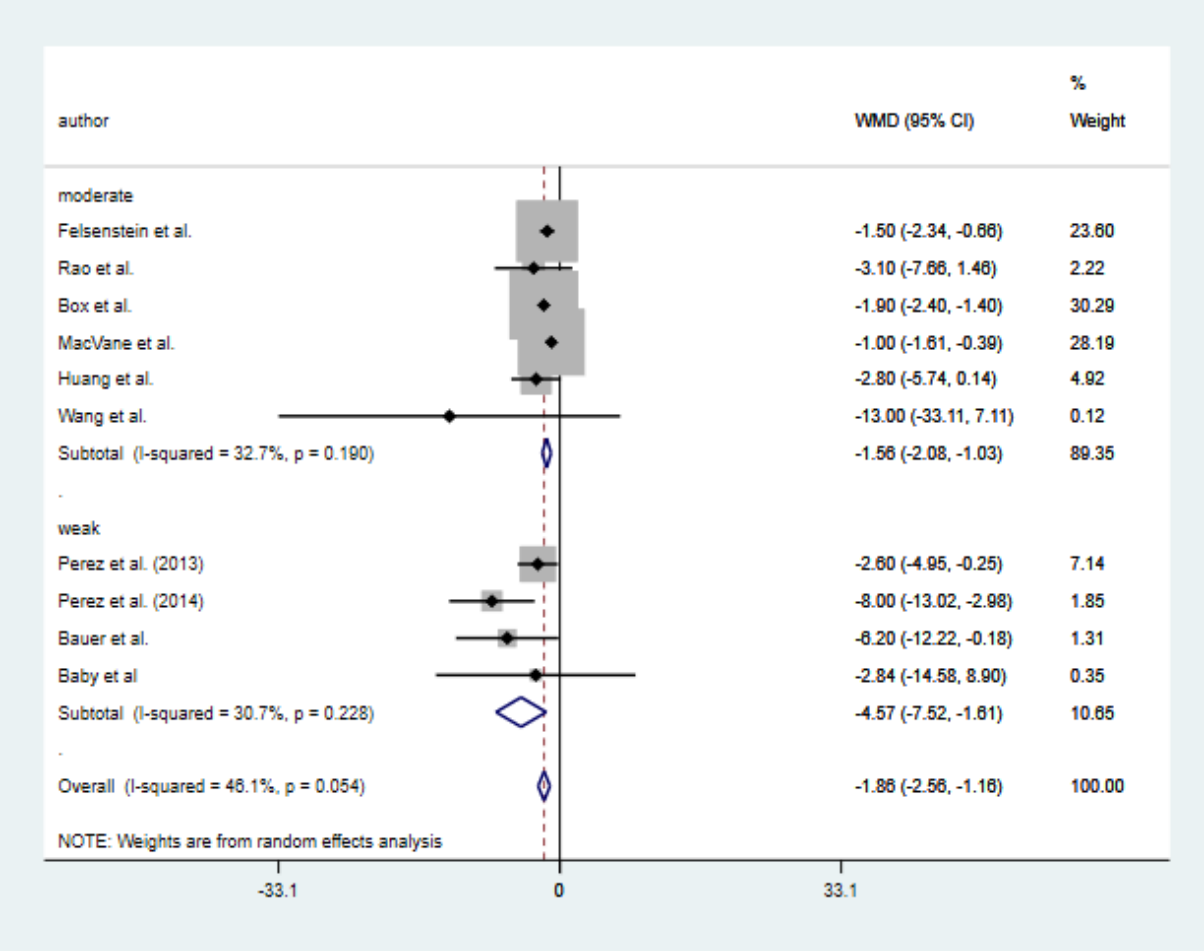
I also sought to determine whether study design (or more precisely, study quality) was impacting the summary effect estimate. Some systematic reviewers (and, indeed, the Cochrane handbook) recommend the exclusion of so-called 'weak' studies, however, as previously discussed, this is a field with relatively few studies, and no extant comprehensive systematic reviews.(202) As such, it may be helpful to have a published, first estimate of the evidence base from which future reviewers can select as more studies are published in this area. Moreover, including all of the evidence – and then conducting subgroup analyses about the impacts of different calibres of study on summary effect estimates – can provide valuable information about how this variation can impact the field.(147)

I separated the papers into those that were deemed to be moderate evidence, and those that were considered to be weak forms of evidence. The results are presented in Figure 3, below.

While these groups are not statistically significantly different, the meta-analysis of moderate quality studies had a smaller effect estimate for length of stay than the weak evidence base.

Some systematic reviewers weight studies according to their quality in the overall, pooled summary effect estimate,(140) however this is considered to be a unreliable approach, because even though it is an attempt to capture the relative qualities of the papers, the weighting is an arbitrary process that leads to the introduction of subjectivity into the summary effect estimate.(203)

Figure 3 Subgroup analysis of moderate and weak studies, as categorised using the EPHPP



Meta-analysis and subgroup analysis of observational studies

While the benefits of meta-analysis and subgroup analysis are well-understood for RCTs, there is some debate in the literature surrounding the appropriateness of meta-analysis of observational data.(148,204) The investigation of heterogeneity becomes more important in the observational study context, and the known risks of this approach are confounding and selection bias – aggregating a selection of biased studies can lead to a spurious result.(140)

However, ignoring observational studies, especially in an area like diagnostics where the majority of research on effectiveness is observational or quasi-experimental in nature, is to ignore the vast majority of extant evidence in this discipline.

There are ways to reduce the risk of spurious overall summary effect estimates in observational studies, and these have been discussed above, and adopted wherever possible. These strategies tend to be similar to those adopted for experimental studies: the use of a random effects model; the rigorous exploration of heterogeneity; sensitivity/subgroup analysis. For the observational studies, I have adopted a more cautious approach, having moved away from a reliance of a mechanistic calculation of summary effect estimate.

Rejected supplementary analyses

Meta-analysis includes many types of advanced analysis to the seasoned reviewer. Where appropriate, I adopted some strains, but others were rejected in the protocol writing phase as not likely to be useful or pertinent for this review. Nevertheless, it is relevant to understand the breadth and depth of these analysis options for future work in this arena; it may also help the examiners at this point to understand why these analyses were not undertaken in this particular review. In general, the reasons for rejecting certain analyses are relatively straightforward, and include, *inter alia*, the number of included papers, statistical power (or lack thereof), and their relevance.

Multi-variate meta-regression

With one exception, there were too few studies to conduct any meaningful meta-regression, whether multivariate or univariate. Where appropriate, I have conducted a univariate regression, but this was only for one meta-analysis.

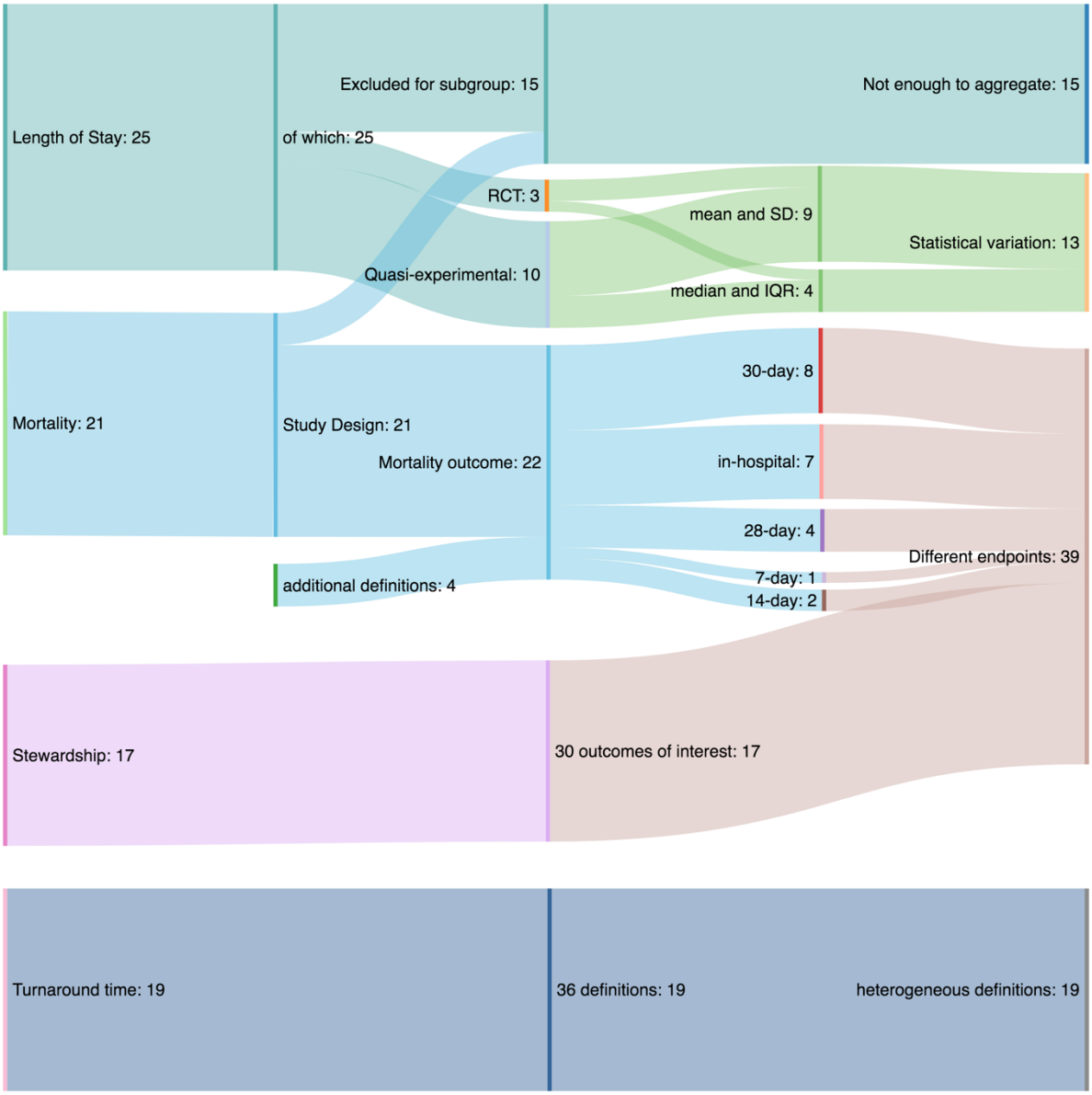
Maximum likelihood/ restricted maximum likelihood estimation

Restricted maximum likelihood estimates are useful if conducting fixed-effect models for better estimating the between-trial variance and standard error of that variance.(140) However, as described previously, fixed effects models are not relevant for this systematic review context.

7. *Methodological innovation*

One constant problem I faced throughout this review is the sheer number of papers that reported on an outcome of interest broadly speaking, but that were different enough to warrant exclusion from meta-analysis. Because there is little guidance in the systematic review literature on analysing the nature of papers that fall out of analysis between narrative synthesis and meta-analysis, I have worked to develop a process, making use of a Sankey diagram (Figure 4). This has not been done before in systematic reviews, which rely on the simpler, and I believe much less informative, PRISMA flowchart. The diagram can be read from left to right. For my four outcomes of interest (length of stay; mortality; antibiotic stewardship, and turnaround time) I include the number of included studies that report on these: 25, 21, 17, and 19, respectively. These do not add up to the total number of studies (58) because many studies report on multiple outcomes of interest. Then, I describe the "whittling down" process toward meta-analysis for each of these. In some cases, such as for length of stay, the subgroup reported on in the study can be particularly narrow, so because of the absence of similar subgroups, these are excluded from the meta-analysis. In other cases, including for length of stay, the whittling down process does not lead to exclusion from meta-analysis, but rather, to a strikingly small pool of studies that end up being included. This can ultimately help to explain the larger confidence intervals, and the frustration that many readers of systematic reviews feel when they see that there is 'insufficient evidence to reject the null hypothesis' or that there were 'too few studies' to draw conclusions about the impact of an intervention on a particular outcome of interest. It was never the case that there were insufficient studies. Instead it was more likely, that those studies could not be combined because of particular reasons which can be clarified using a Sankey diagram.

Figure 4 Sankey Diagram with outcomes of interest (number of papers included in narrative synthesis) and across, how those papers break down into subgroups, and on the right, what happens to them in the final analysis.



The Sankey diagram, presented above, in combination with an abstract or paper, allows a reader to interrogate the body of work at a glance. For example, I have not meta-analysed antibiotic stewardship outcomes. The reader would know this by reading the entire paper, but the Sankey diagram summarises the point; there are 30 antibiotic stewardship outcomes reported in 17 papers. A visual scan allows for an understanding that these 30 outcomes were different endpoints and could not be combined quantitatively. An additional table describing the data can be found in Appendix: Document 3.

The Sankey also confers the advantage of being able to see that the meta-analysable and non-meta-analysable areas are subjected to the same problems and scrutiny and are often a question of volume or degree. For example, I include in my review two meta-analyses of length of stay; one that is of 30-day mortality, and one of in-hospital all-cause mortality. I include no other meta-analyses in spite of the fact that 21 papers reported mortality figures, and of these, some papers reported multiple types of mortality data. A cursory examination of the Sankey mortality flow demonstrates that, though there are problems with different reported endpoints of mortality data, there are enough papers that report on 30-day (8) and in-hospital (7) to attempt a statistical aggregation. In this case, the Sankey reveals that there are still multiple types of mortality data being reported, in spite of recent work on appropriate endpoints for evaluation of antibiotic therapies (a relevant proximal field to the evaluation ofrapid diagnostic tests for antibiotic susceptibility and resistance) and the fact that there is a push exclusively toward 28-day, 30-day, or in-hospital mortality reporting.(205)

The nature of an Sankey diagram may be patterned, or at least somewhat sector specific. Areas where systematic reviews rely primarily on RCTs may be more likely to fall out of meta-analysis due, for example, to patient sub-populations; poor or moderate study quality; or endpoint heterogeneity, whereas areas with complex interventions may suffer from different types of problems, such as variation in definitions (as with turnaround time in my study) or multiplicity of endpoints (as with antibiotic stewardship outcomes in my study).

8. Interpretation

Divergent subgroup analyses

A theme of this review has been that often, when subgroup analyses have been undertaken, they have produced statistically significantly different summary effect estimates. This has occurred for the length of stay analyses, the 30-day mortality analysis, and the transformed/untransformed mean analysis. This presents two possibilities for interpreting the results. The first is to critically appraise each subgroup's summary effect estimate, and examine the factors that have gone into each, adopting external assessments of quality (EPHPP) or external hierarchies of study design (i.e. favouring RCTs over non-RCTs) in order to select the summary effect estimate more likely to represent the true effect size. I have, to some extent, adopted this approach in the paper, especially since the subgroup analyses tend to demonstrate that the traditionally 'less good' study design, 'less correct'

statistical reporting of length of stay, and higher heterogeneity analyses are consistently the subgroups with the larger summary effect estimates. Where there are RCTs, the effect estimates are smaller, if not non-existent. Where heterogeneity is lower, summary effect estimates are smaller. Overall, I find reassurance in the fact that external, hegemonic markers of quality and hierarchies allow one to order these analyses; in this externally imposed order, it becomes clear that these diagnostics are not clearly improving clinical care. They appear not to harm clinical outcomes, though this is not taking into consideration the fact that the money spent on these tests could very well be being spent on a more cost-effective health intervention, but the evidence does not seem to support wide-scale adoption of these technologies.

However, in the face of such divergent data, it also makes sense to question why these data are so heterogeneous. In my quest to aggregate different types of data, have I run a systematic review from which little, if any, main messaging can be drawn? Have I obfuscated the picture, rather than clarified it? Have I appropriately used and manipulated these data in a way consistent with the accepted approaches? The previous sections should go some way to systematically evidencing the types of systematic review and meta-analysis decisions that I have taken throughout the course of this research. I believe my methods to be sound.
If this is the case, then it is also possible that the relatively small number of included patients in these largely unrandomised, uncontrolled studies have not captured the true summary effect estimate. While a clarion call for "more research" is not the conclusion that any systematic reviewer would like to put forward – though any systematic review should include a more specific description of the areas where new research studies are needed - in this case such a call is caveated by the following: there seems to be a fundamental problem with the way that outcomes of interest are (i) selected, and (ii) reported in the literature. This has meant that areas where there may be benefits from adopting these tests (including antibiotic prescribing and stewardship outcomes) are lost to meta-analysis, and areas where there may be efficiency gains by test adoption (if not concomitant clinical improvement) such as turnaround time are again obfuscated by vague taxonomies.

9. *Writing the review*

I have five co-authors on the systematic review paper. A typical question asked of PhD candidates who undertook their research as a part of an academic work stream is how much of it is their own work. In my case, my co-authors were important throughout my work, and were consulted about most decisions that I took. However, ultimately, I led all stages of the review and the decisions were mine alone. Second, all co-authors contributed materially to the paper. However, I wrote the first full draft of every document involved on my own (research question; protocol; report; paper), and conducted the analysis and wrote the first full draft of the paper for co-authors to comment on.

10. Facing potential criticism of grouping diagnostic technologies

One critique that I have yet to receive, but for which I am prepared, may come from one category of stakeholder I have not yet consulted, the medical diagnostics industry.
Though I have thus far received expert feedback from clinical microbiologists (experts on using the tests), health services researchers (experts on evaluating pathways of care), and systematic reviewers (experts on appropriate systematic review methodologies), it is true to say that these tests are materially different from one another. However, since they occupy similar spaces in the care pathway, and since they purport to achieve similar benefits for similar subgroups of patients, I considered that it was appropriate to group them together for analysis. This is discussed above. However, one potential criticism of this approach would be the well-known 'complexity' argument from the industry, who may argue that individual products are sufficiently different in aims or position in the care pathway so as to make grouping (for the aggregation of data) inappropriate. This argument would be beneficial for the relevant companies, because it allows them to reject the results of unhelpful analyses, like this meta-analysis as being a(n overly) simplistic analysis of a complex phenomenon, in this case, health technology implementation. This is an argument that has been levied against public health researchers in other fields previously, though primarily in unhealthy commodities industries (UCIs).(109) However, I recognise the risk of this reaction, particularly since this review has been cautious in its interpretation of the impact that these diagnostics are likely to have on primary clinical outcomes. UCIs have used the concept of complexity to dissuade against regulation and public health work in these areas.(109)

While there are important differences between UCIs and the medical diagnostics industry, there is one important similarity, namely that they would prefer to sell more of their products, not less.

The final version of the submitted paper follows. Please be aware that the paper is currently under review at the Journal of Clinical Epidemiology.

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

SECTION A – Student Details

Student ID Number	402062	**Title**	Ms
First Name(s)	Rebecca		
Surname/Family Name	Glover		
Thesis Title	Antimicrobial resistance in the United Kingdom: a mixed-methods dissertation on diagnostics, discourse, and decision-making		
Primary Supervisor	Mark Petticrew		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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<u>SECTION C – Prepared for publication, but not yet published</u>

Where is the work intended to be published?	Journal of Clinical Epidemiology
Please list the paper's authors in the intended authorship order:	Rebecca E. Glover (ORCID ID 0000-0001-9150-9977), Mustafa Al-Haboubi, Mark P. Petticrew, Elizabeth Eastmure, Sharon J Peacock, Nicholas Mays

Stage of publication	**Undergoing revision**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	NM secured funding for the study RG, NM, MPP, SJP, and EE developed the research question and fed into the protocol development for the study. RG and MAH screened all the articles for inclusion, and extracted all the data RG wrote the draft manuscript and analysed the data RG, NM, EE, SJP, MAH, and MPP edited the manuscript and approved its submission.

SECTION E

Student Signature	Rebecca Glover
Date	29 December 2020

Supervisor Signature	[redacted]
Date	06 January 2021

Paper I: Applying the Sankey diagram to a systematic review and meta-analysis of rapid diagnostic tests for antimicrobial resistance: a novel method for showing flow of evidence through a review

Submitted to Journal of Clinical Epidemiology - December 2020

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SJP is a Professor of public health and microbiology at the University of Cambridge

Contributorship statement
NM secured funding for the study
RG, NM, MPP, SJP, and EE developed the research question and fed into the protocol development for the study.
RG and MAH screened all the articles for inclusion, and extracted all the data
RG wrote the draft manuscript and analysed the data
RG, NM, EE, SJP, MAH, and MPP edited the manuscript and approved its submission.

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Abstract:
Background Antibiotic resistance is a serious problem worldwide, hampering appropriate antibiotic therapy. Rapid diagnostic tests (RDTs) for bacterial identification and antibiotic susceptibility testing are promoted as a possible solution to this problem, though their clinical effectiveness in practice has been questioned. Assessing the evidence is also difficult because of the use of multiple inconsistent endpoints in the primary studies. We synthesized the evidence on the impact ofrapid diagnostic tests for bacterial identification and antibiotic susceptibility testing on clinical and antibiotic stewardship outcomes compared with standard practice in hospitals, and used a Sankey diagram to help present the findings and illustrate study heterogeneity.

Methods We conducted a systematic review of experimental and observational studies which included at least one prescribing or clinical outcome ofrapid diagnostic tests in hospital in-patients. Sub-group analysis and meta-analysis were used to synthesise the results, including exploration of heterogeneity in summary effect estimates. A Sankey diagram was then used to show the flow of evidence through the review.

Results 58 studies from 14 countries were eligible for inclusion. The introduction ofrapid diagnostic tests did not significantly reduce in-hospital mortality (RR 0.83, 95% CI 0.60 - 1.15) or length of stay (weighted mean difference for experimental studies = -0.36, 95% CI -1.67 to 0.96). There was high heterogeneity in antibiotic stewardship outcomes, prescribing outcomes and the definitions of turnaround time used in study reports.

Discussion Currently, there is no evidence that the routine use ofrapid diagnostic tests for bacterial identification and antibiotic susceptibility testing improves clinical outcomes. The lack of standard definitions such as turnaround time precludes full use of the evidence, as the Sankey diagram showed. Sankey diagrams may be a useful adjunct to the PRISMA diagram in complex systematic reviews where evidence is heterogeneous and not easily amenable to meta-analysis.

Key words: antibiotic resistance, antimicrobial resistance, systematic review, meta-analysis, health technology appraisal

Strengths and limitations of this study:

Strengths

We developed a novel method to identify, group, and analyse the flow included studies; systematic reviewers can use a Sankey diagram to visually assess points of methodological concern in systematic reviewing.

The study shows how Sankey diagrams can help compare patterns of methodological quality and variation in end-points across sectors and topics.

We demonstrated this technique in an area where systematic review and meta-analysis is underused, namely the clinical effectiveness of rapid diagnostic tests for bacterial identification and antibiotic susceptibility testing.

Limitations

While there appears to be evidence of reporting bias (publication bias, small study effects), the paucity of studies included in our systematic review means that Egger's test is underpowered at this time.

There is a lack of standard terminology used to report 'turnaround time' and standard antibiotic escalation and de-escalation outcomes of interest; in addition to our methodological innovation we also recommend standardised definitions and greater care selecting endpoints.

Data sharing

Data can be obtained by emailing the corresponding author.

Patient and public involvement

Patients and the public were not involved in conducting the systematic review and meta-analysis, though two PPI representatives reviewed the research question at the beginning of the research process, and also aided us in the development of plain English summaries for public engagement work related to this research.

Introduction

The identification and synthesis of core outcomes is a key step in systematic reviews, and a key focus of methodological research in clinical epidemiology.(206) Selection – and selective reporting - of outcomes is also a major source of bias in reviews and primary studies, which can lead to overestimates of effectiveness of interventions, and under-reporting of harms. It can involve the reporting of outcomes that represent no clinical benefit to patients, and for this reason there is an increasing emphasis on the incorporation of patients' views into the development and synthesis of outcome measures, as a way of ensuring the utility and credibility of trial findings: "Clinical trials are only as credible as their endpoints".(207)

Guidance from the Cochrane Handbook is that reviewers should choose only outcomes that are critical or important to users of the review, such as healthcare consumers, health professionals and policy makers, and outcome measures should be defined in advance.(196) In a mature field, where there are many trials reporting on direct patient benefit, this often involves require selecting and synthesising evidence on a narrow set of outcomes. However in fields where new technologies are rapidly emerging, it may be more useful to incorporate a wider range of health and non-health outcomes, to help assess what claims are being made about the balance of costs and benefits of the intervention, and to help make judgements (in the absence of patient-level outcomes) about the potential effects of the intervention, drawing on evidence from different parts of the care pathway.

Synthesising and reporting on such a heterogeneous and complex set of outcomes is however challenging. Common approaches such as tables and forest plots do not make full use of the data – for example, showing clearly how different studies contribute to understanding how interventions work at different parts of the care pathway. This is particularly the case for

diagnostic tests in AMR. Diagnostic test accuracy, but not clinical effectiveness, has often been used to support the routine use of these tests.(49,208–211)

This is because it is difficult to meta-analyse the evidence on diagnostic tests for three reasons: its relative paucity,(212) different proprietary technologies that undertake different functions in the bacteriology care pathway; and different selected endpoints in each study. We undertook a systematic review to synthesise this evidence. It is important to know what the evidence shows in this area because rapid diagnostic rests have been recommended as an essential of managing the threat of increasing antibiotic resistance. However it is unclear whetherrapid diagnostic tests for bacterial identification and antibiotic susceptibility testing confer clinical advantages over standard tests, and there is no existing systematic review. Instead, there is a heterogeneous and difficult-to-interpret evidence base, with different RDT technologies, using different definitions. For example, some tests have been described as "rapid" when they take 14 hours, while others are considered rapid when they take 15 minutes.

There is also a proliferation of different endpoints, which may in itself be a reason why no previous systematic review exists. It is therefore not enough to simply review the evidence, but also to understand how it varies. We therefore developed a Sankey diagram as a way of presenting the current state of the evidence base onrapid diagnostic tests in AMR. Sankey diagrams are a type of flow diagram which represent flows (e.g. flows of information, or of any property) within a process. They are used for example in industrial processes and in science in engineering.(213) The overall aim of this paper, then, is to demonstrate how Sankey diagrams, alongside the PRISMA guidelines, can facilitate reporting and comparisons across trials, using the systematic review as a case study.

Methods

(i) The systematic review*:* We conducted a comprehensive systematic review and meta-analysis of the impacts of introducing rapid molecular diagnostic tests for bacterial identification and antibiotic susceptibility testing, following PRISMA guidelines.(9) . The systematic review aimed to synthesise the evidence of the effects ofrapid diagnostic tests on clinical and prescribing outcomes compared with standard care in acute hospitals. The technologies included are: multiplex, real-time, and quantitative polymerase chain reaction (PCR); matrix-assisted laser desorption ionisation time-of-flight mass spectrometers (MALDI-TOF MS); peptide nucleic acid florescent in situ hybridisation; and rapid procalcitonin testing. We registered our protocol on PROSPERO (CRD 42017060566).

We searched (with no language restrictions) Ovid Medline [1950-2017], Ovid Embase [1947-2017], PubMed [1950-2017], Web of Science [1970-2017], Open Grey [1997-2017] and Cochrane CENTRAL [1997-2017]. Two reviewers double-screened 20,592 titles, 1,445 abstracts and 319 full-text studies. We included 60 studies in our final analyses. The Kappa statistic for inter-rater reliability of inclusion and exclusion decisions was 0.6 (95% CI 0.553 to 0.648), indicating moderate agreement.(214)

Inclusion/exclusion criteria

Eligible participants were adults and children admitted to, and treated within, an acute hospital. The intervention of interest was the change in clinical or antibiotic prescribing outcomes that could plausibly be associated with an introduction ofrapid diagnostic tests into the hospital. The comparator(s)/control was current hospital practice without RDT, defined as use of either a manual or automated culture system (Table 1). The primary clinical outcomes were length of stay and mortality, and the primary antibiotic outcome was duration of antibiotic therapy. We allowed for the collection of any type of mortality outcome but made

provision for separate (30-day and all-cause in-hospital) mortality meta-analyses. Secondary outcomes were reported changes in antibiotic plan, time to treatment and turnaround time. (Table 1) We included both experimental and observational study designs, synthesised separately. Observational studies comprised prospective and retrospective cohort studies, quasi-experimental studies and interrupted time series analyses. Risk of bias was assessed using the Effective Public Health Practice Project (EPHPP) toolkit for quantitative studies.(189)

All statistical analyses were run in Stata 15.1.(198) When medians and interquartile ranges were reported as effect estimates, we transposed these into means and standard deviations using the methods of Luo et al, and then conducted subgroup analyses to validate the methodology.(215) We grouped thoserapid diagnostic tests that were intended to replace either manual or automated culture, thereby reducing analysis time in the laboratory.

The principal summary effect estimates (summary measures) that were calculated were length of stay (mean difference), in-hospital mortality (risk ratio) and 30-day mortality (risk ratio). Random effects meta-analysis was used due to the heterogeneous interventions and settings of each included study.(196,216) Not all studies that were included in the narrative synthesis were included in the meta-analysis (See Table 5). We also conducted a univariate meta-regression of the effect of concurrently adopted antibiotic stewardship programmes on the length of stay effect estimate. Higgins' I^2 was used to assess heterogeneity among outcomes in the meta-analyses.(216) Egger's test was only appropriate to conduct in one case, where there were ten studies in one meta-analysis.(196,217)

(ii) The Sankey diagram*:* As there were many antibiotic stewardship outcomes of interest reported, but few studies reported the same outcomes of interest, we developed a Sankey Diagram to show the outcomes of interest (number of papers included in narrative synthesis), how those studies can be categorised subgroups, and how they contribute to the final analysis. Our Sankey diagram was constructed in a free, open source, online tool called SankeyMATIC (BETA) (sankeymatic.com). The code for this tool is available on Github and builds on the open-source infographic design language D3. The tool allows users to: specific the number of flows in and out between nodes; specify the number of nodes, and checks the diagram to ensure there are no imbalances in the count. Flows can transfer between nodes, as they have done in our Sankey diagram.

Results

There were 58 studies included in the final review. The study selection process is summarised in Figure 5. The included studies are described in Table 5.

Figure 5 PRISMA diagram

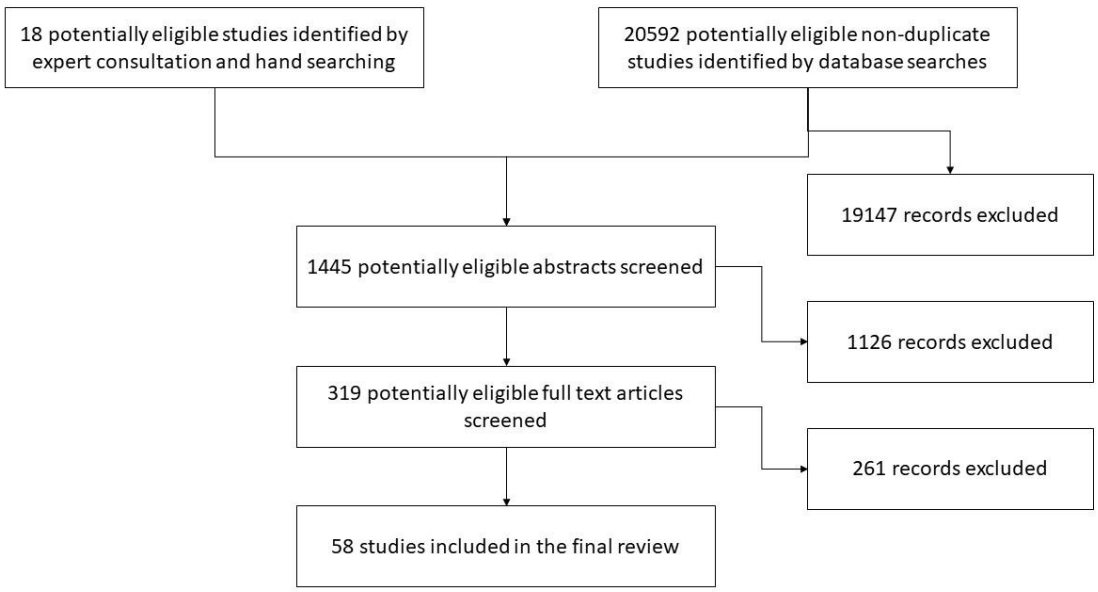


Table 5 Included studies in the narrative systematic review and meta-analysis

Author (year)	Study Design	Test	Comparator	Patients tested usingrapid diagnostic tests	Patients tested using conventional treatment	LOS	Mortality	Reason for exclusion from MA	EPHPP rating (weak/moderate/strong evidence)
Allaouchiche *et al.* (1999) *France* (218)	Randomised Controlled Trial	Multiplex PCR assay	Conventional lab procedures	72	72	✓		Patients in LOS analysis were subdivided by specific genes (oxa-S positive)	moderate
Banerjee *et al.* (2015) *USA (219)*	Three arm-randomised controlled trial	FilmArray Blood Culture ID Panel (rapid multiplex PCR)	Control group: Standard BCB processing	198	207	✓	✓	*NA*	moderate
Bouadma *et al.* (2010) *France (220)*	Multicentre Randomised Controlled trial	Procalcitonin	International and local guidelines for AB treatment	307	314		✓	28-day and 60-day mortality reported	moderate
Cambau *et al.* (2017) *France (221)*	Cluster-randomised crossover trial	LightCycler® SeptiFast	Conventional (standard) work-up	731	685		✓	Patients with "severe sepsis", febrile neutropenia, or suspicion of F11IE; 7-day mortality reported.	moderate
Creamer *et al.* (2010) *Ireland (222)*	Non-randomised clinical trial	Xpert® MRSA assay	direct culture on chromogenic agar plates	349	60			Isolation and turnaround time reported as outcomes	moderate
Cattoir *et al.* (2011) *France (223)*	Controlled trial (non-randomised)	LightCycler® System	Standard phenotypic method	122	128			Favourable and unfavourable outcomes at 12-weeks follow-up reported.	moderate
de Jong *et al.* (2016) *Netherlands (224)*	Randomised Controlled Trial	Procalcitonin-guided antibiotic treatment	Standard of care group	761	785		✓	28-day and 1-year mortality reported.	Moderate
Idelevich *et al.* (2015) *Germany (225)*	Randomised Controlled Trial	LightCycler® SeptiFast Test MGrade assay	VITEK 2	74	76	✓	✓	Febrile neutropoenic patients.	moderate
Jeyaratnam *et al.* (2008) (226)	Randomised unblinded,	BD GeneOhm MRSA Assay	Conventional culture	3553	3335			Isolation days and time to results were the reported outcomes.	moderate

	crossover trial design								
May *et al.* (2015) *USA (227)*	Randomised Controlled Trial	Xpert ® MRSA/MSSA SSTI assay	culture-based testing	126	126			Those prescribed appropriate antibiotics were the clinical outcome.	moderate
Osthoff *et al.* (2017) *Switzerland (228)*	Prospective, non-blinded, controlled clinical trial	MALDI-TOF (Micro flex; Bruker)	Conventional processing	168	200	✓	✓		moderate
Roisin *et al.* (2014) *Belgium (229)*	Cluster-randomised crossover trial	Xpert® MRSA assay	Conventional culture screening	1788	1916			MRSA acquisition and isolation were reported outcomes.	Strong
Shenoy *et al.* (2013) *USA (230)*	Randomised controlled trial	Xpert® MRSA real-time PCR	Local standard of care	259	198			Discontinuation of contact precautions was reported outcome.	Weak
Suzuki *et al.* (2015) *Japan (34)*	Clinical Trial	Verigene system (multiplex molecular)	Conventional testing	298	469		✓		Weak
Wassenberg *et al.* (2010) *Netherlands (231)*	Prospective non-randomised trial with a nested cohort study	BD GeneOhm MRSA PCR Xpert MRSA Chromogenic Agar	Conventional culture	1764	1764			Turnaround time, additional isolation days were secondary outcomes. Cost was a primary outcome.	Moderate
Wassenberg *et al.* (2012) *Netherlands (232)*	Prospective non-randomised trial with a nested cohort study	BD GeneOhm MRSA PCR Xpert® MRSA assay	Conventional culture	89 BD; 74 Xpert	163			Duration of isolation was the primary clinical outcome.	Weak
Wu *et al.* (2017) *United Kingdom (233)*	Cluster-randomized cross-over trial	Xpert® MRSA system	Conventional laboratory-based culture screens	5039	4978			MRSA acquisition number (rate), and MRSA transmission were primary outcomes.	Weak

Birgand *et al.* (2013) *France (234)*	Observational study	Cepheid Xpert® vanA/vanB PCR	Conventional culture method	NA	NA			Two cases only.	Weak
Bruins *et al.* (2017) *Netherlands (31)*	Retrospective cohort study	BACTEC FX®	Conventional BACTEC culture method	241	224	✓	✓	NA	Weak
Callefi *et al.* (2013) *Brazil (235)*	Retrospective cohort study	BD Phoenix®	Conventional culture and susceptibility testing	106	90		✓	Cure rates, 14-day mortality, and 28-day mortality were primary outcome measures	Weak
Conterno *et al.* (2007) *Canada (236)*	Quasi-experimental	IDI-MRSA assay (GeneOhm) PCR	selective broth enrichment culture method	8528	10551			MRSA colonisation, infection, transmission were primary outcomes.	Moderate
Cunningham *et al.* (2007) *United Kingdom (237)*	Quasi-experimental	IDI-MRSA PCR assay,	Traditional culture method	693	612			Acquisition of MRSA and transmission reduction were the outcomes reported.	Moderate
Dureau *et al.* (2017) *France (238)*	Retrospective cohort study	platform Cepheid Xpert® real-time PCR assay	Bacteriological culture	115	121	✓	✓	NA	Weak
Felsenstein *et al.* (2016) *USA (239)*	Quasi-experimental	BC-GP molecular assay	BacT/ALERT automated blood culture system	194	189	✓		NA	Moderate
Flore *et al.* (2010) *Belgium (240)*	Quasi-experimental	BD GeneOhm MRSA real-time PCR system GeneXpert System	Culture-based	85	77			Stewardship outcomes only	Moderate
Forrest *et al.* (2008) *USA (36)*	Quasi-experimental	EFOE PNA FISH	Standard microbiological methods	95	129	✓	✓	NA	Moderate
Frye *et al.* (2012) *USA (241)*	Retrospective interventional cohort study	BD GeneOhm® PCR assay	Standard microbiological methods	68 S aureus; 66 CoNS	58 S aureus; 52 CoNS	✓	✓	Reported outcomes subdivided by positive or negative gram positive cocci.	Moderate
Giancola *et al.* (2016) *USA (242)*	Retrospective cohort study	Xpert® MRSA Assay in GeneXpert Dx System	Respiratory culture	200	n/a			Anti-MRSA therapy commencement is the primary outcome.	Moderate

Hallin *et al.* (2003) *Belgium (243)*	Prospective cohort	PCR	Conventional methods	35	n/a			Anti-MRSA therapy is the primary outcome.	Weak
Hardy *et al.* (2010) *United Kingdom (244)*	Prospective, cluster two-period cross-over	BD Gene-Ohm® PCR assay	Chromogenic media	6459*	7493*	✓		MRSA acquisition/colonisation/length of time on ward were primary clinical outcomes.	Moderate
Huang *et al.* (2013) *USA (245)*	Quasi experimental	MALDI-TOF (Microflex; Bruker)	Conventional culture method	245	256	✓	✓		Moderate
Jog *et al.* (2008) *United Kingdom (246)*	Observational cohort	BD Gene Ohm® MRSA Test	No screening	681	n/a			MRSA acquisition rates are the primary clinical outcome.	Weak
Keshtgar *et al.* (2008) *United Kingdom (247)*	Interrupted time-series	BD GeneOhm® MRSA Test	No screening	20447	n/a			MRSA rates	Weak
MacVane *et al.* (2016) (248)	pre-post quasi experimental (with ctrl)	Biofire® FilmArray BCID	Antimicrobial stewardship Program + cultures	104	115	✓	✓	NA	Weak
MacVane *et al.* (2016) (249)	Quasi-experimental	Biofire® FilmArray BCID	Conventional methods	23	45	✓	✓	Only vancomycin-resistant patients – subgroup too narrow	Weak
Marshall *et al.* (2013) *Australia (250)*	interrupted time-series	IDI-MRSA assay (culture + PCR)	BD culture swabs + chromogenic MRSA media	2196	2183			MRSA acquisition rate.	Moderate
Na *et al.* (2016) *Republic of Korea (249)*	Retrospective cohort	BacT/Alert 3D or BD BACTEC FX ®	Standard culture techniques	570	664			Antibiotic stewardship outcomes.	Moderate
Page *et al.* (2017) *Ireland (251)*	pre-post intervention	Xpert ® MRSA/SA blood assay	Gram stains performed on +ve bottle; results relayed to clinical team	22	35	✓		Subgroup of LOS patients in maternity ward (those who had c-section)	Weak
Perez *et al.* (2013) *USA (252)*	pre-post quasi-experimental	MALDI-TOF MS	Direct notification then BD Phoenix	101	100	✓			Weak

Perez *et al.* (2014) *USA (253)*	pre-post quasi experimental	MALDI-TOF MS	BACTEC FX + conventional microbiology procedures	112	153	✓	✓		Weak
Rajan *et al.* (2007) *Ireland (254)*	Non-randomised (pilot) study	IDI-MRSA assay on the Smart Cycler II	Blood agar, CHROMagar MRSA	65	n/a			Identification of MRSA carriers.	Weak
Rao *et al.* (2016) *USA (255)*	Pre-post quasi-experimental	PBP2a assay	cefoxitin disc test	71**	69**	✓			Moderate
Ruimy *et al.* (2008) *France (49)*	Interrupted time-series	Triplex RT-PCR	Phenotypic species ID and AST methods	410	Na			Change of antibiotic therapy	Weak
Shenoy *et al.* (2016) *USA (256)*	Prospective cohort with no control	Xpert MRSA®	Conventional testing	648	n/a	✓		LOS subgrouped by MRSA positive and negative.	Weak
Smith *et al.* (2017) (257) *USA*	Retrospective, non-controlled	BD Max® and RSA XT	Conventional testing	400	n/a	✓		LOS subgrouped into de-escalated and continued antibiotic therapy.	Weak
Stano *et al.* (2013) *Italy (258)*	Pre-post quasi-experimental	Xpert MRSA®	Culture-based testing	577	431			MRSA infections during ICU stay.	Weak
Stano *et al.* (2012) *Italy (259)*	Cohort design (no control group)	Xpert MRSA®	Pts identified as MRSA-negative by test	376	n/a			MRSA infections during ICU stay	Weak
Terp *et al.* (2014) *USA (260)*	Retrospective review of medical records	Xpert MRSA/SA ® SSTI test	Culture	165	n/a	✓		MRSA clinical outcomes measured.	Moderate
Verroken *et al.* (2016) *Belgium (261)*	Interrupted time-series	MALDI-TOF MS	Subculture MALDI-TOF MS ID on day 1 followed by AST with results available on day 2. Direct AST by Phoenix.	309***	272*** 266***			Antibiotic therapy outcomes	Weak
Walker *et al.* (2016) *USA (262)*	Retrospective pre-post	Verigene BC-GN	Vitek 2 system	97	98	✓	✓		Weak

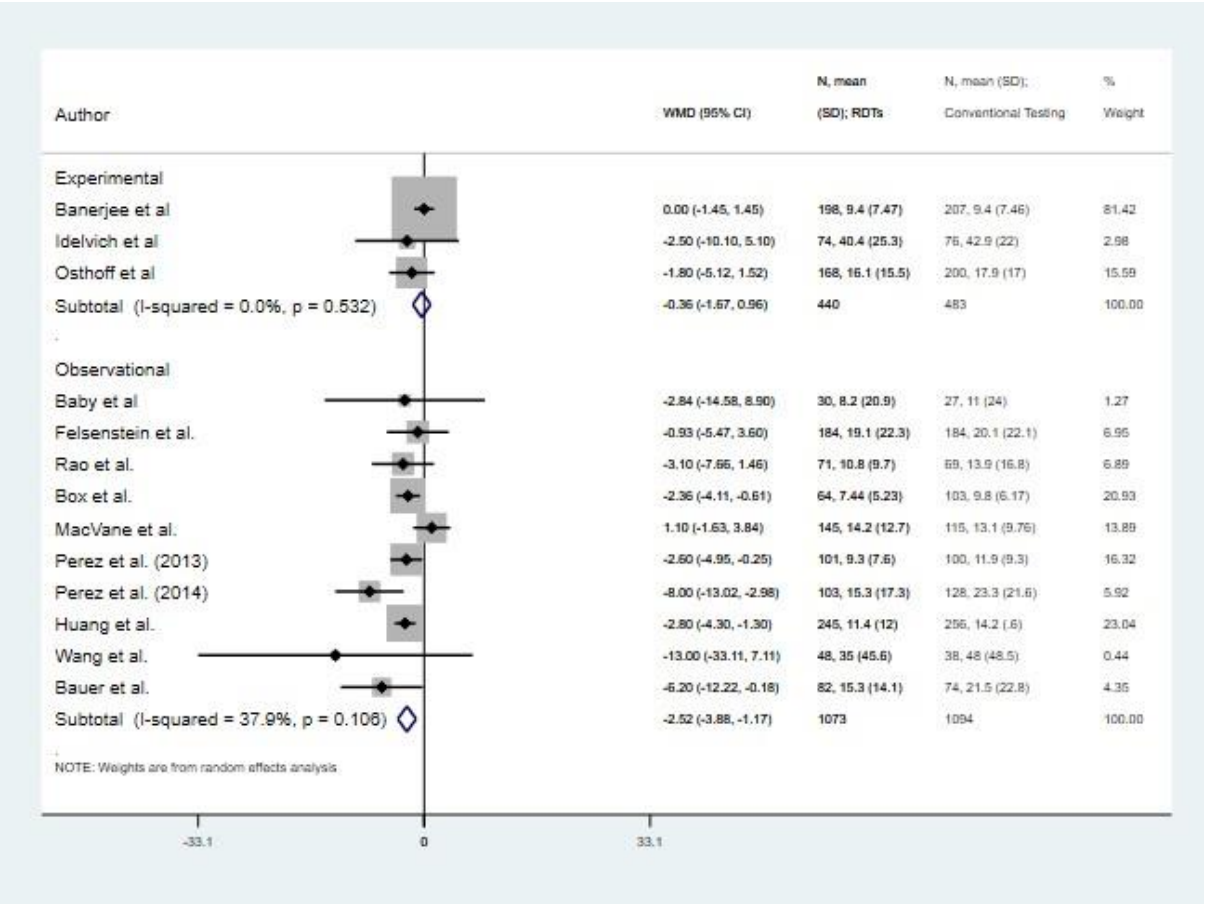
Wang *et al.* (2013) *Canada (263)*	Pre-post quasi-experimental	Direct mecA PCR assay	Testing of bottles batched and the results not reported to physician	48	38	✓	✓		Moderate
Ward *et al.* (2015) *United Kingdom (264)*	Non-randomized with retrospective control	Verigene BC-GN/GP cartridges FilmArray BCID	conventional culture-based laboratory methods	191**	180**			Turnaround time and antibiotic appropriateness.	Weak
Box *et al.* (2015) *USA (265)*	Pre-post quasi-experimental	Verigene BC-GP	Blood culture, Gram Stain, notify nurse, nurse notifies physician	103	64	✓	✓		Moderate
Baby *et al.* (2017) *USA (266)*	Quasi-experimental	Copan ESwab	No PCR	30	27	✓	✓		Weak
Hill *et al.* (2014) (267)	Retrospective cohort study	Verigene Gram-negative blood culture (BC-GN) assay	Conventional methods	54**	n/a			In-patient change to antibiotic therapy is the primary prescribing outcome.	Weak
Harbarth *et al.* (2006) *Switzerland (268)*	Quasi-experimental	qMRSA	Conventional culture	510	322			Time outcomes, though not LOS.	Weak
Jones *et al.* (2014) *USA (269)*	Retrospective data analysis	Nasal MRSA screening	Initial anti-MRSA antibiotics	326282	243533			Surveillance of antibiotic for MRSA (initial and subsequent).	Weak
Seki *et al.* (2015) *Japan (270)*	Retrospective analysis (with no pre-intervention period)	BD GeneOhm MRSA assay	Bacterial culture methods	95	n/a	✓	✓	Length of stay subgrouped by PCR +/- Culture+/-	Weak

*patient ward episodes
**isolates
***patient episodes

Of the 58 included studies, 13 met the criteria for inclusion in meta-analysis for length of stay, eight for meta-analysis of 30-day mortality, and seven for meta-analysis of in-hospital all-cause mortality. There were 30 antibiotic stewardship outcomes reported in 17 studies, but the lack of overlap of reported outcomes among studies made meta-analysis for these co-primary outcomes impossible.

Patients whose tests were undertaken usingrapid diagnostic tests stayed in hospital an average of 0.36 (95% CI -1.67, 0.96, n.s.) days fewer than patients whose samples were processed using conventional methods in experimental studies, and 2.52 fewer days than patients whose samples were processed using conventional methods in the observational studies (95% CI -3.88 to -1.17). This can be seen in Figure 6. We conducted separate meta-analyses for experimental and observational studies. There was no significant heterogeneity among the RCTs (I^2= 0%, p=0.532) and moderate heterogeneity among the observational studies (I^2= 37.9%, p=0.106). (271)

Figure 6 Meta-analysis of studies reporting length of stay



While multi-modal meta-regression of these observational studies would be inappropriate due to the small number of data points, only reaching ten in one group (the observational meta-analysis for length of stay), we conducted univariate meta-regression to explore the contribution of specific organisational factors in the treatment pathway for length of stay. We examined the impact of three binary variables: the presence/absence of other antibiotic stewardship improvements alongside the adoption of therapid diagnostic tests; whether a laboratory was processing samples 24 hours a day or not; and whether the type and duration of test had any bearing on the summary effect estimate. Of these three, the only one that had a statistically significant, unadjusted p-value (p=0.008) was whether there was an antibiotic stewardship programme (ASP) bundled into the introduction of therapid diagnostic tests. As

expected, those which had an ASP attached had a greater reduction in length of stay than those which did not. However, when adjusted for multiple testing, this difference became non-significant.

Figure 7 Meta-analysis of studies reporting 30-day mortality

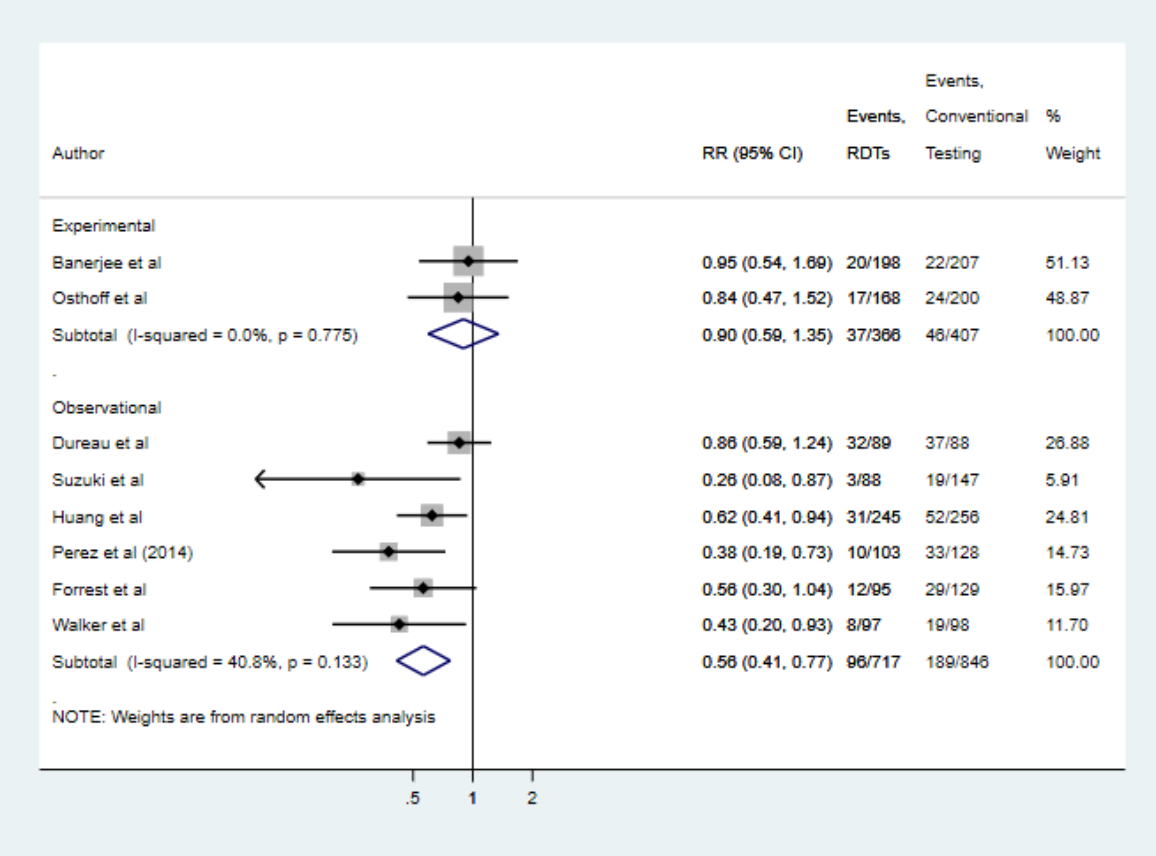
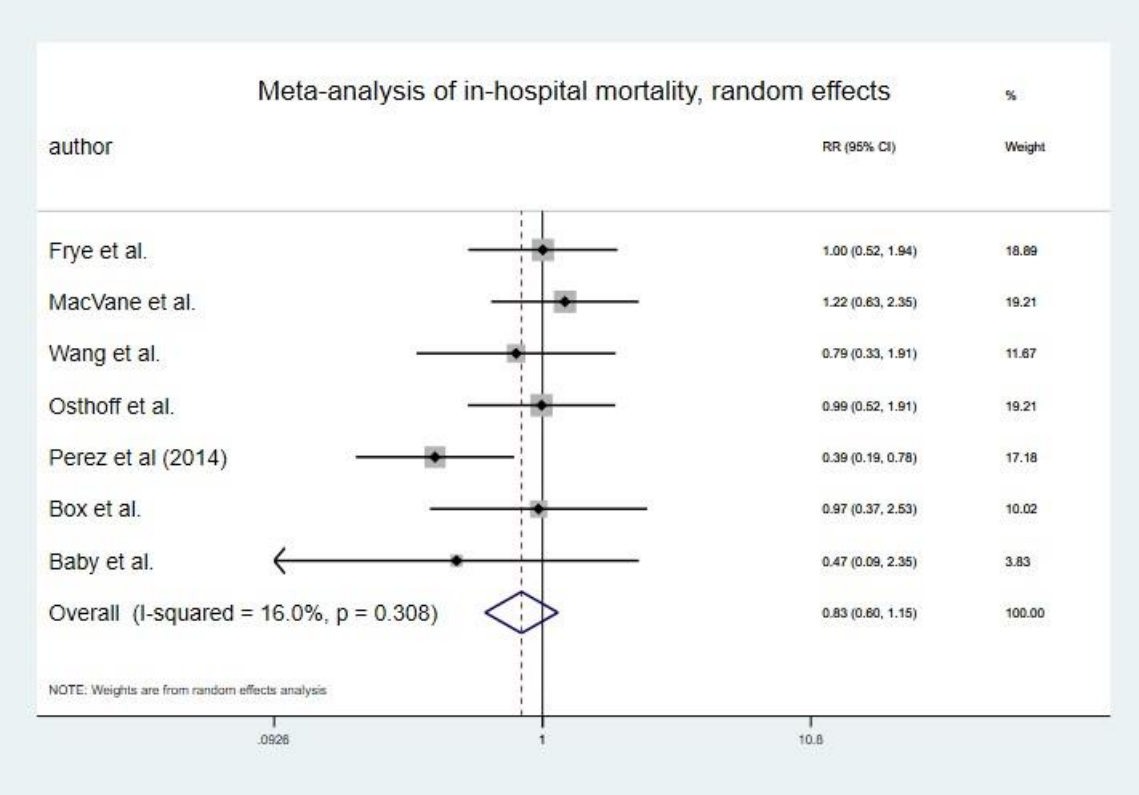


Figure 8 Meta-analysis of studies reporting in-hospital mortality

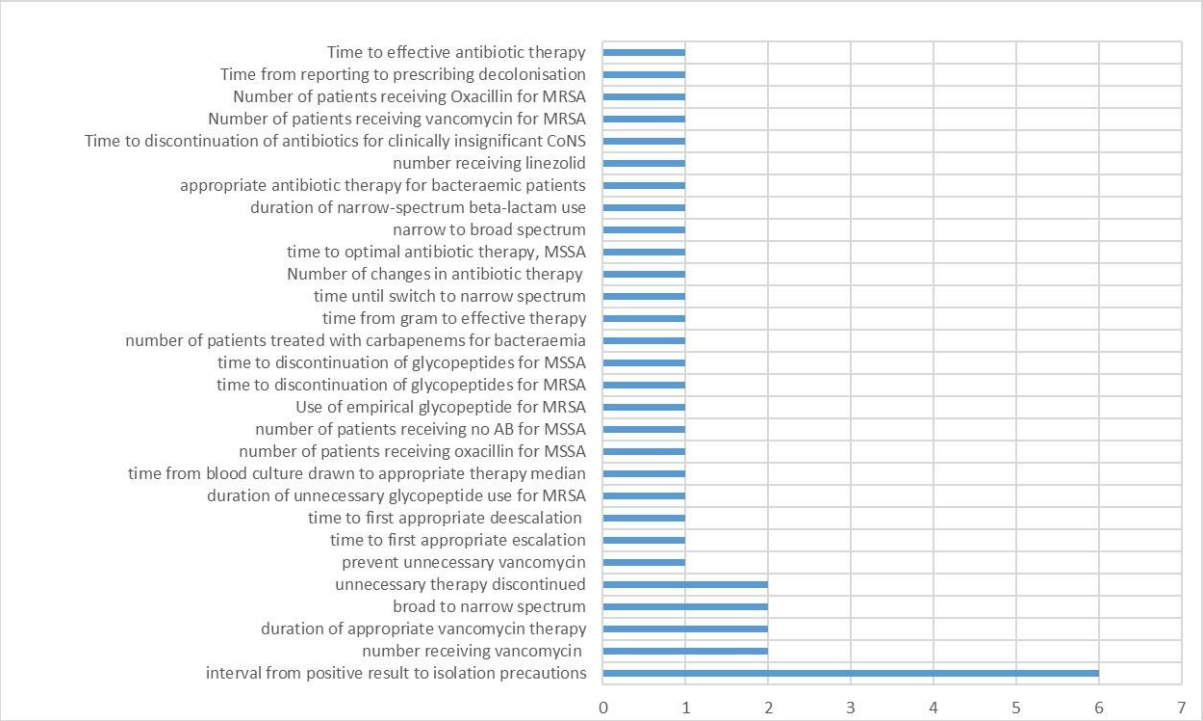


While 18 studies reported mortality measures, only eight reported 30-day mortality (Figure 7) and seven reported all-cause in-hospital mortality (Figure 8). The overall risk ratio for 30-day mortality was 0.90 (95% CI 0.59-1.35) for experimental studies, and 0.59 (95% CI 0.41-0.77) for the observational studies. Among the experimental studies, there was no significant difference in 30-day mortality betweenrapid diagnostic tests and conventional methods. By contrast, there was a strong reduction in mortality in the observational studies, although, as with the length of stay analysis, many observational studies included ASPs in their post-test timeframes, something that the RCTs controlled for by either not having them or by including a third-arm in the trial.

Another seven studies reported in-hospital mortality (Figure 8). Some studies reported both types of mortality estimates and are included in both meta-analyses. Heterogeneity was lower than in the 30-day mortality estimate. The random effects summary estimate of in-hospital

mortality was 0.83 (95% confidence interval 0.60 to 1.15; n.s.). When these seven studies were combined for random effects meta-analysis, heterogeneity was low (X^2=7.14) and the variation in the risk ratio attributable to heterogeneity was also low (I^2=16.0%, p=0.308).

Figure 9 Range of antibiotic stewardship outcomes reported in the included studies



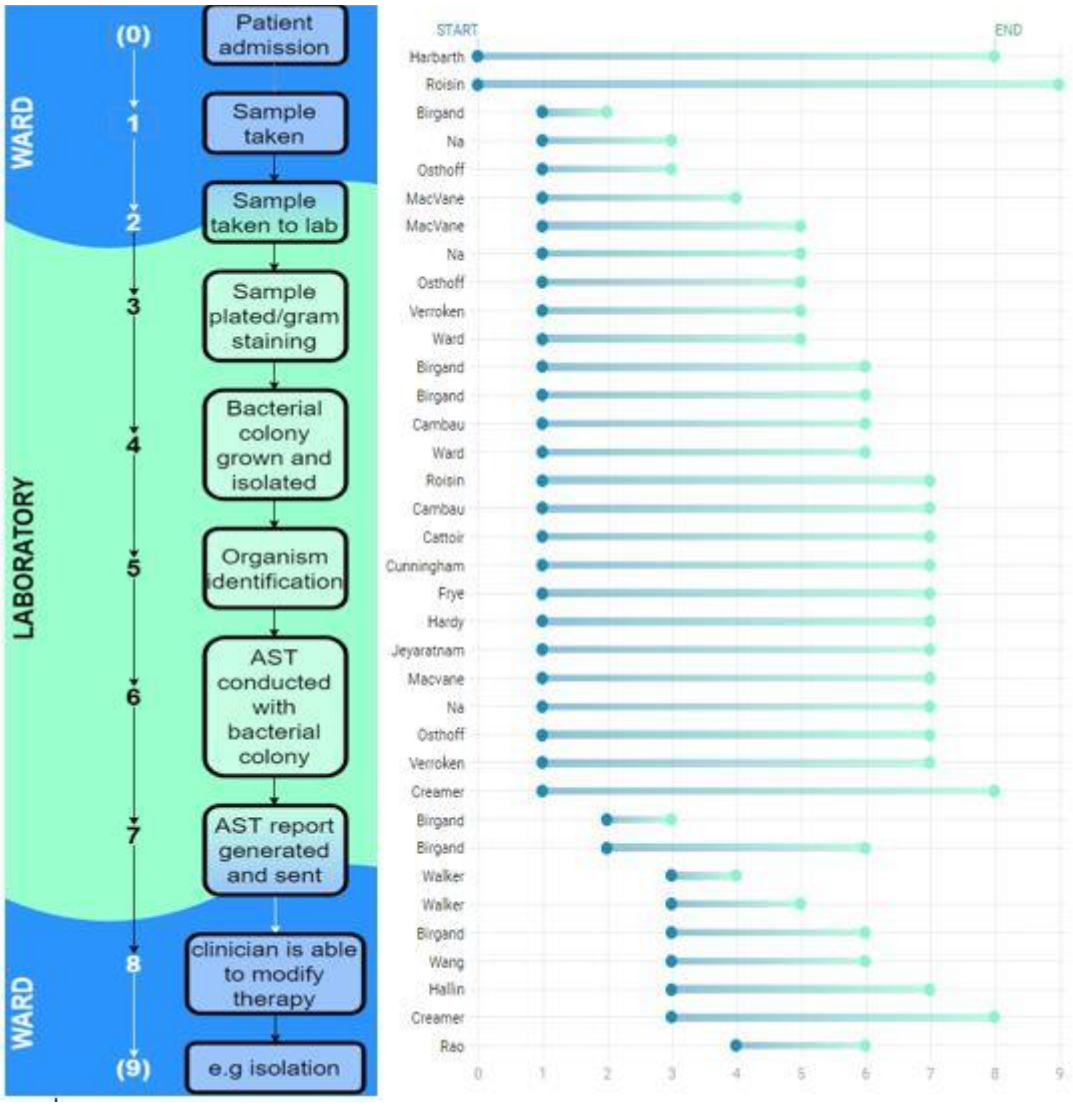
The wide range of antibiotic stewardship outcomes reported in 17 studies is summarised in Figure 9. Many were reported as statistically significant but no meta-analysis was possible due to the high degree of heterogeneity. Publication and other biases were only formally assessed for observational studies describing length of stay, as this was the only subgroup with more than ten studies reporting on the outcome of interest.(217) Egger's test for a small study effect was not statistically significant.

Given the small numbers of included studies, there were few opportunities for subgroup analysis. However, we were able to assess the impact of study characteristics on the length of stay summary effect estimates: study quality (comparing moderate and lower quality studies);

and the impact of the statistical transformation of the reported length of stay from median and range to mean and standard deviation. In neither case did the subgroup effect estimates differ statistically from the aggregate effect estimates.

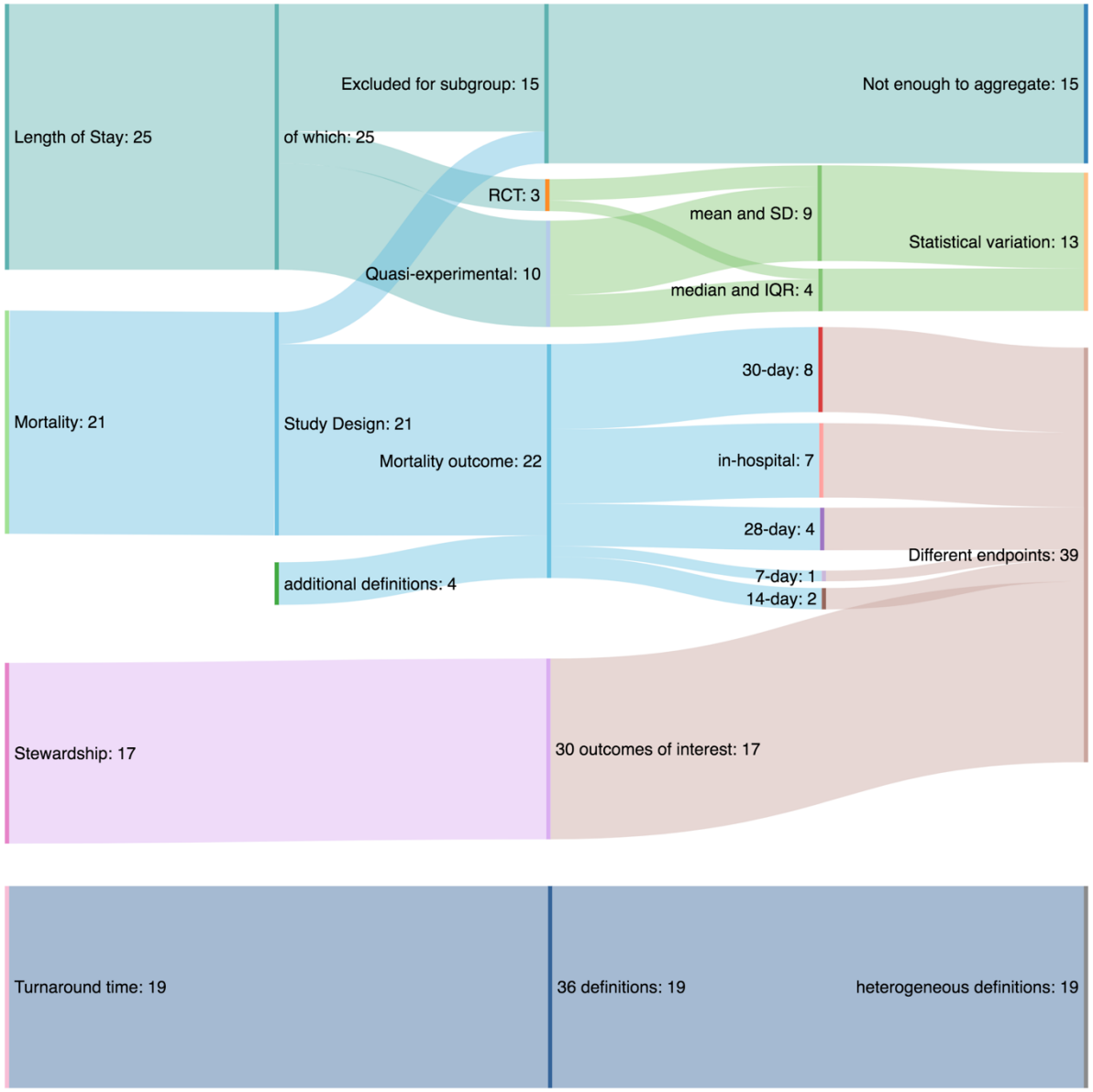
The definitions of ‘turnaround times’, ‘reporting times’ and ‘time to result’, which are the most frequently cited improvements attributed torapid diagnostic tests, overlapped and varied enormously (See Figure 10). While this stylised pathway neither captures the nuances of the entire care pathway, nor indicates that some activities can be undertaken concurrently, we validated it with a consultant clinical microbiologist, who judged it to be an appropriate general description of the key steps in the process. The most commonly reported (11/36) timed pathway segment was from “sample-to-report”. Many studies reported on multiple slices of time in the care pathway, however, only one study reported on patient admission through to isolation (see Figure 10).(229) One further study reported on patient admission through to the clinician’s receipt of an AST (and consequent ability to modify therapy, if appropriate).(268)

Figure 10 Bacteriological care pathway (L) and each paper's definition of turnaround time or time to result, mapped to the bacteriological care pathway in a Q-tip diagram (R)



(ii) The use of the Sankey diagram to synthesis the findings

Figure 11 Sankey Diagram with outcomes of interest (number of papers included in narrative synthesis) and across, how those papers break down into subgroups, and on the right, what happens to them in the final analysis.



The Sankey diagram (Figure 11) helps the reader to interrogate the body of evidence in the review at a glance. For example, we have not meta-analysed antibiotic stewardship outcomes. The reader would know this by reading the entire paper, but the Sankey diagram summarises the point; there are 30 antibiotic stewardship outcomes reported in 17 papers. The diagram also shows that these 30 outcomes were different and could not be combined quantitatively.

Discussion

Overview of diagnostic testing

Appropriate antibiotic therapy is one of the most important aspects of the successful treatment of bacterial infections.rapid diagnostic tests for bacterial identification and antibiotic susceptibility have been developed to try to reduce the time to appropriate antibiotic therapy, shorten length of stay and improve patient outcomes such as mortality. However, our synthesis of the evidence suggests that the introduction ofrapid diagnostic tests for bacterial identification and antibiotic susceptibility testing is unlikely to lead to lower in-hospital mortality or reductions in length of stay. Moreover, while the available observational studies do suggest a significant reduction in 30-day mortality and length of stay, these studies are heterogeneous, have methodological flaws, and these findings should be treated with caution. The meta-regression also shows that neither type nor duration of diagnostic test affects the summary effect estimate, although the number of studies was low and this question should be re-examined in future reviews when more studies become available.

The Sankey diagram revealed that there is still great heterogeneity in the types of mortality data being reported, in spite of the recent emphasis on the need for appropriate endpoints for evaluation of antibiotic therapies (a relevant proximal field to the evaluation ofrapid diagnostic tests for antibiotic susceptibility and resistance) and the pressure towards greater use of core outcomes, in particular 28-day, 30-day, or in-hospital mortality.(205) We suggest that Sankey diagrams can be a valuable aid to transparency in systematic reviews, particularly as a way of showing why studies and study outcomes are excluded from the final synthesis. They can also allow for comparisons to be made between disciplines where there is industry investment in research, and where there is less.

The review itself highlighted major problems in the RDT evidence base. One is that the primary studies are often underpowered. Neither bloodstream infections nor resistant bacterial infections are particularly rare, yet samples sizes are small throughout all included studies. A further problem is the lack of consistency in terminology - it is often unclear which parts of the care pathway are being reported when the term 'turnaround time' is used in primary studies, and frequently there is no explanation as to why a particular part of the pathway has been chosen, and whether it was chosen *a priori*. This lack of standard reporting of these outcomes of interest makes it difficult for service providers and policy makers to use evidence to decide whether to invest inrapid diagnostic tests in general and, in turn, which to purchase. Standardising these definitions would help. For example, 'turnaround time' is most useful to clinical commissioners if defined as the time from patient sampling to results being acted upon by clinicians, as this represents the full care pathway likely to be modified byrapid diagnostic tests. To this end Table 6 proposes some definitions to help standardise and clarify these phrases for future studies.

Table 6 Suggested definitions for diagnostic pathway outcomes in RDT evaluations

Turnaround time	The time from collecting a sample from a patient to a laboratory result being actioned by a clinical decision-maker
Time to result	The time from collecting a sample from a patient to the result being released by the laboratory
Running time	The active time of a technology from sample being inserted/inputted into a technology until when the test is complete and an output has been generated.

Limitations

There are several limitations to this study. First, it proved impossible to synthesise the evidence of the effects ofrapid diagnostic tests on turnaround time or other antibiotic stewardship outcomes because of the lack of standard definitions of reported outcomes across studies. Antibiotic stewardship outcomes represent the main positive impact ofrapid diagnostic tests according to some commentators, but this remains a controversial assertion given the limitations in the evidence. Also, while experimental studies sometimes

incorporated antibiotic stewardship as a discrete third arm in trials so as to disaggregate the effect of the rapid diagnostic test from the effect of the stewardship intervention, many of the pre-post quasi-experimental studies bundled antibiotic stewardship programmes with the addition of a novel diagnostic test. It remains possible that bundling stewardship measures with the diagnostic test may be confounding the impact of the diagnostic intervention. This would reflect previous research in this area.(248,272–276) We suggest that care should be taken in future studies not to attribute an impact to diagnostics where the impact could have come from improved stewardship measures.

Given the small number of studies, this is an important avenue for future research. There is also a need for better measures of in-hospital impact. Some mathematical modelling studies have endorsed intra-hospital infections averted as a useful metric, but the advent of whole genome sequencing could be employed alongsiderapid diagnostic tests to validate attempts to capture this outcome in real-world evaluations. This is another important area for research; if rapid diagnostics are to demonstrate clinical value, it is likely to be on such indirect outcomes.

Conclusion

We recommend that future systematic reviews of similar diagnostic technologies consider adopting a health services research perspective, in line with the current review, which takes account not just of final outcomes (mortality; length of stay) but also intermediate outcomes (appropriate antibiotic therapy). This review shows that neither length nor type of diagnostic technology impacts on the summary clinical effect estimates, likely because of presumptive treatments and the complexity of the care pathway, and such an approach allows a wider range of the available evidence to be synthesised to help understand the clinical and health services effects of new technologies destined for the hospital laboratory. Sankey diagrams can help with showing how this wider range of evidence contributes, or does not contribute,

to a review's conclusions. They may be of particular value in improving the transparency of systematic reviews of complex interventions where the evidence is disparate, multi-endpoint and very often not amenable to meta-analysis.

Transparency Declaration

All authors have submitted an ICMJE COI form. SJP reports personal fees from Specific, and stock options from Next Gen Diagnostics, outside the submitted work. REG, MAH, NM, EE, and MPP have nothing to disclose.

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Ethics approval
All the evidence were published, peer-reviewed journal articles and ethics approval is therefore not required to conduct a systematic review or meta-analysis.

Impact, engagement, and dissemination

In this case, I was given a particularly straightforward feedback mechanism in order to effect policy. As previously discussed, this research was commissioned by the Department of Health in order to feed into the refresh of the UK's five year AMR Strategy. As such, I was tasked with reporting interim findings to DH/DHSC throughout the life course of the review. In parallel, the DHSC was drafting the 2019 – 2024 AMR strategy, and was looking to units like PIRU for some guidance on how they could improve the 2013-18 Strategy.
There were four opportunities to feed emerging evidence into the DHSC planning process
In December 2017, I provided an update for PIRU's interim report to DHSC. In this report, I detailed the analysis plans for the review. This was a one-way update, rather than a conversation.

In March/April 2018, I made specific comments on a DHSC slide pack outlining their plans for the new strategy. At this time, I had undertaken preliminary analysis on my findings, and there seemed provisionally to be little evidence to support the notion that molecular diagnostics would provide the types of clinical gains that were hoped for; as such I urged caution about the emphasis placed on diagnostics in the new report, as they were occupying an increasingly large part of the proposed solution to AMR. I commented multiple times to this effect, and suggested decoupling the recommendation to invest in research and development for newrapid diagnostic tests from the concept of urging faster adoption of currentrapid diagnostic tests.
In June, 2018, I presented my initial meta-analyses at the department of health. These were provisional findings, but, while they have changed somewhat upon further analysis, the interpretation is the same (i.e. the findings that were strongly significant and the results that were demonstrating no effect are still occupying the same statistical space). This presentation was to a room of internal DHSC policy and statistical experts. They were highly engaged in my presentation, and I received some critique of my conclusions, since I had not been able to meta-analyse the antibiotic stewardship outcomes, and they felt that that was likely where the marginal gains forrapid diagnostic tests were. However, on the whole, they were interested and engaged in the message of a cautious, caveated approach to diagnostics roll-out and messaging.

(In September 2018 I did not attend a DHSC briefing where other colleagues from this work were presenting. However, I was informed that the conversation turned to my review, and that they wanted to discuss the systematic review report that I had produced and submitted at the end of August to DHSC. My colleagues reiterated my findings to the group, and in particular, reiterated the messaging that this particular subset ofrapid diagnostic tests are unlikely to improve clinical outcomes when adopted by NHS trusts.)

In November 2018, I spoke to a meeting of senior DHSC, PHE, DEFRA, VMD, and NHS England officials. At this point, the new DHSC AMR strategy had been drafted, and only final changes were being made before the document would be sent to government officials over Christmas. It was interesting to note that the reception to my work at this point was largely positive. The concept of diagnostic stewardship (i.e. the right, evidenced diagnostic, at the right time, in the right part of the care pathway) rather than a pan-diagnostics approach, was agreed upon, and one senior figure said, after a lengthy discussion of my research "I think we're on board with your message. Now can you convince Matt Hancock?"
Here lies the important point; it is impossible to say why this room of senior officials were more receptive to my point than at any other point in the research and feedback process. It is possible that my work impacted their views over the course of the years, but it could very possibly have been a different piece or pieces of evidence. Either way, the messaging regarding diagnostics seemingly changed throughout the policy drafting process from one of 'more diagnostics' to one of 'the right diagnostics'. This concept did, in fact, make an appearance in the new five-year AMR Strategy, where the concept of diagnostic stewardship was introduced and explained. However, I remain highly pessimistic about my messaging having landed with key senior government officials; in January and February 2019, the Minster for Health and Social Care, Matt Hancock, launched NHSX, an agency dedicated to facilitating the adoption of novel tests and technologies – including diagnostics for AMR – into NHS trusts. I continue to attend relevant events, such as the all-party parliamentary groups on AMR (April 29, 2019), in order to communicate my findings.
I also presented my ongoing work to the academic community at the following academic conferences:

PHE September 2018 (oral speed talk)
EUPHA December 2018 (moderated poster walk)

ECCMID March 2019 (five-minute poster pitch)

RESIST April 2019 (10-minute talk)

Chapter 3: Applying Diffusion of Innovation Theory to perceptions of healthcare professionals about rapid diagnostic tests for antimicrobial resistance in the United Kingdom: *who wants tests, who doesn't, and why*

Preface

In the last chapter (Chapter 2), I examined a subset of rapid diagnostic tests (RDTs) in use in hospitals and assessed their clinical effectiveness. I found that somerapid diagnostic tests in hospitals were unlikely to result in clinical gains. In the chapter that follows this one (Chapter 4), I will describe and analyse the discursive agenda-setting occurring at the macro-level, and demonstrate how medical diagnostics and pharmaceutical companies are lobbying the government for increased investment, and a beneficial regulatory environment in AMR. In addition to questioning the evidence base underpinning somerapid diagnostic tests, and the dominant discourse surrounding their adoption, I also, in this chapter (Chapter 3), interrogate the pre-eminent idea that diagnostic tests are in fact wanted, or considered to be helpful, on the front lines of care in the UK.

When I first began planning the qualitative strand of research for the dissertation, I was still operating under the assumption that it would be inherently beneficial for diagnostic technologies to diffuse. I based my interview topic guide on Rogers' Diffusion of Innovation Theory and the characteristics theorised to be crucial in the 'successful' diffusion of any innovation: trialability, observability, relative advantage, compatibility, and complexity.(74) I felt sure that, if I asked doctors, pharmacists, and nurses in secondary care about the role of these diagnostics, I would likely be developing my understanding of the barriers and facilitators of taking up diagnostic tests. There would, I felt, be Clinical Commissioning Groups (CCGs) or equivalents in my case study sites where uptake had been 'successful', or rather, rapid diagnostic tests (RDTs) were being used, and there would be other areas which had been 'unsuccessful', and were not able to use the tests in question. I had intended to determine what those conditions were so I could develop a series of recommendations for NHS Trusts looking to expand the commissioning of diagnostics.

Having begun my semi-structured qualitative interviews with key experts in six case study sites across the UK before finalising my systematic review analyses, I was struck by the fact that many NHS professionals were not as unilaterally pro-diagnostic as I had thought they would be. There were, of course, some champions of the technology, but many were ambivalent, and some (in fact, those who had tried certain technologies already) were well aware of the costs and problems associated with introducing expensive medical technology throughout the clinical care pathways. And ultimately, what I found when I coded my interview data, is that many respondents who were negative about the prospect ofrapid diagnostic tests entering their practice identified one particular reason why they did not want to adopt the technology: they felt it was not fit for purpose.

Of course, my assumptions in this research were imbued with pro-innovation bias; Rogers himself understood in subsequent editions of his grand theory that equating adoption with success was a facile and under-developed view of the role of technology.(74) This is for a simple reason: not all technology makes things better. Trisha Greenhalgh's recent work on the NASSS framework and other critiques of innovation in science and technology studies make this clear.(277,278)

Below, I present an analysis of 71 qualitative interviews undertaken in six UK study sites that I will also be drawing on in the final chapter in this thesis. I employed Rogers' Diffusion of Innovation theory in order to analyse these interviews, undertaken with many different types of professional, including: pharmacists, doctors, nurses, finance managers, senior NHS trust executives, CCG commissioners, and others. I tailored Rogers' theory somewhat following an initial coding session in order to include the provision of the *limitations* of the technologies in question by adding a 'relative disadvantage' code. I interviewed these key informants about their views on the use and implementation of diagnostic tests in their context. In this chapter, I will use Rogers' Diffusion of Innovations as my base because I developed my case study interview questions using it, and I coded my data using it as well. It is a flexible enough grand theory to allow me to discuss the limitations of applying it to my data, and has not been so rigid as to have prevented me from analysing the unexpected, surprising, and contradictory themes that came to the fore in this research. Though not a grand theory, Greenhalgh's NASSS framework would have been very – indeed, perhaps more – appropriate. However, there is a very simple reason why I did not use it. It did not exist when I planned this study.(277,278) Other frameworks and theories also exist that I could

have chosen. If I was particularly interested in translating research into practice, understanding implementation outcomes, or evaluating those outcomes; Nilsen helpfully summarises implementation science theories, models and frameworks available based on research question and study design.(474). Given my research question, which looked to understand current process rather than guide or evaluate practice, it would be appropriate to select a determinant framework, a classic theory, or an implementation theory. I explicitely set out to conduct interdisciplinary research, so it made sense to select a classic theory, one that is widely applied both within and outside the discipline. Still, I could have selected a theory from psychology, such as the Theory of Reasoned Action; or theories frequently used in public health, such as complex systems theory. However, I chose Diffusion of Innovation because it is a) classic, b) widely known, c) used outside the field, and d) explicitely about the relationship beween the innovation and how it is perceived by users. This was the nexus that I was looking to examine, and so Diffusion of Innovation provided me with logical consistency, and the correct empiric level.(475)

I also drew upon a wider set of data than originally planned. I had intended to focus my analysis on secondary care diagnostics only. It was originally intended that another PhD student was going to conduct a secondary analysis on the primary care diagnostic data. However, she never began this work, and so I felt that the inclusion of the primary care data facilitated cross-cutting learnings across care settings. This also means that I was able to draw on views on both a wider range of diagnostics, and a wider group of health care professionals than if I had maintained the narrowness of the diagnostic tests used in bacterial identification and antibiotic susceptibility testing as I had done in the systematic review and meta-analysis in Chapter 2.

The chapter that follows was seminal for me in facilitating the transition away from the lens of ‘what factors are impeding diagnostics uptake’ toward a more critical gaze on the ways in whichrapid diagnostic tests have become more than a technology; they have become the great hope of a crippled health service, arguably funded by a government as, perhaps, a way to avoid interventions involving human and interpersonal complexity in favour of inhuman, private-sector black boxes of technological innovation. Below, I will compare and contrast primary and secondary care settings, examine the characteristics of diagnostic proponents and opponents, and ultimately assert that rapid diagnostic tests are seen by those intended to use

them as at best as a limited but expensive indirect solution to wider health care problems, and at worst, as a facilitator for creeping privatisation and outsourcing of NHS services.

Introduction

With international spotlight on the antimicrobial resistance (AMR) crisis, technologies purported to help with AMR, such asrapid diagnostic tests, have moved beyond the remit of microbiologists, scientists, and infectious disease clinicians into the field of concern of policymakers and social scientists.rapid diagnostic tests were one of the key aims of the 2013-2018 antimicrobial resistance strategy in the United Kingdom, and 'new diagnostics' is third on the list of priorities for the UK's 20-year vision.(13,279) However as demonstrated in the previous chapter, there is only limited, patchy evidence about some diagnostic tests' clinical effectiveness. Recent research has demonstrated that, in the case of AMR, ambivalence about uptake is likely due to insufficient test quality.(280) Nevertheless, national level UK policies are focussed on ways to improve diagnostic uptake, including cash prizes to support innovation, national-level pots of funding that local authorities (LAs) can bid for to run pilot programmes, and medical technology support units to help small-medium enterprises bring their technology to the market.(3) I asked the research question: what are clinicians' and managers' views on the acceptability and feasibility of introducingrapid diagnostic tests for AMR across primary and secondary care, and how do these differ across organisations, and across the UK?

Quantitative research on AMR diagnostic test accuracy, clinical, comparative clinical, and cost-effectiveness – and gap analyses on these - have been undertaken elsewhere.(3,47,135,138,184,281–285) In this study, I investigated the perceptions of diagnostic technologies in the United Kingdom among healthcare professionals and senior NHS managers using qualitative methods. I and four other colleagues undertook 72 qualitative interviews in six case study sites in the four nations of the UK – England, Scotland, Wales, and Northern Ireland – with one interviewee withdrawing consent, and I then analysed all remaining 71 interviews using Rogers' Diffusion of Innovation theory and qualitative thematic content analysis. Please see Appendix: Document 4

The use of a grand theory or theoretical framework can improve the dissemination of research findings into clinical practice.(286) Diffusion of Innovation is a grand theory that has been used to describe the uptake of rapid diagnostic testing and health technologies more broadly.(278,287,288) Facilitating innovation uptake has been viewed as positive in previous research.(74,289–291) This is because the judicious adoption of research on effective innovations for health care contexts is important in any resource-constrained system.(286)

Innovations in diagnostics are thought to combat AMR in the UK National Health Service (NHS) in three ways: (i) supporting decision-making by health-care providers and consequently (ii) improving patient safety and (iii) optimising appropriate antibiotic prescribing, meaning that unnecessary antibiotics are not prescribed.(4,26,208,234,292) This in turn is thought to remove selective pressure on bacteria, thereby reducing the risk that resistance develops, and reducing the need therefore to turn to more expensive and higher risk second-line antibiotics.(293)

I aimed to identify and describe clinicians and managers' views onrapid diagnostic tests relevant for AMR in primary and secondary care usingDiffusion of Innovation. I also sought to catalogue these views across a cross-section of local case study sites that were demographically, organisationally, and geographically diverse in order to present the diversity, or maximum variation, of views on this topic. Examining the attitudes of clinicians and managers allows me to reflect on lessons learned from the 'successful' or 'failed' implementation of innovations across the UK, as well as to critically appraise whether 'success' and 'failure' are adequate lenses for these diagnostics.

Policy context

As explained in Chapter 1 Figure 1, the importance of AMR in the global health policy agenda was initially given impetus by the United Kingdom (UK)'s chief medical officer (CMO) Professor Dame Sally Davies, who issued her first annual report in 2011 on the health burden and future risks of AMR.(12) The UK's Department of Health and Social Care (DHSC, then DH) issued the five-year antimicrobial resistance strategy 2013-2018, which was a wide-ranging strategy with three key aims in seven key areas, where diagnostics were at the top of the list of interventions.(1) In 2014, then UK Prime Minister David Cameron commissioned a review into AMR, in which greater use of rapid diagnostics were promoted as one of the key recommendations.(2) In the UK's five-year strategy 2019-2024, and in the UK's 20 year vision (2019-2039), diagnostics are highlighted as an essential component of the response to AMR.(7,13) Globally, the UK championed AMR at international meetings, and resolutions on AMR appeared at the WHO, the UN General Assembly, and the G20.(14,15,294) The WHO issued guidance to member states on how to develop a national action plan (NAP) for AMR, and by 2019, more than half of all countries (including half of low-middle-income countries) had published one.(295)

With this national and international policy attention on AMR, and in particular onrapid diagnostic tests, a particular narrative has been developing, namely that diagnostic tests are needed tested, and universally understood to be cost-and clinically effective, but were meeting with regulatory and purchasing environments that were not set up for these types of technologies.(5,296) In the more detailed five year 2019-2024 AMR national action plan (NAP) in the UK, five major targets are introduced; two for reducing infections, two for reducing antimicrobial use in humans and animals, and the final target is to 'be able to report on the percentage of prescriptions supported by a diagnostic test or decision support tool by 2024'.(7)

Diagnostic tests for AMR

The term 'rapid diagnostic test' can cover everything from a simple urine dipstick test to a functional Magnetic Resonance image (MRI) test, and everything in between. In this study, we focused on four main types of RDT – bacterial identification and antibiotic susceptibility testing based on polymerase chain reaction (PCR) or matrix-assisted laser desorption ionisation-time of flight-mass spectrometry (MALDI-TOF MS); rapid influenza testing; and C-reactive protein testing for GP practices (Figure 12)

Figure 12 Tests discussed by professionals as 'rapid diagnostic tests' in this chapter, where they sit in the care pathway, and where results are used

Test	**Location**	**Results**
MALDI-TOF MS	Hospital/offsite laboratory	Mainly secondary care
PCR	Hospital/ offsite Laboratory	Mainly secondary care
CRP	GP practice or laboratory	Mainly primary care
Rapid Influenza Testing (RIT)	On-hospital ward or laboratory	Mainly secondary care

These categories were largely defined by the responses our respondents provided to open-ended questions in our topic guide (described below). These categories are of particular relevance to AMR because they are tests that identify specific bacterial infections and

genotypically identify antibiotic resistance (MALDI-TOF and PCR), or distinguish between viral (no antibiotics) and bacterial (antibiotics) infections in hospitals (RITs) or GP practice settings (CRP). In the case of the four types of diagnostics referred to by respondents, my systematic review and meta-analysis described the clinical effectiveness of MALDI-TOF and PCR; Verbackel et al have shown the same lack of clinical impact in a systematic review and meta-analysis on CRP tests. (136). Lee et al have shown the same lack of clinical impact for hospital-based rapid RITs in a systematic review and meta-analysis of clinical utility of rapid influenza diagnostics in ambulatory care.(137)

Typically, PCR and MALDI-TOF MS, and rapid influenza testing (RIT), are conducted in either microbiology laboratories, or in limited cases on hospital wards. PCR and MALDI-TOF can identify the bacteria in a sample, and in some cases can directly identify the presence of antimicrobial resistance genes. RITs are starting to be rolled out in the UK. There are several on the market. Practically, these tests provide a yes/no read-out about whether a patient has Influenza A/B, or respiratory syncytial virus (RSV), which is common in infants and very young children. These tests can therefore often be found on paediatric wards, and can aid in the bed management of patients; directing influenza cases into side bays or isolation rooms, and allowing for the cohort nursing of RSV patients.

Microbiology laboratories conduct diagnostic tests for hospitals, but also for samples taken in the community. CRP tests are routine blood tests in microbiology laboratories for all types of illnesses, and are a non-specific marker of inflammation; when CRP levels spike, this indicates inflammatory processes within the body. They are often used, for example, as an indication of auto-immune diseases. However, when they are situated within GP practices, or shared among GP practice clusters, and when they are used for a patient with an acute respiratory infection, the CRP test for inflammatory markers acts as a decision aid for health care workers treating patients who present with non-specific respiratory tract infections. It helps clinical decision-makers to determine whether the infection is bacterial – and thus may benefit from an antibiotic – or viral – meaning that an antibiotic prescription would be at best useless, and at worst harmful.(297–299) The test measures the volume of CRP, a non-specific inflammatory marker produced in the liver and released into the bloodstream in case of injury or infection that tends to be elevated in bacterial infections but not viral ones.(20,281,300,301)

A note on purchasing. In the UK, diagnostics for hospital laboratories are bought on a lab-by-lab basis, and there is no requirement to standardise the technologies available in different laboratories UK-wide. This means that, on the one hand, tests only require a "CE mark", which is the EU regulation requiring proof of sterility and that the test will not harm a patient) before they can be sold to microbiology/pathology laboratories around the country.(5) rapid diagnostic tests, therefore, could either be not clinically effective but still purchased by a laboratory or, on the other hand, clinically effective but not be adopted by a laboratory because of local budgeting constraints, or an executive board who do not see the benefit of such technologies. Therefore, there is an inherent tension between top-down government decrees and bottom-up decision-making at the local level. Of course, GP practices are free to purchase their own CRP tests as well. But this cost, unless incentivised by local CCGs, or within the context of a pilot or trial, is borne by the surgery, and has consequently met with ambivalence outside those contexts.(281,300,302,303)

Theoretical Framework

To aid my analysis, I *a priori* adopted Rogers' Diffusion of Innovation Theory as our theoretical framework.(74) I adopted this framework in order to inform our analysis of the attitudes of healthcare workers across the UK, in primary and secondary care.

Despite his theory's ubiquity, Rogers was not the first to theorise about the rate of diffusion of innovations. Tarde et al described the rate of technology adoption in 1903 as a sinusoidal curve, Ryan and Gross categorised the types of adopters of novel technology - early adopters, early majority, late majority, and laggards – and Rogers further developed the theory.(74,288,304) He describes five characteristics required for successful diffusion of innovations (Table 7).

Table 7 Attributes associated with rapid diffusion of innovations (74,296)

Characteristic	**Definition**
Relative advantage	Is the innovation perceived to confer advantages or benefits over current versions?

Compatibility	Is the innovation seen as being consistent with past/current practices, values, and needs?
Complexity	Can the innovation be understood and easily implemented?
Trialability	Can the innovation be trialled?
Observability	Can the innovation's impact be seen by others?

Rogers suggests that high (i) relative advantage, (ii) compatibility, (iii) trialability, and (iv) observability, and (v) low complexity, lead to greater uptake of an innovation.(74)
I have used these five broad categories in the development of my topic guide questions, and in the subsequent thematic coding and presentation of these data.

Rogers also categorises the many ways to propel innovations forward. One notable example being used by medical diagnostics companies active inrapid diagnostic tests for AMR can be described using Rogers' hardware versus software "shaver-and-blades" example.(74) In this case, companies separate the hardware (shaver) and the software (blades) of an innovation, and sell the former for little profit – or even a loss – while tying the buyer into purchasing software in the medium-to-long term. For example,rapid diagnostic tests for carbapenem resistance or methicillin-resistant *Staphylococcus aureus* (MRSA) by American medical diagnostics company Cepheid are conducted on machines (shavers) that require the frequent purchase of single-use cartridges (blades).(305)

I also considered that other theories and frameworks might be a more appropriate backdrop to my analysis. Recent research in organisational management has examined how and why health organisations do or do not take up innovations. Ferlie et al turned to a resource-based view (RBV) of health organisations as 'the Firm', with each Firm's unique resource profile and capacity bundled in with a variety of other unique variables that make adoption of one model or practice difficult to emulate in another.(306) RBV's four concepts share some similarities with Rogers' theory. First, RBV's 'core competencies' idea describes internal resources that allow organisations to gain competitive advantage over rivals. In the public healthcare sector, this may be, for example, having a trust that is well-networked in a specialist area due to links with a tertiary care hospital. Second, RBV's 'dynamic capabilities' are the organisational routines central to how and whether restructuring occurs. For example, intense resource constraints or heavy performance management. Third, the

‘absorptive capacity’ describes the extent to which a firm recognises or places value on the importance of an innovation; this is where Rogers’ criteria fit in. There is a body of evidence suggesting that UK public services perform poorly in this metric.(306,307) The final component of RBV is ‘organisational ambidexterity’, or ability of an organisation to adapt to a new environment.

Other research and theoretical work I considered as a backdrop to mine was predicated upon extensions or modifications of Diffusion of Innovation Theory. For example, recent research has demonstrated that homogeneous organisations are more likely to take up innovations than organisations that have many semi-autonomous or autonomous actors. Saenz-Royo adds a sixth category, *social pressure*, to Rogers’ characterisations, explaining that the decision to adopt a novel technology in an organisation occurs in a group, and pressure according to the accepted culture within that group can be exerted.(308) An important corollary to this part of the Saenz-Royo diffusion model is that rigid hierarchy allows for the uptake decision of the higher-ranking individuals to diffuse more effectively. Therefore, executives, if in favour of innovation, are more likely to achieve uptake in a rigid hierarchical organisation with homogeneous and centralised purchasing decisions.(308)

I was cognisant of important critiques of Diffusion of Innovation, including (i) the effect of the size of an organisation on uptake, (ii) the effect of national gatekeepers, and (iii) the lack of regard given to team decision making, such as when multidisciplinary teams across a hierarchy engage in innovation adoption decisions.(309) Moreover, in the context of adopting Diffusion of Innovation as a way to understand barriers and facilitators to change, there is substantial critique of constructs such as ‘barriers’ in the first place.(310) So too is there critique surrounding viewing diffusion as a linear, or even sinusoidal, process though this has been partially addressed in recent literature,(308,311) and also as a theory that does not sufficiently account for implementation context.(312) Saenz-Royo mathematically modelled adoption and non-adoption to demonstrate how Rogers’ work could be adapted to consider the importance of the organizational structures involved.

Greenhalgh et al developed the NASSS framework to understand better the ‘non-adoption and abandonment of technologies by individuals, and the challenges to scale-up, spread and sustainability of such technologies in health and care organizations’.(277) This framework

takes the critical view that technological innovations are not always likely to improve care, nor are they likely to deliver all, or even some, of the promised efficiency gains. The NASSS framework is of particular importance to complex interventions – which the introduction ofrapid diagnostic tests sometimes but not always, can be conceptualised as– and includes seven domains: the condition in question, the technology itself, the value proposition, who the technology is intended for, the organisation(s) and the wider system, and how these first six categories evolve over time (Table 8). These map well onto Rogers' set of criteria, while allowing one to analyse data on individuals *and* organisations using the same framework; Greenhalgh's framework is also tailored to medical settings in that the illness/condition in question is specified as one of the domains.

Table 8 NASSS framework, adapted from Greenhalgh et al, 2017.(180)

Domain	**Description of domain**
Condition	Nature of illness
Technology	Characteristics of technology
Value proposition	Supply-and demand-side value (to developer, and to patient)
Adopters	Who adopts? Staff? Patients? Carers?
Organisation	Ability for organisation to innovate, and the extent of work needed to implement change.
Wider System	Political, professional, and regulatory environment
Embedding and adaptation over time	Scope for adaptation over time, and organisational resilience.

These seven domains are useful for setting out the a priori knowledge aboutrapid diagnostic tests in AMR. Greenhalgh et al emphasise that NASSS is not a theory itself, but draws from several theories in the field, and in particular, complexity and complex adaptive system theory as a 'grand theory' whence the domains originate.(277) The *system* within which the RDT switch is undertaken can readily be said to be complex, under Cohn et al's definition of 'a dynamic and constantly emerging set of processes and objects that not only interact with each other, but come to be defined by those interactions'.(313) Greenhalgh et al point out that

complex systems have many other characteristics that are relevant when describing or analysing the introduction of technology into a heath care setting, including rapid change, human interactions, incomplete data, micropolitics, uncertainties, and so on.(277)

However, one strength underpinning my use of Diffusion of Innovations Theory is quite simply that it is widespread. One 2010 systematic review of knowledge translation frameworks found 33 such frameworks existed, of which eight were directly predicated upon Diffusion of Innovations Theory.(286) Therefore, though there were other frameworks (many of which I was not aware when I chose my framework), such as the Consolidated Framework for Implementation Research, Diffusion of Innovation was widely known and consequently might be within touch for interdisciplinary researchers like me.(476)

Cognisant of its limitations, then, I set out not simply to organise and code my findings, but also to determine how far I could take Diffusion of Innovation Theory when describing individual actors' perceptions about innovations within a large, heterogeneous organisation with commissioning devolved to local-level organisations and groups. I aimed to analyse the important components of Rogers' theory in light of my findings, and the drawbacks in the contexts of organisational complexity, competing priorities, and competing discourses. Overall, I describe what this all means for the uptake of rapid diagnostic tests for AMR in disparate NHS settings.

Methods

Five researchers (of whom I was one) in the Policy Innovation Research Unit conducted 71 interviews in six local case study sites between 2017 and 2018. These interviews were undertaken with many types of professional, including: pharmacists, doctors, nurses, finance managers, senior NHS trust executives, CCG commissioners, and others. Key informants were interviewed using a topic guide that was co-constructed by four of the five researchers. The questions on diagnostics in primary or secondary care were included in this topic guide, which also covered: the UK's five-year antimicrobial resistance strategy; topics on patient care; logistics of bed management; resourcing; electronic prescribing; recruitment and retention of specialists and staffing more broadly; guidance on antimicrobial therapies; quality premiums or equivalents; and audit and monitoring.

Benefits of the case studies methodologies

This work built on data from the whole set of the six local-level study areas. Study areas were set at the CCG-level (or equivalent in Wales, Scotland, and Northern Ireland) because clinical, commissioning, and prescribing guidance are set at the local level. In the case of tests for AMR and antibiotic sensitivity, as previously mentioned, these are bought on a lab-by-lab or practice-by-practice basis, with no legal recommendation or requirement to standardise the technologies available in different laboratories UK-wide. Second, setting the study area at the local level, and selecting areas that are highly distinct from one another, should provide qualitative data on why certain sites take uprapid diagnostic tests and others do not, allowing for a better characterisation of the Diffusion of Innovations in this context.(314–316)

Semi-structured topic guide

The topic guide questions and prompts on primary and secondary-care diagnostic tests can be found below. The topic guide was designed to be semi-structured, and the prompts (written as sub-questions) were normally only asked if clarification was requested by the interviewee, or if the interviewee did not cover a topic in their response.

Use of diagnostic tools in hospitals

- Can you describe any diagnostic tools that are used in the hospital?
    - Some common tests include the tests for MRSA, TB, or gram-negative bacterial infections.
    - Can you describe how those tests are used in the hospital?
    - Can you describe any difficulties with using those tests?
- Have you been involved in developing a business case for tests like these?
    - What happened, decision, feedback?
    - If there was a test for resistance available and you felt it represented value for money, do you think your organisation would purchase it?

Use of diagnostic tools in primary care

- Can you describe any diagnostics / point-of-care tests that are used with the aim of reducing antibiotic prescribing in primary care (or identifying specific pathogens), e.g. CRP tests?
    - How long have you used [test]? Why did you start to use this test?
    - Has [test] had an impact on prescribing? In what way has there been an impact? How do you know?
    - How do you/your colleagues/patients feel about [the test]? Do you/they like/dislike it? Why/why not?
    - Are there any issues with using the test? E.g. difficult to use, expensive, etc
    - Have there been any unintended positive benefits/negative consequences of [the test] that you didn't predict?

Sampling

The sampling frame included hospital doctors, primary care doctors, nurse prescribers, finance managers, pharmacists, and commissioners in six case study CCGs or equivalent across the UK. The characteristics of these case study sites are described in Table 9:

Table 9 Case study sites and description of their characteristics in 2016/2017, taken from Eastmure et al.(317)

Local sites	Popn	Antibiotic prescribing*	HCAI rates*	Acute care	GP practices	Animal case study	Ethnicities	Density
West Norfolk	170,270	High	High for *C. diff* Low for MRSA	Queen Elizabeth Hospital	21	Pigs Poultry	7.5% BAME population	Semi-rural
Western Health and Social Care Trust (Derry – Londonderry)	Approx. 300,000[12]	Not publicly available	High for *C. diff* Low for MRSA[13]	Altnagelvin Area Hospital; South West Acute Hospital; Tyrone County Hospital	50[14]		1% BAME population, predominantly White (including Irish traveller)[15]	Mixed
Betsi Cadwaladr	700,000	High**	High**	Glan Clwyd Wrexham Maelor Ysbyty Gwynedd	108		1% BAME population	Rural
Camden	200,000	Low/ Medium	High	Royal Free UCLH Whittington	35	Small animal hospital	19.1% White, other 16.1%Asian 8.2% BME 5.5% Multiple	Urban
NHS Greater Glasgow & Clyde	1.2 million	High***	Medium	QEUH RAH RH for Children Vale of Leven DH	244		7.5% BAME population	Urban
Blackburn with Darwen	147,489	High	Medium	Royal Blackburn	27		12.1% Pakistani 14.8% Born outside UK	Mixed

* Unless otherwise specified, data taken from PHE Fingertips.
** Data taken from 2015 Annual Welsh Report.
*** Data from SAPG 2016 AMR Report.

These six sites were selected based on three main criteria: indicators; recommendations from the policy clients; and recommendations from external government and academic advisors. These case study site decisions were also made as a team (within PIRU) and whilst I was involved in every meeting and the two sites I ultimately recommended (Blackburn with Darwen and Betsi Cadwaladr) were selected, I was not wholly responsible for case study site selection as it was a team effort.

First, with respect to indicators, we selected those indicators covering the maximum variation of variables that may plausibly affect uptake of technology and AMR rates: urban/rural, affluent/deprived, multicultural/white, high/low HCAI rates, and high/low rates of antibiotic prescribing have all been posited in the literature to influence the emergence, transmission, and burden of AMR.(318–321) To that end, selection of unique sites in diverse contexts provided greater opportunities for learning. (315,316,322–324)All sites were approached and consented. Ethical approval was received (See Appendix: Document 8) A note on maximum

variation sampling of sites; while I have summarised Camden as low/medium prescribing – and the only site that reports low prescribing, in fact many GP practices in Camden were at the time the study was designed reporting very low prescribing rates indeed. UCLH had, on paper, moderate levels of prescribing, but adjusting for the fact that it was a tertiary care centre of excellence (so adjusting for patient mix), and also adjusting for the fact that UCLH's data was most the most complete, with robust antibiotic stewardship processes in place that were being evaluated – with publicly available data being scraped from an electronic prescribing system - we considered that this site was both highly engaged in antimicrobial stewardship, and also likely reporting slightly more complete data than elsewhere.

PIRU was also directed by our policy client that one case study site had to be placed in Scotland, Wales, and Northern Ireland. I also sought advice from national-level Welsh government officials, with two days of informative high-level meetings in Cardiff, before selecting Betsi Cadwaladr on their advice. In Northern Ireland, there discussions with PIRU's policy client about the impact that Brexit would likely have on the Northern Irish border, with issues such as access to medicines likely to come to the fore. Moreover, knowing that the border was porous, with some people registered at Northern Irish GP practices but living across the border (and vice versa), and the importance of local antibiotic prescribing heterogeneity, it was a unique opportunity, so in discussions with the team, we chose a site on the border with Ireland.

With respect to additional colleagues' input, NHS Greater Glasgow and Clyde was selected because it is unique in that the boundaries extended to include several aquaculture farms. Our Royal Veterinary College colleagues were, correctly, concerned about the One Health components of AMR, and sought to incorporate some aspect of animal health in each case study site. Likewise, West Norfolk was both a high prescriber – with a hospital that had recently been in special measures, and so interesting from an organisational perspective – and also an area known for the rearing of both pigs and poultry, and important consumers of antibiotics in the food chain.

Analysis

Data were coded using thematic content analysis guided by an inductive approach to the analysis. Interviews were transcribed, and these data were inputted into NVivo 11.(325) The

interviews were then coded and analysed. One researcher was assigned to each case study; I was the only researcher responsible for coding two sites. I then read and recoded all 71 interviews using theDiffusion of Innovation lens. This qualitative research allowed for an iterative and reflexive approach to coding. Close attention was paid to deviant cases (45, 47).[1]

Results

Seventy-two interviews were undertaken, with one interviewee withdrawing consent. Seventy-one interviews across six case study sites were coded in NVivo 11.(325) These interviews usually lasted between 30 and 60 minutes, and were primarily face-to-face, though a minority were conducted as telephone calls. The interviewees included different grades of prescribers (consultants, junior doctors, nurses, pharmacists), managers, and service commissioners.

Types of technology

The semi-structured nature of the topic guide meant that the first part of our interviews on diagnostics were spent determining what the respondent was referring to when they were discussing diagnostic tests. Different professionals are wont to describe certain tests as rapid; or are thinking of certain diagnostics above others when they describe their affinity or lack thereof forrapid diagnostic tests. Therefore, to introduce the topic, as described in the methods section above, we asked participants to describe whatrapid diagnostic tests they knew about, and whatrapid diagnostic tests they used in their clinical practice. They most often described tests that can distinguish between bacterial and viral tests, and were somewhat less concerned about antibiotic susceptibility testing, or rapid bacterial identification tests. In primary care, this means CRP testing, and in secondary care, RITs. When not prompted, these were the two types of tests that were described most frequently across the case sites. Other diagnostic tests mentioned (mostly by microbiologists) included a MALDI-TOF MS; and real-time, quantitative PCR tests for specific pathogens such as carbapenemase-producing *Enterobacteriaceae,* wild-type and resistant tuberculosis, and methicillin-resistant staphylococcus aureus (MRSA). The commonality between these PCR

[1] Primary data collection was a group effort, however, I conducted all the interviews in Blackburn with Darwen and Betsi Cadwaladr Local Health Board. I also conducted four interviews in the Camden CCG. Overall, I conducted 30 out of the 71 interviews. This chapter is based on analysis of all 71 interviews, based on the subset of questions on diagnostics that I designed and embedded into the topic guide.

tests is they tend to sit within the laboratory, though some trials place them on the hospital ward at the nurses' station.

Relative advantage

The richest and deepest coding across all six sites, in primary and secondary care, occurred in 'relative advantage', an original category in Rogers'Diffusion of Innovation work that describes one of the five key conditions required for successful innovation.

Across both care settings, speed of diagnosis was referenced the most as a likely advantage compared to current practice. Speed, however, is only beneficial as a proxy for other actions that can be taken as a consequence of returning a faster diagnosis. In hospitals, that action was predominantly bed management, and rarely to do with the treatment of an individual patient. A consultant in Greater Glasgow and Clyde explained that the RITs would facilitate cohort nursing in over-stretched services:

I've been involved in some of the stuff around flu. From a Public Health perspective, we're involved because of the need to manage the level of increase in service need [and] testing was part of those discussions. So, this meant a higher flu season than recent years, although not horrendously. We were very much having minus bed capacity and point of care testing was important because we made a decision to start cohorting our flu patients, rather than isolating them. So, the rapid point of care testing meant that we could quickly decide whether someone could be cohorted or not.

A nurse in Blackburn with Darwen also described the benefits of RITs. The nurse explained:

I think the confidence in getting the clinicians the result speeds up the process of discharge. So, I think a lot of our patients went home quicker because we knew, all right, you've got COPD, all right, you've got asthma, but actually what's flared it up is flu. You're going to feel rough for a while, here's your rescue pack, on you go.

In this particular hospital pilot of the RIT, though, there were supply shortages. The nurse later explained that, if they had been relying on the RIT as a part of their normal laboratory services, they would have had serious problems, but despite this, the trust was planning on

integrating the diagnostic test for the following influenza season if supply challenges were worked out with the provider.

In primary care, some professionals would describe the hoped-for relative advantages of CRP testing, without even having access to them. Theoretically, this makes sense; for diffusion to occur, the relative advantage(s) of a technology must be understood even before uptake. One GP in Western Health and Social Care Trust explained that they had hoped to have access to a CRP kit because:

…it would help you limit the amount of deferred scripts you give. It would help eliminate uncertainty, and it might stop you from handing out prescriptions.

Crucially, though, professionals who did not use rapid diagnostic tests at all were most positive about them. A nurse practitioner working in a GP practice in Camden, when asked aboutrapid diagnostic tests, was very positive indeed:

Interviewer: have you ever heard of a practice that's used rapid diagnostic tests […]
Respondent: No, that would be brilliant. That would be brilliant, yeah.
Interviewer: Would you like it do you think?
Respondent: Yeah, yeah, yeah, absolutely.
Interviewer: Okay. The ones that I'm thinking about -
Respondent: It would be brilliant.
Interviewer: - are the CRP tests, the ones that tell you sort of ranges -
Respondent: Yeah, and I think we were a pilot I think for … or did a study, you know, our practice is involved in research and things like that so there was … there were some but it's not a recognised thing. I think those kind of near point testing I think they're brilliant as well in terms of that patient education of saying look … and there's always that worry you know that the kind of clinical presentation doesn't match up, you know, the Strep A or something, and -
Interviewer: Yeah, the regular presentations.
Respondent: Yeah, yeah, those kind of things. It's always a … it's such a difficult one even for, you know, experienced GPs sometimes to call, and then there's always that underlying 'what if'.

In this interview, where the nurse thrice used the word ‘brilliant’ to describe their impression of the perceived advantages of the test, the interviewee identified the advantage as sitting squarely within two main areas: patient education and managing uncertainty for physicians.

Perceived consequences

Over time, a counter-code of ‘perceived consequences’ was iteratively added to the coding frame in order to counteract the pro-innovation bias in the original theory. Interviews were recoded again to included this theme. In actual practice, there was a substantial degree of overlap when coding ‘relative advantage’ and ‘perceived consequences’, since many respondents expressed a positive sentiment aboutrapid diagnostic tests, and then caveated it.

A GP in Blackburn with Darwen succinctly explained the conflict that they felt about CRP tests:

Interviewer: How do you feel about [CRP tests]?
Respondent: Mixed.
Interviewer: Okay, tell me about that.
Respondent: Okay, well it would be nice in a way to have the tests because it might help us to be reassured that we're not missing anything serious, but my worry would be that if we had it people would find out about it and then they'd think, oh well I'll just go and see this doctor and have the test and then I'll know it’s nothing serious.

When rapid antibiotic susceptibility testing was described, the reaction was were also quite muted. One consultant microbiologist in Western Health and Social Care Trust said of ASTs:

The solution is fundamentally in the doctors’ minds. It’s not in the lab, because if you look at the number of patients in that building that may be on antibiotics today, and how many, or what proportion of them are on laboratory guided confirmed results, and it seems quite small. So, a lot of antibiotic use is empiric, and that’s where your overconsumption is. So, we somehow need to get our doctors thinking better empirically, and the lab will not have any data to produce that will make that any better.

So, the proportion that technology or the lab can contribute is the honing of the treatment of difficult bugs with the right drug, but the general consumption of antibiotics is for people that are marginally unwell[…]

In fact, the ambivalence tended toward negativity in those who had experience of adoption of these tests. In the Camden case study, a rapid MRSA test had been adopted, but following a trial, the Trust decided to revert back to culture plates. A consultant explains:

Respondent: MRSA screening in this Trust we used to do a PCR test which was a two-hour test. Actually if you were at Queens Square it would take you at least a day to get that PCR test to the laboratory and it would probably be two days from the day you're taking it that you get a result. So you advertise it as a two-hour test which was £32 but actually two days later you got the result. And as it was usually in outpatients it was pretty much a waste of time. So switching over to agar-based test which took 48 hours was absolutely no change whatsoever. So in fact we ended up, because the clinicians and the microbiologists couldn't decide what to do, […] ended up leading on the project to switch over -

Interviewer: So you went back to culture?

Respondent: Yes. We went back to culture, saved £1 million. Actually I don't think anybody noticed to be honest because at the same time because we'd introduced this risk assessment bit at the beginning so that we knew which patients were likely to be at risk. So already we were proactively assessing them to see if they needed antibiotics. We'd already made some changes in some of the areas.

This quotation demonstrates the importance of considering the lens of non-adoption as a possible 'success'; in this case the Trust in our Camden case study felt that the time gains advertised byrapid diagnostic tests were spurious when rolled out to usual care. This is not unique. The time gains can fall away when diagnostics are integrated into a larger care pathway. Sometimes this is due to the fact that, for the value proposition of tests to be met, they need to be purchased by centralised 'hub' laboratory services operating a 'hub-and-spoke' model, and serving multiple hospitals in order to reduce the cost-per-test. In the example at this Trust, laboratory centralisation is both the requirement forrapid diagnostic tests to be adopted and, paradoxically, the reason that tests did not deliver promised gains to patients. This emerged as one of the strongest inductive themes from the data, and will be discussed later in this chapter.

Camden was the site that identified the widest range of perceived consequences of implementingrapid diagnostic tests. These were identified in both primary and secondary care, and throughout the different professions that were interviewed. Camden was also the site with the most experience of adopting the wide range ofrapid diagnostic tests in question.

A nurse in the Camden site described their experience with the RITs:

So actually, what happened in the flu season was we could do this test in I think it took us 25 minutes but actually … because we couldn't get a porter because the porters couldn't just take one specimen down, so a nurse had to leave the ward, get in a lift which might take you 20 minutes to do that journey, and take it to the hot lab. Which if you think about how cost-effective that is, it's completely nuts. So in the end the infection control team would be saying, you need to do a rapid test, I'll come and do it, because the nurse is too busy to take the test, […] then [they] would go and do the test, take the test, put it in the thing, sample it up, take it down to the hot lab, get the result back, take it back. And so it was the system, although we are totally pro near patient testing, it's actually how do you implement this? The system has to support it. It sounds great but it's not that simple.

Here, the nurse describes how disruptive a rapid diagnostic can be to the work, order, and structure of a shift. This seemingly straightforward test required many groups of professionals to change – and in many cases, augment – their work habits, and in a way that disrupted the health system.

Compatibility

Rogers' definition of compatibility included the degree to which an innovation could be slotted into a pre-existing process of work, but also went beyond that to include the concepts of an innovation being compatible with the pre-existing *values, needs, and ideologies* of work and workers within an organisation. The example where I heard most interviewees discuss compatibility with values, needs, and ideologies, was in the overlap between diagnostics and centralisation and privatisation of laboratory services. In short, due to the high cost of diagnostics, these costs were seen by management as most easily borne by centralised laboratories. Of course, centralisation is distinct from privatisation, and does not *require*

privatisation at any stage of the process. However, the top-down policy push since 2006 from DHSC, formerly DH, has been to centralise *and* privatise laboratory services into super-labs, wherever possible.(326,327)

Centralisation

Centralisation is a theme that emerged from the larger code of compatibility with respect to the pattern and provision of novelrapid diagnostic tests within the current modalities of work. A major theme to emerge from many interviews with staff in Blackburn with Darwen related to the centralisation of laboratory services. When I conducted interviews there, they were in the middle of a consultation process expected to centralise laboratories across a geographically large area. There was seemingly top-down pressure to conduct this centralisation, and interviewees felt this plan was inappropriate for several reasons: first, the lack of local desire for the reorganisation; second, concerns surrounding patient safety; and finally, the time required to feed into the STP consultation process by already-overstretched staff in the context of a service that had been unable to fill vacant positions within the microbiology and infectious disease services for several years. A number of informants expressed reluctance about entering into the suggested STP, which was set to cover the area between Morecombe Bay, Blackpool, Preston, and Blackburn.[2] A microbiologist said "it's a

[2] Following these qualitative interviews, details of the proposed STP have been published, and the four councils in Lancashire and South Cumbria have agreed to centralise their laboratory services (Blackburn with Darwen, Blackpool, Lancashire, and Cumbria Councils), though plans to locate the laboratory in Lancaster in 2019 were rejected following public outcry and professional concern that the laboratory was too far away from rural and remote patients. The following message was included in their (quorate) public meeting minutes from that day: "As a largely non patient facing service patients will not notice any difference but will have a better quality experience (in terms of reduction in duplication of testing meaning having blood taken only once and turn round times of some tests)." However, though COVID-19 had delayed the process, there are some indications that the crisis is being used to facilitate a command and control decision to restart the laboratory merging process. Unite, the labour union, put out a statement to this effect in May 2020. "Unite finds it totally unacceptable that during the Covid 19 crisis you have seized upon this opportunity to force through merger plans and exclude the participation of Unite, the main representative of laboratory workers for this project. Unite calls upon this project to cease until the Covid-19 crisis has ended. I can say that apart from the despicable manner the trusts have chosen to progress this matter, be aware that when it is appropriate Unite, if necessary, will move to immediately ballot its members for industrial action."(328) As of late October 2020, Leyland was put forward as the new site candidate,

couple of hours maybe to the place that they're suggesting […] we're quite big on our own, you see. But there is a huge push from above. Nobody *cannot* be interested in […] the project. […] The idea of it's all the last decade's idea, having a big set-up."

Centralisation also called into question the role of therapid diagnostic tests themselves. A microbiologist said of the centralisation that 'there have to be access to rapid diagnostic tests onsite for at least a core amount of – because particularly the ones where perhaps it affects ED, or where you might be able to get the patient out the door rather than being admitted, then the idea that you'd send it down the road for an hour and eventually get the result back…'.
A senior manager agreed with the microbiologist's reluctance to centralise, saying 'Within the trust, I think there is a reticence to go along that centralisation plan'.
Another senior manager was more direct in their assessment of the centralisation plans, saying 'It is the worst idea'. They continued, comparing current practice to the proposed plans: 'My local lab downstairs, you know, five minutes' walk away isn't near enough […] What the hell are we doing trying to move it up the motorway?' When asked who was pushing the plan onto senior managers, a senior manager said 'well, the Department of Health are pushing it, for a start […]'. And when asked what national level initiatives would help them most with their job, the same senior manager said 'not to do it', referring to the laboratory centralisation.

Only one senior manager – the only one that was not clinically trained - felt that the STP was a step forward, due largely to the money that the Department of Health had earmarked for the centralisation process. Again, rapid diagnostics came up, and this senior manager felt that 'the role of point of care testing is to allow and support greater centralisation of services'. This position which is ostensibly completely flipped – appearing at first glance to be a problem of reverse causality – in fact outlines the ways that perverse incentives can emerge from and be linked to - the push forrapid diagnostic tests across the UK.

with the expected cost of the merged laboratories to be £31 million, and Unite again critiquing the site again, asserting that it was 'equally inconvenient for everybody'.(329)

In the Camden case study, a consultant microbiologist described the state of the evidence as they understood it:

Consultant: And there's a huge report […] which basically said that the MALDI-TOF didn't make any difference.
Interviewer: Yeah.
Consultant: Because of the delays in the system.
Interviewer: Because of the mega lab, the transfer?
Consultant: The mega lab, yeah. Well, it's the mega lab and then when the RAPIDO studies, when the results came out, it was already too late. And people out of hours, doctors out of hours, whose patient it was, not they were just covering, wouldn't change their treatment.

This is an important point, reflected throughout the hospital-based interviews. With the push for novel, often biochemical, rapid diagnostics, moving services off-site will make it harder, if not impossible, to glean marginal gains from any diagnostic rapidity due to the addition of delays in the transport and processing of the samples.

The different attitudes with respect to compatibility divided along hospital/community lines more than was the case with other codes. This is likely due to the differences between community and hospital built environments. CRP tests as envisioned within primary care are a box sitting atop an already-busy and cramped consultation room. This is still true within a hospital laboratory, but there is somewhat more of a division between the user of the test and its operator in this system; even if the laboratory is on-site, and even if the health care professional is 'adopting' the diagnostic in that they have to choose to sample the patient using the novel method and kit, it is not that same healthcare professional who has to run the test. Their concerns, then, about compatibility with current systems would necessarily be less developed since their involvement in the process is lower.

An important caveat is that some newer generations of rapid diagnostic tests are intended to sit on the nursing station, or be undertaken at the bedside of a patient. These tests, then, place an additional burden on the healthcare professional who are meant to be the ones to adopt them. Where this was the case, which was almost exclusively with nurses charged with adopting RITs in A&E, compatibility was mentioned alongside complexity, trialability, and

observability as areas of concern. Embedding these new practices in these care contexts has occurred; the staff were reporting that they were using the tests, and also reporting relative advantages of therapid diagnostic tests. However, as might be expected, the more complex, nuanced, and detailed assessments of the strengths and limitations ofrapid diagnostic tests came from respondents who were most involved in all parts of the testing process; from patient admission, to decision analytics about whether and what to sample; to running the diagnostic; through to interpreting the result; and finally to deciding whether to modify a patient's care based on the result.

Complexity and Trialability

Complexity and trialability were hardly mentioned at all throughout the data set. Where complexity was mentioned, it tended to be concentrated in secondary care, and also was coded in a way that may have been different from the original category that Rogers set out. For example, it was the complexity of the logistics, the pathway, or the interpretation, that is mentioned more than the complexity of the tests themselves. One full-time GP in Western Health and Social Care Trust said of primary care-based CRP testing that the process was not initially straightforward:

There was a wee bit of … a few hiccups at the start getting the cassettes sorted and just kind of getting that running and trying to get into a habit of remembering because they had to be out of the [fridge] for 20 minutes, but once they go out for 20 minutes they can stay out for a month. So, there was a few wee hiccups at the start but nothing exciting.

Complexity highlights the importance not simply of examining the technology, but its context. The major complexity, or perhaps more accurately, complication highlighted by interviewees was the process of moving into and out of trials. Trials, or pilots, tended to be the way in which most respondents came into contact with rapid diagnostics. One nurse in Blackburn with Darwen explained how they funded one test:

As a pilot to say, right, well, the three machines weren't going to cost us anything but they're £20 a swab.

This is a known marketing tactic when companies are trying to promote the diffusion of particular innovations. The client receives the hardware at low or no cost, and is tied into

paying for the software, such as the shaver and blade model of pricing described earlier in the chapter.

A senior manager at Blackburn with Darwen explained that they had trialled an influenza test over the past winter and that the test will likely be taken on board from the 2018/19 flu season. In fact, trials tended to be how most other professionals first came into contact withrapid diagnostic tests. The consultant microbiologist at Camden explained that they had just been a part of a multi-site trial of the MALDI-TOF

Yeah, so the trial paid for somebody to [run the MALDI-TOF], but when the trial finished and there was no money coming in, they stopped doing it.

This quotation demonstrates that it is not unusual for sites that are part of trials to stop using the diagnostic once the trial funding runs out, even in large tertiary care, well-funded hospital settings. Pilots were another way through which users, especially in primary care, became familiar with novel diagnostics. However, the evidence coming out of pilot programmes, especially when pilots are informal, is often compromised. One GP in Northern Ireland explained:

I asked, I believe, a very reasonable question, why or how do you pick your pilots, which was met with a deathly silence. And I said why are you not using practices that are early adapters, why are you not using training practices, practices that have high levels of clinical governance […] the next time there's a pilot about CRPs or there's anything I want [my GP practice] to get it. [The trust] said no, that we were good prescribers and therefore we wouldn't get the [CRP machine]. So, my argument was absolutely not. We have evidence that pilots haven't been successful in the past, and we have evidence that poor prescribing practices are doctors that are older usually and they are not going to engage with a pilot well, they need to be … in my opinion filling out the forms, keeping on top of the data, monitoring quality improvement, and keeping an eye on the … you know, the quality assurance and verifying the machine. I said all that stuff needs a level of sophisticated organisation, and therefore the practices that are good prescribers and more likely to provide you that service.

In Betsi Cadwaladr, the interviews generated an excellent explanation of the dangers of interpreting too strongly from pilot programmes for CRP testing. In Anglesey, some GP

practices were provided with CRP tests. And in Wrexham GP practices around the same time (2016/2017), they made use of antimicrobial pharmacists to deliver professional education interventions to GPs. Both pilot sites achieved a reduction of approximately 10% on their year-on-year antimicrobial prescribing. The Anglesey site attributed their improvement to the CRP machines, whereas the professional education and support of antimicrobial pharmacists required personnel but no equipment and achieved the same gains at a fraction of the cost.

Observability – Monitoring and evaluation

For Rogers, observability is the degree to which the impact of an innovation is visible to others. The theory is that if individuals can see the results of an innovation, they are more likely to adopt it. The part of the observability definition that was relevant to the six case studies was that rapid diagnostics gave the service users rapid feedback about their antibiotic prescribing; and allowed healthcare professionals to course correct.

Being able to access prescribing data more readily was seen as a positive overall by interviewees. This was particularly the case in secondary care, in the two more resource-deprived case study sites. A pharmacist informant reported that secondary care was a more challenging environment for audit and evaluation than primary care in Betsi Cadwaladr. Another pharmacist informant likewise lamented the limited data and analysis resources available. They named a particular staff member responsible for data and analysis, and showed some reports generated by that person. They said that the risk to the institution of losing that staff member was great, since institutional memory all rested with one individual. A nursing informant reported that manual checks were carried out by some staff auditing other staff based on prescribing and drug charts, looking at the duration of the antibiotics, and whether the patient needs that specific dosage or length of treatment. However, this is less of a benefit of diagnostics themselves, and more a benefit of large electronic prescribing systems. However, perhaps because both interventions are examples of medical technology in antibiotic prescribing, there was some elision between the two when respondents were describing diagnostics.

Discussion

This study applies Rogers' Diffusion of Innovation Theory to a qualitative analysis of 71 interviews from six case studies across the UK. In response to my research question, I found that there was support for some aspects of testing – most particularly RITs - in certain contexts – for example paediatric A&E, and for patients living with comorbidities – but most respondents were ambivalent about the role of testing, and, in particular, the concomitant issues surrounding uptake, such as centralisation of laboratory services, cost, implementation, and logistical considerations.

What was helpful in Rogers' theory

I developed findings based on the data that I had coded according to Rogers' Diffusion of Innovation Theory.

Speed was the most commonly cited relative advantage ofrapid diagnostic tests. However this was not universally accepted as a given with respect to the introduction ofrapid diagnostic tests to clinical care; the introduction ofrapid diagnostic tests in offsite centralised laboratories was a particular perverse incentive that would appear to reduce the clinical benefits of these technologies. The perverse incentive, in this case, is that the speed of diagnostics would mask the care pathway delays accrued in centralising and in some cases privatising laboratory services. In the Greater Glasgow and Clyde locality, the RIT diagnostic was considered to have been successful in improving care in the context of a pressure-ridden system. The benefits of the RDT in that case would be considered to be tied to, and contingent upon, its implementation into a cash-strapped and infrastructurally-limited service. If the infrastructure of the service were to be improved, then the relative advantage of therapid diagnostic tests would likely be minimal.

Where interviewees reported relative advantages of therapid diagnostic tests to be minor, they sometimes caveated their answers. For example, when a GP in Blackburn with Darwen described the benefit of professional reassurance, they also addressed serious perceived consequences centred upon the availability of sufficient capacity in the health service to manage the potential behaviour change that these diagnostic technologies might engender. This is not an unfounded concern; the evaluation of GP at Hand, an app that allowed for

smartphone access to GPs in the UK, increased demand for appointments, and those appointments were for relatively more minor health concerns.(330) Medical technology has the ability to substantially shift demand for NHS services.

Barring one enthusiastic Northern Irish GP, who was an outlier, few GPs spoke positively about the value of introducing CRP machines to their practice. Even the GP from Northern Ireland saw a case for CRP kit helping only with the subset of prescriptions that are delayed scripts. This aligns with previous research on CRP tests which indicates that it is indeed either the most severe cases or marginal cases where GPs would prefer to have a decision aid.(331) Even in these cases, CRP testing is unlikely to reduce prescriptions or hospital admissions.(281)

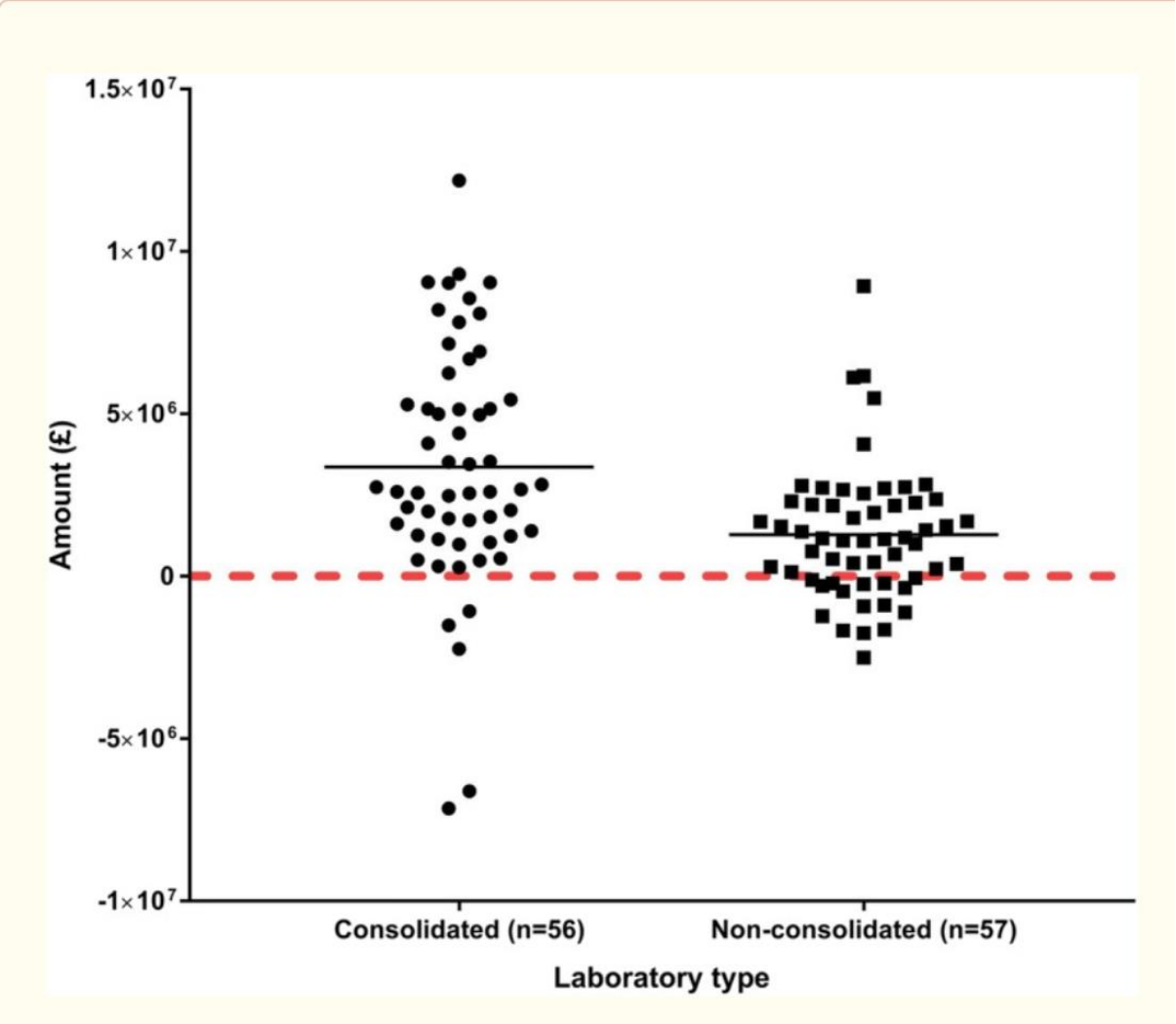
Broadly speaking, when professionals were positive about CRP testing in primary care, they tended to be positive about patient education and professional reassurance. This was also true in influenza diagnostics. It is relevant that, when asked to enumerate the benefits of rapid diagnostic tests, respondents discussed ancillary benefits such as the ones listed above; the areas whererapid diagnostic tests' perceived benefits are accrued tend not to be in patient prognosis, but rather in hospital bed management, professional reassurance, and the management of uncertainty. This is true in both primary and secondary care contexts.

In the rural sites, there were also concerns about the consequences of current geographically disparate options for sending tests off for further or specialised testing, beyond Glan Clwyd, for example, which is where the laboratory is situated for Betsi Cadwaladr. Overall, local experts in microbiology, antibiotic resistance, and prescribing in all three rural sites professed a desire for more diagnostics, but for them to be on-site. This was reflected in the secondary care findings in Blackburn, though not elsewhere. The Camden case study interviewees did also profess a desire for more laboratory services to be onsite, though not for more diagnostic capacity, but rather, less reliance on novel diagnostics, and more proximity to diagnostic staff and expertise.

I added an inductive code, *centralisation,* to the coding frame, since it emerged from the data strongly. Though ostensibly centralisation appears to be distinct from Rogers' category of compatibility, if we consider the idea of compatible *values*, centralisation was raised as being incompatible with the values of interviewees. In other words, interviewees were unlikely to

feel that rapid diagnostic tests were compatible with their views on how best to develop best practices and maintain good standards of patient care. This can be better understood in the context of the recent history of centralisation in UK laboratory services, how it is closely related to privatisation, and the perception of lab sciences managers and staff that the underlying values (lab sciences vs centralisation) are often in opposition. Previous research has spoken to why the core values of laboratory sciences are at odds with the values of industrial management. Table 10, adapted from Plebani, describes how laboratory service staff view their occupation, and how that contrasts with management values.(332) Yet laboratory services, as a non-patient facing component of the NHS – and, due to automation gains, as increasingly siloed even from other health professionals – have been targeted by managers and central government for off-siting, centralisation, and privatisation under the guise of 'efficiency gains' for the last fifteen years since the 2006 Carter Report recommended that 'economies of scale' due to centralisation were 'increasingly attractive'.(326) Moreover, this report equated gains afforded by centralisation (including provision of more expensive diagnostic services due to lower cost-per-test) with privatisation, citing private and centralised examples in Canada, the USA, and Sweden to support the assertion that independently contracted laboratory services could afford important clinical gains.(326) The recommendations were to swiftly and on a wide-scale consolidate laboratory services.(326) Four years later, Lord Carter issued a second report into laboratory services which confirmed that cost savings were expected and indeed being achieved by the first wave of consolidation.(327) However, subsequent academic analysis demonstrated that the results of consolidation of laboratories were in fact far more mixed than the Carter Reports would suggest. In 2016, one study demonstrated that consolidated laboratories have indeed made cost savings compared with non-consolidated laboratory services, but that consolidated laboratories also were the most likely to run large deficits (Figure 13).

Figure 13 Taken from Satta and Edmonstone, in 2015, the cost savings in consolidated laboratories compared with non-consolidated laboratories.(333)



And there has been a cost to consolidation, which has been: a decrease in total numbers of laboratories, and an increase from effectively 0% private involvement in the pathology market in the NHS in 2006 to over 13% in 2015, with the number likely to be higher still in 2020.(333)

Table 10 Adapted from Plebani, a table showing how values between laboratory service staff and management may be inherently at odds(332)

Laboratory service values	**Management values**
Appropriateness (in type of test, and in interpretation)	Efficiency
Test quality	Cost per test
Patient and patient-safety centred	Revenue

Useful clinical outcomes	Throughput/productivity

Taken together, this discussion of consolidation/centralisation and privatisation demonstrates how the elision between the two concepts can occur, though it is not, of course, pre-determined. When, however, centralisation is pushed for as a top-down efficiency generating, and cost-per-test minimising event, however, it is likely that it will be at odds with the preferences and value system of local clinical leads.

Non-spread of innovation, or rejection of innovation

Diffusion of Innovations Theory deals with the spread of ideas, technology, and practices, both among individuals and organisations.(74) The Diffusion of Innovation work tends – though less so in recent years - to operate under the assumption that innovation is the ultimate goal. This is a critique that Rogers acknowledged and addressed in the fifth edition of his own work.(74) There is also little provision made for how best to link individuals' views to the overarching meso-and macro-level organisational characteristics governing diffusion. Nevertheless, the choice to use Diffusion of Innovation Theory to classify and analyse participants' views on diagnostic technologies was largely successful.

At any rate, I determined early on in my coding process that I would be missing rich and nuanced themes if I did not also add a 'perceived consequences' code to the codebook. This broadly encompassed domain 2 in Greenhalgh's NASSS framework, when Greenhalgh discusses that an important reason for non-adoption of technology is limitations of the technology itself; namely adoption has consequences that are perceived to worsen the status quo rather than improve it.(277)

At the most generous end of the interpretation of this work, a select few rapid diagnostic tests were described as a positive development for a small subset of patients; and in order to aid with largely non-clinical (or indirectly clinical) concerns. This is important; it foregrounds the fact that where positive factors were described, these were centred on professional and patient education; and in hospitals, logistical considerations. Also, it points to serious limitations of current health technology assessment for those diagnostic tests that healthcare professions *do* want to adopt in their practice; the questions of how to comprehensively cost these so-called off-label benefits into business cases sits within Greenhalgh et al's NASSS framework, in domain three, 'value proposition'.(278) Greenhalgh et al describe how for the

value proposition to be sufficient both the supply and demand-side value propositions need to (i) be demonstrated, and (ii) align. Complexities, such as – in my data – misalignment of value propositions can be associated with non-adoption.

How best to link individuals' views to meso-and macro-level organisational characteristics?

Overall, RDT adoption was, predictably, different in disparate NHS settings. Though not unexpected, it does call for some consideration of what this means for widespread RDT adoption, and how ideas of implementation, spread, and non-spread are socially constructed. Discursively, there does appear to be a chasm between local discourses around individual diagnostic tests, pilots, programmes, and experiences, and the national-level discourses around diagnostics. A further analysis relating these data to documentary analysis and ethnographic research using critical discourse analysis might better be able to uncover the tension between the micro- and macro-level discursive traditions. Previous research has theorised around these distinctions. Alvesson and Karreman distinguish between 'local-situated' discourse and 'macro-systemic' discourse.(334) This is also reflected in the mechanisms for these macro and local-level data. The macro-systemic discourse advocating for increased uptake of diagnostics is in formal, government reports, quality premiums, national action plans, and multiple departmental policy documents, whereas these interviews are a form of 'social text' and methodologically would be expected to diverge from macro-level discursive analysis.

Strengths and limitations

A major strength of this study is that it represents some of the most comprehensive qualitative research on the views of rapid diagnostic tests for AMR at a local level, across proprietary technologies, and drawing across primary and secondary care contexts in the UK.

There were several limitations. Chief among them is that there were no repeat interviews over time. Our data were single interviews and thus not adapted to describe the innovation process in its entirety; Rogers follows his characteristics of a successful innovation with a set of stages of innovation uptake in a given setting: knowledge, persuasion, decision, implementation, and confirmation.(74) In some ways we have seen snapshots of all of these (plus non-adoption, or reversion) in different case study sites, but as with the Blackburn with

Darwen off-site laboratory services example, persuasion is not necessarily a prerequisite, especially in organisations with strong top-down implementation diktats. More recent organisational management research in this area has contested the linearity of this implementation process. Ferlie recognized that not only were decisions on innovation non-linear, there *was* no single decision. In fact, decisions were taken, multiply, across various parts of the organisation and among various groups and subgroups, and even the decisions themselves are broken up into smaller bundles where possible.(335) We see this in our data on rapid diagnostic tests. Top-down, the policy direction is to adopt rapid diagnostics wherever possible. At the clinical and local level, however, there is neither a blanket demand for more diagnostics where there are none, nor is there demand for blanket use of diagnostics where prescribers do have access to them; CRP tests are useful for borderline cases, MALDI-TOFs are useful for rapidly testing the samples of the most acutely unwell, and RITs are useful in the paediatric A&E in winter. This maps well onto previous research in this area.(289,335) Greenhalgh's NASSS framework's fifth domain makes provision for the importance of the healthcare organisation in the non-adoption of technology, drawing from areas like normalisation process theory, which unpacks the work undertaken to make coherent and embed a change to a new practice from an old one.(278) In the case of rapid diagnostic tests, this is work such as situating the diagnostic into best practice, bringing on board the intended users, and enact and monitor the new practice. All these processes need to be functioning at an organisational level before individuals – even willing health care practitioners – are able to begin to adopt an innovation.

Our lack of longitudinal understanding of practices and views was particularly relevant for those case study sites where antibiotic prescribing changed markedly over the course of the study. For example, Betsi Cadwaladr went from being the highest prescriber in Wales to being the second lowest prescriber of the Welsh Local Health Boards. However, we have only a snapshot of views and prescribing on the weeks of our interviews. Finally, there were multiple researchers conducting the interviews. Each interviewer was afforded some autonomy with respect to interviews. This means that the skew within interviews does tend to be toward an interviewer's area of interest. This is a known limitation within qualitative studies.(336)

To conclude, adopting Diffusion of Innovation Theory, I found that the 71 interviewees had cautious and nuanced views on diagnostics across the board, with particular concerns with respect to the linkage betweenrapid diagnostic tests and centralisation of laboratory services. I also critically engaged with the appropriateness of Diffusion of Innovation Theory as a grand theory in this area. With the intentional adoption of some of the counterpart codes suggested in the NASSS framing – such as 'perceived consequences' – Diffusion of Innovation Theory remains both flexible enough as a grand theory, and wide-spread enough in the field, to be applicable even where the diffusion of an innovation may not the desired outcome.

Impact, engagement, and dissemination

These data were presented to the DHSC at least three times: first, in a presentation led by Alec Fraser in 2017, next in a 188-page complete end-of-project report, and finally in a 30-page summary report. These two reports were both delivered at the end of 2018, and fed into the refresh of the 2013-18 AMR strategy as it was superseded by the 2019-2024 AMR National Action Plan.

Finally, PIRU presented these and other summary findings at a round-table patient and public involvement afternoon (3 September 2018) and we compiled and collated a list of participants' reactions and priorities, which was also included in the 188-page report to DHSC.

Chapter 4: Critical discourse analysis of submissions to the UK Health and Social Care Committee on Antimicrobial Resistance

Preface

At this point in my research, I had found (i) that the evidence did not seem to support the wide-spread adoption and use of somerapid diagnostic tests in hospitals and (ii) the intended service users did not want, on the whole, to introduce them either. And yet a new AMR strategy had just been published in early 2019 (the AMR National Action Plan 2019-2024) which yet again highlighted the critical importance of introducing rapid diagnostic tests in the fight against AMR.(7) I wanted to understand why, given (i) and (ii), recommendations for diagnostics were omnipresent in national-level documents and top-down policy mandates. I decided to undertake a critical discourse analysis of the late 2018 submissions to the UK House of Commons Health and Social Care Committee on AMR. Here I delved more deeply into how the AMR narrative was being presented by different stakeholders. I asked the research question: Are the narratives describing the 'problems' and 'solutions' for AMR different between the public and private sector public submissions to the UK House of Commons Committee on AMR? I answered this question, finding that, irrespective of sector, submissions presented the problem of AMR similarly. The solutions, however, diverged, with industries using discursive strategies, including the development of three main 'market paradoxical' positions; on the one hand, asking for subsidies and incentives, but on the other hand explaining that regulation would be detrimental to 'innovation'. Public sector submissions did not do this.

This chapter includes my second paper, which is under review at Critical Public Health as of December 2020. This paper is an analysis of the submissions to the 2018 Health and Social Care parliamentary committee on antimicrobial resistance. The findings enumerate the tactics being used by industry bodies in the framing of the narratives that they put forward. Overall, the analysis demonstrates that commercial interests deploying the crisis narratives do so in order to lobby heavily for solutions, namely deregulation and corporate subsidies. The analysis stops short of being able to ascribe motivations to various actors, nor does it purport to assign a value to the success of these tactics in permeating the national policy mandate.

However as with many health policy academic analyses, the policies have changed since this article was written. After the analysis was complete, a policy pilot was launched that was lobbied for by every non-generic multinational pharmaceutical submission, and also in the submission of the trade association representing these companies. This policy pilot was related to the notion of decoupling antibiotic sales from volume sold. This recommendation appears in the Pfizer, MSD, GSK, and ABPI submissions and will be described further in the paper below. In 2019, a year after the call for evidence to the committee, NICE, PHE, and the DHSC announced that they were going to pilot a decoupling scheme, called the 'subscription model', where the government pays companies for the right to use newly developed antibiotics, not for the amount of the antibiotic that it buys.

I wrote with colleagues about how this was not a sustainable solution, in an editorial in the BMJ in September 2019 (Appendix: Document 5), and responded to a request for a quotation for the BMJ again once the pilot was rolled out.(8,9) So, while I did not conduct an official analysis of the successes and failures of submissions to capture policy bandwidth in this paper, the DHSC/NICE/PHE pilot scheme represents one of the largest investments in AMR in the UK in recent history, and as often happens in applied health policy research, the external world has continued to change and policy develop whilst the research is being undertaken. This particular large-scale policy development adds even more credence to the conclusions in the paper that warn of the risks of corporate capture of public funds in AMR. I reprised this message again in an opinion piece in the BMJ to coincide with World Antibiotic Awareness Week in November 2019 (Appendix: Document 6).

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

SECTION A – Student Details

Student ID Number	402062	**Title**	Ms
First Name(s)	Rebecca		
Surname/Family Name	Glover		
Thesis Title	Antimicrobial resistance in the United Kingdom: a mixed-methods dissertation on diagnostics, discourse, and decision-making		
Primary Supervisor	Mark Petticrew		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

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Please list the paper's authors in the intended authorship order:	Rebecca E. Glover (ORCID ID 0000-0001-9150-9977), Mark P Petticrew, Nicholas Mays, Claire Thompson

Stage of publication	**Undergoing revision**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	REG developed the idea, extracted data, conducted the analysis, drafted the paper, edited the paper, and approved the manuscript for submission MPP and CT coded data and edited the paper, and approved the manuscript for submission NM edited the paper and approved the manuscript for submission

SECTION E

Student Signature	Rebecca Glover
Date	29 December 2020

Supervisor Signature	[redacted]
Date	30.12.20

Paper II: Stakeholder narratives of 'problems' and 'solutions': submissions to the United Kingdom House of Commons Health and Social Care Committee's 2018 enquiry into antimicrobial resistance

Authors: Rebecca E Glover, Mark P Petticrew, Nicholas Mays, Claire Thompson

Paper under review at Critical Public Health, December 2020

Abstract

Background Antimicrobial resistance (AMR) is often characterised as a 'wicked problem', requiring (i) action by public, private, and third sector stakeholders, and (ii) local, regional, national, and supranational implementation of strategic change across (iii) low, middle, and high-income countries. Crisis narratives may be co-opted to privilege solutions promoted by the private sector; in AMR, this may occur in the pharmaceutical and medical diagnostics industries.

Methods We conducted a critical discourse analysis of the seventy-one written submissions to the 2018 'Antimicrobial resistance' House of Commons Health and Social Care Committee. Two researchers collaboratively coded the findings and categorised the submissions.

Results We identified dominant narratives and compared the private sector submissions with public, third sector, and academic submissions. We found that, irrespective of sector, submissions presented the problem of AMR similarly. The solutions, however, diverged, with industries using discursive strategies, including the development of three main 'market paradoxical' positions; on the one hand, asking for subsidies and incentives, but on the other hand explaining that regulation would be detrimental to 'innovation'. We expand on these paradoxes, and catalogue the meta-discursive tactics used to achieve them, including: obfuscating funding sources, stake inoculation, and lobbying for influence.

Conclusion Our analysis demonstrates that commercial interests deploying the crisis narratives do so to lobby for self-serving solutions, in particular deregulation and subsidies. Discursive choices shaped by a technocratic-industry complex are redefining the pathways to success, monitoring, and decision-making in the global AMR arena.

Introduction

Antimicrobial resistance (AMR) is an area of global policy attention. Patients with bacterial diseases that were treatable with widely available and inexpensive drugs find themselves with fewer or no treatment options as bacteria develop resistance to antibiotics. Antibiotic resistance is often characterised as a 'wicked problem' like climate change, because it (i) requires simultaneous action by public, private, and third sector stakeholders, (ii) requires local, regional, national, and supranational commitment (and implementation of strategic change) across low, middle, and high-income countries, and (iii) spans human, animal, and environmental health.(337,338) The corollary to AMR being described as a wicked problem is that so-called 'crisis' narratives have been co-opted by public health policymakers and practitioners to marshal political attention and resources. Recent work in this area demonstrates that there are risks associated with these discursive approaches.(339) For example, they may cause crisis-fatigue with the many publics who are targeted by such narratives. (340) They may push behaviour change in the opposite direction intended, with patients seeking more antibiotics rather than fewer (341), They also risk stigmatising some minority groups, such as farmers, in the name of 'biosecurity'.(342) Moreover, crises are subjective, and the choice to employ crisis vocabulary is necessarily 'agentive and strategic'.(343) This language has been adopted in both the mainstream media coverage and also the political discussions of the breadth and depth of the problem.(296) Appropriation of the AMR narrative has led to the privileging of solutions promoted by, and involving, the

private sector; and with this comes the risk of devoting public sector funds to subsidising the private sector – in particular, the pharmaceutical and medical diagnostics industries.(8)

AMR policies, narratives and strategies

In 2011, England's then new Chief Medical Officer (CMO), Professor Dame Sally Davies, commissioned her first annual report on the global risks of AMR. This report was published in 2013, and, in response, then Prime Minister David Cameron commissioned a review, led by the economist Jim O'Neill, into AMR, which took the form of a series of reports published between 2014 and 2016.(2) From the beginning, the O'Neill Review presented AMR as a crisis; the first and second reports were titled 'Antimicrobial resistance: tackling a crisis for the health and wealth of nations', and 'tackling a global health crisis: initial steps', respectively. Alongside this work, the UK Government developed a five-year AMR strategy (2013-2018) and, while no specific monies were attached to the policy recommendations, it was expansive and took a One Health approach – incorporating both human and animal health, and the environment.(279) The Strategy was co-produced by the Department of Health, the Department for the Environment and Rural Affairs, and the governments of the three devolved UK nations, namely Scotland, Northern Ireland, and Wales.

In 2018, as the first five-year AMR strategy was coming to an end, the UK Government was refreshing the Strategy based on new evidence that had come to light in the intervening five years, and was seeking the involvement of academic and industry partners in this venture. On 4 September 2018, as the draft version of the AMR strategy was being finalised for publication, the Health and Social Care Committee of the UK House of Commons (henceforth 'the Committee') sent out a call for written submissions of evidence. The submissions came from government departments, the private and third sectors, trade

associations and private individuals, and were guided by two questions set out in the call for evidence: what results had been delivered by the UK AMR 2013-18 Strategy; and what the key actions and priorities for the Government's next AMR strategy should be. This allowed motivated stakeholders to frame the AMR 'problem' and their chosen 'solutions' with a view to influencing the Government's policy agenda. In this paper, we deconstruct these discourses, consider their symbolism and material effects on health policy, and analyse how the promoted 'solutions' to the AMR crisis diverged between industry and non-industry submissions.

The need to critically interrogate submission narratives

Policy discourse and rhetoric can have a material effect on health. The recent policy discussions surrounding AMR are a prime example of this. Recently tabled resolutions at the UN, G20, and G8 have attracted front-page, mainstream media headlines, and more than half of the UN countries have produced AMR national action plans (NAPs) intended to mitigate the risks of AMR to human health.(295) The Committee's consultation on AMR belongs to the Aristotelian tradition of deliberative democratic action, since UK Parliamentary Select Committees weigh submissions – termed 'evidence' but with no requirement to meet a particular standard of proof – in order to arrive at a way forward. This is more inherently argumentative and interpretive as a process than other formats for gathering evidence, since not all submissions 'win' equal weighting in the final report produced from the Committee's proceedings. The material benefits accruing from winning the discursive framing or problematizing of a crisis are clear; resources, (de)regulation, market access, workforce and subsidies are all possible policy prizes, but depend on successfully embedding in AMR policy a carefully constructed set of narratives and solutions. In particular, recent discussions in the Department of Health and Social Care in the UK have centred on the creation of a market

entry reward for pharmaceutical companies who develop new antibiotics.(344) There are similar – though not as substantial - market entry rewards for diagnostics companies, namely the Longitude Prize, which has yet to be awarded.(35)

In the sections that follow, this paper will use critical discourse analysis to examine the submissions to the Committee and, in doing so, deconstruct the AMR crisis narratives (put forward by O'Neill, and subsequently taken up and developed by other commentators), identify alternative narratives, and explore the consequences of these discursive strategies.

Methods

Critical discourse analysis

This paper draws on critical discourse analysis (CDA) to analyse the Committee's AMR-related submissions. CDA is a constructivist tool aimed at unpicking ideas, decisions and ways of thinking that are constructed by discursive choices.(345) This approach allows us to identify the power dynamics and value propositions implicit in the different discourses used between and within private sector, trade association, government and academic submissions.

We assessed the industry and trade association narratives (which are under-studied compared with the narratives used by government, academic, and third-sector actors) to determine whether they differed from the other submissions; and catalogued how these narratives were deployed to promote particular policy solutions.

Sources of data

There were 71 written submissions made in advance of the Health and Social Care Committee's report. These were published online on 22 October 2018. A summary can be found in Table 11.

We accessed these submissions from the Health and Social Care committee's website on April 26, 2019. We downloaded the documents and extracted relevant data in three main areas: for problem delineation, we referred to Bacchi's 'what is the problem represented to be'; for the promoted solutions, we turned to Entman's 'remedy promotion' theory in media studies and bias; to elaborate on the crisis narrative, we refer to Foucault's lectures on security and population in 1977-78.(75,343,346) Language and narratives can be critically explained using a Foucauldian lens when infectious diseases are described in terms of security and control - of attempting to 'contain' infection from non-infected people, other organisms, or the environment.(76) These terms arise in AMR discourses, in relation to issues such as travel medicine, immigration and migration in general – and necessarily involve 'apparatuses of security around bioterrorism'.(347)

Once we had summarised each document, we were able to identify the dominant and biosecurity narratives that were used by the various stakeholders which had submitted evidence. We then compared the narratives, framing and language used by the private sector with public and third sectors, and academia; we subsequently analysed the three main emergent 'remedies' to the AMR problem and categorised them within an emergent 'market paradox' framework. Two researchers (REG and CT) collaboratively coded the findings, thematically. Two researchers (REG and MPP) categorised the submissions by sector.

Results

Who responded to the Committee?

The sectors represented in these submissions were industry, trade associations, non-governmental organisations (NGOs), professional associations, academia, government, public-private partnerships, and homeopathy proponents.

There were twenty-five from industry (including industry alliances, and public private partnerships). There were twenty-eight submissions from NGOs, civil society, health-related trade or professional associations, academic organisations (non-industry sources). Five submissions were from complementary or alternative medicine proponents, two each from funders and government / statutory bodies, and nine were from individuals (see Table 11). Some submissions fell into two categories, however we coded the submissions using the primary affiliation agreed upon by two individual coders.

Framing of the AMR problem: don't waste a good crisis

We found that, irrespective of sector, all of the submissions presented the *problem* of AMR in line with the framing presented previously in the O'Neill Review(296) by highlighting dire projections of mortality or economic loss due to AMR and reiterating the crisis narrative it used. No submissions suggested that additional AMR work was unnecessary, nor that the status quo was sufficient. The potential benefit of framing the AMR issue as a crisis is to capture the policy initiative and marshal resources. Where the submissions differed and sometimes diverged dramatically, was around what the *solutions* to problem of AMR should be.

Crisis narratives and biosecurity

The crisis narrative is dominant throughout the submissions. Antibiotic Research UK, an AMR charity, quoted Professor Dame Sally Davies, writing that AMR was 'one of the most pressing issues of our time'. The joint submission from two learned societies, the

Microbiology Society and the Society for Applied Microbiology, stated that AMR 'remains a key immediate and long-term global challenge'. The Quadram Institute, a centre funded by academic, NHS, national and international funders, charities and industry, argued that 'we are already seeing tens of thousands of deaths attributable to AMR each year – without action this would become millions'. In other words, actions could reduce the risk of a threatened exponential increases in cases.

In some cases, the AMR narrative is not simply presented as a crisis, but specifically as what a Foucauldian interpretation would term a biosecurity crisis. Technologies and institutions respond to crises by forming *dispositifs* – mechanisms – of security, such as regulatory decisions, as well as investments in certain types of solutions predicated upon discourses, science(s), morality and other societal institutions, such as the border. This does not run counter to the crisis narrative; rather, it is an elaboration and development of this crisis theme in a subset of submissions and one that has been identified and critiqued elsewhere.(348) Terms such as 'imported case', and 'hidden outbreak' are perennially prevalent in AMR academic research, policy settings, and media coverage and evoke Foucauldian framings of 'risk', 'danger', and crisis'.(348,349) The TB alliance, the Royal College of Nursing, RUMA (Responsible Use of Medicines in Agriculture), the AHDB (agricultural and horticultural development board), and Homeopathy International explicitly used the language of 'biosecurity', 'crisis', or 'case' in their submissions. Of particular note as the only medical/human health submission to deploy an explicit biosecurity risk narrative, the Royal College of Nursing developed a patient/country isolationist tone in its evidence:

> *AMR poses a security threat to the UK. Risks associated with biosecurity, include unforeseen consequences of deployment of UK staff in humanitarian crisis or through the receipt of patients after major incidents such as the*

Romanian nightclub fire, where victims with burns were treated in the UK and Norway. Whilst the risk of AMR should not prevent the UK from supporting such humanitarian needs, risk assessment and mitigating actions to prevent the transfer and importation of highly resistant organisms must take precedence when planning such operations.

The text lists 'major incidents' in other countries to emphasis risk from 'others' and to portray the UK as a net exporter of expertise and a net importer of risk.

In contrast, the Agriculture and Horticulture Development Board (AHDB) (the levy board which represents farmers, growers and others in the supply chain) and RUMA (Responsible Use of Medicines in Agriculture – a non-profit organisations whose membership represents interests in agriculture, veterinary practice, animal medicines industry, farm assurance, training, retailers, consumers and animal welfare) both focused on agricultural biosecurity as a purported likely area of antibiotic reduction. Both highlighted the gains made in the field; RUMA wrote that it had been 'encouraging retailers to review their standards for meat and animal products and to set clear specifications, concerning biosecurity, antimicrobial stewardship and good husbandry throughout the supply chain', and the AHDB stated that 'biosecurity and husbandry are key to reducing the need for antibiotics and are key areas' of their work.

<u>Solutions: market paradoxes</u>

After establishing their crisis narratives, the submissions lay out where the AMR response should move in the future. All of the divergent solutions called for by different organisations and authors in the texts are grounded in market ideology with a paradoxical effect overall.

This paradox is played out in three main discursive dilemmas: (i) interference vs non-interference; (ii) power vs powerlessness; (iii) for-profit vs not-for-profit.

Market Paradox I: interference vs non-interference

The assertion frequently made in industry submissions is that intervening in the market in a specific set of ways – for example, through subsidies and incentives for antibiotic and diagnostic development – will help to reduce antibiotic resistance and avert morbidity and mortality. On the other hand, increasing regulation or targets, or increasing negative incentives, is presented by industry and trade associations as a mechanism that will cause or increase suffering. This paradox is, simply put, that action on AMR is purported to require both interference and non-interference in the market.

The AMR Industry SME group submission states that there is insufficient ring-fenced government funding to provide a sustainable pipeline of 'life saving' medications for AMR. A the Bioindustry Association claims that if the UK government does not provide (financial) incentives to its members, it will not be seen as 'credible' on the world stage. The submission from the British Generic Manufacturers' Association insists on the one hand that any additional regulation in this area may cause drug shortages - thereby summoning the discourse of fear and linking it to a heightened regulatory environment – but requests, on the other hand, that generic medicine prices be raised and economic incentives be introduced for the generic pharmaceutical industry to invest in drug manufacturing and the supply chain. In this latter case, the fear of shortages is again referred to; the remedy of economic incentives will, the reader is assured, avoid the risk of having to switch to second line (more costly) antibiotics because of shortages in the first line, generic versions.

The non-generic industry submissions from pharmaceutical companies Pfizer, MSD, and GlaxoSmithKlein (GSK), and the submission from their trade association, the Association of the British Pharmaceutical Industry (ABPI), all centre on economic incentives; specifically, the decoupling of antibiotic volumes sold from reimbursement, a popular incentive model that was announced in June 2019 as a joint NICE, DHSC, and PHE pilot scheme, and implemented in June 2020.(9) However, they also spend considerable time in each submission explaining regulatory areas that would harm their businesses. For example, GSK explains that it is working to reduce its factories' contamination of the environment via effluent waste, but insist that is concerned that regulation would hamper, not help, this effort. This is a common argument used by many industries for example to push back against regulation, guidelines, and environmental and consumer protections.(350,351) And yet, GSK, and the others, are clear that they would welcome piloting of new reimbursement models by government.

This is not to say that central government and government-sanctioned bodies such as the O'Neill review do not suggest market incentives for pharmaceutical companies; indeed, they are insisted upon in the submission by Anthony McDonnell and Flavio Toxvaerd, who were original contributors to the independent, government-commissioned O'Neill Review. They suggest both market entry rewards for new drugs and funding for research and development of early-stage diagnostics, among other financial interventions. However, the pharmaceutical companies present these ideas for interference in the market while simultaneously arguing against interference in the areas that do not suit them. They may be attempting, therefore, to circumscribe a narrow area of market interference while defending against the risk that their call for economic interference is akin to tacit agreement for subsequent, further market interference that may not be as aligned with their interests.

Market Paradox II: power vs powerlessness

The ABPI emphasises the enormous scale of the pharmaceutical industry's investment in the United Kingdom, including having dedicated at least $2 trillion to AMR-related products. In so doing, this submission is emphasising the global scale of this industry, and its power; this is made clearer still when its other discursive choices are taken into account, such as using USD when describing investments, and employing the term 'global' throughout the submission. Such a show of strength also inoculates the industry against a potential critique that they are not doing enough to alleviate the AMR crisis, and signals that companies are committed to this area of work.

In contrast to the rhetoric of global reach and power, the industry simultaneously portrays itself as powerless to influence other interests which it holds responsible for encouraging the spread of AMR, and powerless to invest in research without help from the public sector. The ABPI submission claims that:

> *Antimicrobial research presents unique scientific and economic challenges. The pharmaceutical industry recognises the need to develop more antimicrobials but a new funding and valuation model is needed to improve sustainability of R&D investments in antimicrobials. Creating a sustainable model that rewards innovation and shares the risk will be challenging.*

Due to the standard format of the written submissions to the committee, which are open to everyone, publicly available, and read by the MPs chairing that committee, they are dialogic - containing deflections of anticipated objections and attacks. In this case, the pharmaceutical industry submissions are, paradoxically, referencing their purported inability to act due to unfavourable market conditions in order to deflect away from anticipated objections about their position of international power in the field. MSD writes that the current market 'does

not support the sustainable investment in antibiotic research and development'. In addition to this work, these actors are pursuing stake inoculation. In this particular case, MSD writes that many pharmaceutical companies have left the field of R&D for antibiotics; the implication is both that MSD is not solely responsible, and also that this mass market exit validates the powerlessness of the industry.

Many multinational pharmaceutical companies also have a diagnostics wing; these companies have a unique discursive aim – to craft a narrative that benefits both wings of the business. Roche is one such submission. It presents itself as powerless in the *antibiotic R&D* wing, in order to lobby for antibiotic market entry rewards:

> *Lack of clear return on investment, not least given the high costs associated with developing a new medicine, coupled with the unpredictable patterns of resistance, over time create uncertain and unfavourable conditions for industry. This threatens the investment that is needed to address this critical public health issue now and in the future.*

By contrast, Roche also expounds upon its powerful suite of diagnostic technologies and their role in hospitals and laboratories in the UK, claiming that it is a lack of *diagnostic uptake* that has led to the overuse of antibiotics (and thus, presumably the increase in resistance). While industry may ostensibly be seen to be a partner to the technocracy in this field, this is largely because the dominant technocratic narratives are beneficial to the pharmaceutical and medical diagnostics industries in particular. These outliers help to demonstrate this case, since those that operate in both pharmaceutical development and medical diagnostics are pushing both arenas as a mandate.

Market paradox III: for-profit, but not-for-profit

Pharmaceutical companies may feel they are gaining by positioning themselves between a discursive tradition of for-profit and not-for-profit work, because most of the submissions undertake this discursive work. For example, the ABPI emphasises the corporate social responsibility (CSR) activities of its members in relation to AMR, namely 'providing lesson plans and toolkits' to improve public awareness of AMR. GSK reminds the reader that it led the development of the 'Davos declaration' on AMR, and Pfizer writes that it signed the Davos declaration.

In addition to insisting on their not-for-profit work, many corporate submissions adopt "access" and "equity" terminology. GSK uses the word 'access' 22 times in a seven-page document, and insists multiple times that 'more people die from lack of access to antibiotics than from antibiotic resistance, mainly in low-income countries.' The problem, then, from this perspective, is lack of access to drugs, and so too is the solution, 'improving reliable, appropriate access to high quality antibiotics is therefore an urgent priority, requiring public, private, and third sectors to work together.' Becton Dickinson, a medical technology company, is particularly concerned about patient safety, advocating that 'the next strategy should include a specific section on how best-practice diagnostics must be utilised to optimise patient safety in this area.' Pfizer describe their sponsorship of an AMR exhibition held at the Science Museum (while simultaneously shifting blame for AMR to the 'personal responsibility' industry narrative), writing:

> *Pfizer believes that education is critical if we are to enlist the public's help in combating AMR. This is why we sponsored a free exhibition on AMR at the Science Museum; called 'Superbugs- The Fight For Our Lives', the interactive exhibit aims to show the Museum's 3.2 million annual visitors how society is responding to the enormous challenge of antibiotic resistance, featuring scientific research from across the globe and the personal stories of those waging war on the superbugs.*

This early insistence in submissions on activities that appear charitable or philanthropic is useful discursively to provide a counterpoint to the fact that pharmaceutical companies are required to be primarily profit-driven, not public health-driven. The discursive work being undertaken by industries who use their corporate social responsibility activities to deflect from their non-engagement with research and development, or their lobbying for public subsidies, is also to obtain privileged insider status; industry partners may be listened to more attentively by a wider range of policy makers than would be the case if they only adhered to legally mandated for-profit activities.

Discussion

We identified dominant narratives and compared the private sector submissions with public, third sector, and academic submissions. We found that, irrespective of sector, submissions presented the problem of AMR similarly. The solutions, however, diverged, with industries using discursive strategies, including the development of three main 'market paradoxical' positions; on the one hand, asking for subsidies and incentives, but on the other hand explaining that regulation would be detrimental to 'innovation'.

Forms of CDA have been used to analyse industry documents in the past, including in unhealthy commodity industries (UCIs) such as alcohol, tobacco and food.(79,123,351) UCIs have been found to: invest in the creation of evidence in order to moderate government guidelines and protect business interests; use corporate social responsibility (CSR) to improve brand image and boost brand recall; and, crucially, reject pricing or supply that would undermine profit.(79,123) Some of these findings, termed the 'industry playbook' have also been observed in the discursive strategies of pharmaceutical companies.(352)

Drawing on this work, we theorised that the AMR industry submissions would be materially different in their narratives from the academic, government and third sector submissions. While there has been some theoretical and analytical work undertaken to underscore industry involvement in AMR research, the 'crisis' label appears to have hindered critical appraisals – and oversight - of industry's involvement the AMR policy agenda.(353)

Many of the discursive strategies in the submissions to the Committee actively engage in blame shifting; from pharmaceuticals to diagnostics, from animal health to human health, from acute care professionals to community care professionals and back again. There were also several instances of submissions purporting to identify culprits worse than themselves in the context of work to reduce the rates and risks of AMR. The BMA insists that AMR is a 'One Health' problem, which would not be surprising alone, as this is a concept often relied upon in AMR research. However, the BMA uses some of its submission to argue for tighter regulation of the use of antibiotics in farming, which shifts responsibility for the crisis from the human health to the animal health and environmental sectors. This shifting of blame around the triangle of human-animal-environmental causes is not one-sided. The British Poultry Council, by contrast to the BMA, writes that the risk of resistance being passed to humans through food is 'relatively low'.

The submissions also deploy what we term **meta-discursive tactics** in the development and dissemination of their texts in order to increase their influence and amplify their presence. First, the industry and trade association submissions succeed in *crowding* the policy discourse – fully fifty percent of submissions come from them. Next, there is the tactic of *coordination.* Submissions cross-reference each other, indicating a coordinated approach. This coordination may magnify the effect of their submissions. For example, the MSD and

Roche submissions both officially endorse the ABPI submission. This creates multiple representations and configurations of the same actors and lobbying points and words to create the impression of a louder and clearer majority within the body of the submissions in their favour.

The tactic of *coordination* is amplified when accompanied by the tactic of *obfuscating funding sources.* In many cases, the trade associations representing multinational companies describe themselves as not-for-profit or independent, when their funding comes directly from industry. An example of this is RUMA, which describes itself as both 'independent' and 'non-profit', but who only have a few dozen members organisations, including some of the largest agricultural bodies in the UK.

The particular environment and structures of a committee facilitate the discursive and meta-discursive tactics described in this paper. The environment of a Committee influences the content of submissions, since all actors are aware that others will be submitting claims on the same topic, though perhaps not adopting the same framing. The unique environment means that submissions can, and do, adopt particular strategies to maximise their impact. This paper has focused primarily on the pharmaceutical, medical diagnostics, and trade association submissions as these comprise the plurality of the submissions to the health and social care committee.

The call for evidence to a Parliamentary committee appears consistent with an Aristotelian vision of deliberative democracy open to all view points, but, in this case, the voices of those promoting public health-related responses such as infection prevention and control, plus stronger environmental control tend to be crowded out by those lobbying for solutions that

match their self-interest such as greater public subsidies for the development of diagnostics and new antibiotics. These are not necessarily more cost-effective than the alternative but are much more strongly promoted in the body of evidence received by influential committees. If we believe the crisis narrative in AMR, it is important to draw out the best solutions, not simply the best-lobbied ones.

There are several limitations of this research. We are not examining the motivation or the funding of the submissions in-depth, and have focused primarily on where the industry and trade association documents diverge from government, royal society, or charitable documents. This is because industries in AMR have been relatively uncritically accepted into the 'solutions' part of AMR discourse in the UK, and are on track to receive the largest investments in the near future. However, a citation analysis or in-depth network analysis of all actors in this discursive field would be an appropriate next avenue of research. Furthermore, we cannot make an objective comparison about the various actors, their internal positions, or intentions. We have no information about any submission's motivation(s), but with the text included in these submissions, we have put forward some analysis about how certain tactics have been used preferentially by particular actors. We also have not examined the success of industry or other actors in embedding their policy solutions – though the June 2020 implementation of a major UK Department of Health and Social Care pilot programme aiming to provide pharmaceutical companies with up-front payments for antibiotic development should provide some insight into which solutions have been privileged.(9)
In summary, we should not uncritically accept the framing of the AMR problem/solution as a private sector-led 'fight'. It is widely stated that industry should be part of the solution to AMR.(354,355) The industry solutions presented throughout the submissions focus on the co-optation and sequestering of public funds. Industry are using discursive strategies that

mirror their involvement in other areas of public health, such as UCIs. We should require parliamentary committees to have more rigorous methods for taking and receiving 'evidence'. These could involve: moving to an arm's length regulatory position of the private sector; requiring parliamentarians to undergo short courses in the critical appraisal of submitted evidence; and independently fact-checking submitted evidence before it reaches the Committee.

Table 11: Written Submissions to the Antimicrobial Resistance House of Commons Health and Social Care Committee

Submission	Code
Association of the British Pharmaceutical Industry (ABPI)	**1.**
Age of Autism	**Other**
Agriculture and Horticulture Development Board (AHDB)	**2.**
Ainsworths	**3.**
Alliance of registered homeopaths	**4.**
Alliance to save our antibiotics	**5.**
AMR Centre ltd (1)	**6.**
AMR Industry SME group submission	**1.**
Andrew Ward	**4**
Anthony McDonnell and Flavio Toxvaerd	**11.**
Antibiotic Research UK	**5**
BD	**1**
BGMA (British Generic Manufacturers Association)	**1**

Biochemical Society	**7**
Bioindustry Association	**1**
BIVDA	**1**
Bloodwise	**5**
BMA	**7**
boots uk	**1**
British Poultry Council (BPC)	**2**
BSAC & BPS	**7**
Bureau of investigative Journalism	**5**
BVA	**2**
Caroline Ford	**11**
College of Medicine London	**5**
CUTIC	**5**
Cystic Fibrosis Trust	**5**
DataLab (Goldacre)	**8**
David Jenkins	**11**
David Tredinnick	**11**
Deb Group Ltd	**1**
DHSC	**12**
East and North Herts CCG	**12**
Edinburgh Infectious Diseases	**8**
GSK	**1**

HCA healthcare	**1**
Healthcare Infection Society	**7**
Homeopathy International	**4**
Hygeia Project	**5**
Infection prevention Society	**7**
Institute and Faculty of Actuaries	**5**
Institute for Global Innovation - Birmingham	**8**
Johnson & Johnson	**1**
Matoke Holdings Ltd	**1**
michael ferguson	**11**
Microbiology Society and SfAM	**7**
MRC PhD student AMR residential training course	**8**
MSD	**1**
MSD animal healht	**1**
national office of animal health ltd	**2**
National Pig Association	**2**
Pfizer ltd	**1**
Quadram Institute	**6**
Results UK	**5**
Results UK - 2	**5**
Roche Products ltd	**1**
Rony Armon	**11**

royal college of nursing	**9**
Royal College of Physicians and Surgeons of Glasgow	**9**
Royal College of Physicians of Edinburgh	**9**
Royal Pharmaceutical Society	**7**
RUMA	**2**
Society of Homeopaths	**4**
STOPAIDS	**5**
Stuart Calimport	**11**
SULSA	**8**
TB alliance	**5**
UKRI	**10**
Wellcome Trust	**10**
Xiao-Ning Xu	**11**
Yubraj Sharma	**4**
Category: 1. Pharmaceutical or diagnostics Industry body, or trade or other association or alliance; 2. Non-AMR organisation – including agri/horticulture Industry body, or other trade or other association or alliance; 3. Pharma company; 4. Submission related to homeopathy (incl homeopath orgs); 5. NGO/Civil society organisation (including charities) or similar non-profit; and professional societies; 6. PPP; 7 Health-related trade or other professional association; 8 Academic organisation or similar; 9 Royal or other college; 10 Funder; 11. Individual submission; 12. Govt or health or NHS dept or similar; Other	

Impact, dissemination, and engagement

Early analysis from this paper was presented as a full-length oral presentation (with high-scoring abstract) at SSM 2020, which occurred online.

This analysis also formed part of an oral presentation to the Antimicrobial Resistance Centre at LSHTM in November 2020

This paper is currently (December 2020) under review at Critical Public Health

Chapter 5: Antibiotic Resistance, antibiotic prescribing, and medical sociology

Preface

So, the plot thickens. At this point in the thesis process, I had come to realise that the evidence base for some diagnostics for AMR is inconclusive (Paper 1; Chapter 2); the experts meant to adopt them in local-level NHS primary and secondary care contexts are unconvinced or in some cases downright sceptical (Chapter 3); and yet there appears to be wide-scale adoption of diagnostics in the top-level policy documents as the solution to the 'wicked problem' of AMR (Paper 2; Chapter 4). The 'crisis' alarm that was rung first by the public sector's technocrats, scientists, and doctors has been co-opted by the private sector, specifically the medical diagnostic and multinational pharmaceutical industries, to great success. This is in part because AMR suffers from being seen through a technocratic, value-neutral lens, and consequently, questions about uptake of diagnostics and investment in new drugs, appear to involve the private sector as a partner in an unquestioning way that would be far less likely in the unhealthy commodities industries. Such CDoH research was drawn on in the previous chapter. This is partly due to the 'blind spot' of value neutral technocracy. But CDoH and diagnostics are not the only areas where value neutrality and a positivist lens can influence AMR. The assumption underpinning the entire strategy of promoting, funding, developing and adopting diagnostics, as has been described in Chapters 2 and 3, is that faster, more accurate diagnosis of bacterial and viral infection, and drug resistance, will reduce antibiotic prescribing, reducing selective pressure on bacteria, and consequently reduce antibiotic resistance (or at the very least, slow down the rate and burden of resistant infections). However, it is rarely, in fact, the stated aim of AMR national action plans or international strategies that prescribing should decrease. What is frequently stated instead, is that the goal is to reduce *inappropriate* antibiotic prescribing. This is measured indirectly by reductions in prescribing, and monitored and audited using various prescribing feedback mechanisms in the UK. However, what is rarely known is whether a reduction of prescribing is, in fact, a reduction in *inappropriate* prescribing, or whether it means that equitable access to needed antibiotics for infections is reducing.

The concept of prescribing *appropriateness* is a normative construct being ascribed to a positivist position. There is a wide body of literature across the social sciences on antibiotic

prescribing and the challenges therein. Many academic traditions have developed an understanding of how and why some prescribers are given to 'inappropriate' prescribing of antibiotics. Health services research in this area has focused on the role that decreasing primary care appointment times has had on prescribing rates.(356) Other research in this area has also problematised the concept of 'appropriateness' in medical care.(357,358) In behavioural economics, there is an increasingly long list of interventions that can nudge patient and prescriber behaviours toward the more 'appropriate' end of the spectrum (such as letters to 'high' prescribers from the Chief Medical Officer.(359) We can turn to medical anthropology to understand that an antibiotic prescription is not simply a drug to cure an infection, it is imbued with cultural and social signifiers; it represents care, it represents a validation of patients' poorly state, and it represents a 'quick fix' for the pressures of modernity, including the inability for most workers globally to simply rest for 5-15 days with a self-limiting infection.(348,349,360) Recent work on etiquette in hospital prescribing and copious work undertaken in primary care furthers the field with respect to prescribing decisions, and medical identity, by showing how social norms, hierarchies, and professional jurisdictions shape these practices.(361–364)

This paper conducts further analysis of the 71 interviews from Chapter 3 chapter to help understand the issue of appropriate prescribing in AMR, and the ways in which this kind of disciplinary language is actively counter-productive. In this chapter, I am conducting secondary data analysis, as I am coding the parts of the qualitative interviews that I did not develop questions for in the interview topic guide.

In this paper I have explored Negotiated Order to move toward a generalised understanding of prescribing behaviour that is not jurisdictionally bound within a hospital, or GP practice. I have asked the research question: is it ever possible for health care professionals to prescribe 'appropriately'? I aim to bring into discussion the views of primary and secondary care antibiotic prescribers, rather than viewing The Hospital as distinct from The GP Practice. I have focussed on the cultures of prescribing as informed by the negotiations leading up to, and including, what I termed the *prescription moment* as informed by Strauss and Abbott. And, I aimed to develop, from my qualitative data, an explanation of why 'appropriate' prescribing is at best a misnomer, and at worst, actively unhelpful. Most of all, I aim to critically link this chapter with the wider concepts coming to the fore in this dissertation – namely, to the ways in which the private sector, government, and academics who present

AMR concepts such as appropriateness in value-neutral ways are in fact contributing to the framing as one that is highly amenable to corporate capture. Atheoretical and normative linguistic and discursive choices such as ‘appropriate’ are short-hand for shifting the burden of responsibility of prescribing behaviours past the health services constraints, the resourcing constraints, and the very real constraints of an aging population living with multiple comorbidities due to, *inter alia*, a decade of austerity and discrete choices to reduce health and well-being in the most disadvantaged in society, and co-opting the ‘personal (and professional) responsibility’ narrative so common in CDoH research.

The paper that follows is submitted to Critical Public Health, as of January 2020.

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First Name(s)	Rebecca		
Surname/Family Name	Glover		
Thesis Title	Antimicrobial resistance in the United Kingdom: a mixed-methods dissertation on diagnostics, discourse, and decision-making		
Primary Supervisor	Mark Petticrew		

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Student Signature	Rebecca Glover
Date	29 December 2020

Supervisor Signature	[redacted]
Date	07 January 2021

Paper III: Is it ever possible for health care professionals to prescribe antibiotics 'appropriately'?

Submitted to Critical Public Health, January 2020

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Abstract
In recent years, the United Kingdom has developed policies to reduce antibiotic resistance. The primary policy levers in the UK are focused on reducing antibiotic prescriptions. Reducing antibiotic prescribing has been conceptualised as equivalent to reducing *inappropriate* antibiotic prescribing, because of the difficulties associated with measuring the latter. We aim to shed light on negotiations and uncertainties as they pertain to the prescription of antibiotics in the UK. We conducted 71 qualitative semi-structured interviews in six local-level clinical commissioning groups (or equivalent): one site in Wales, Northern Ireland, and Scotland, and three in England. We thematically coded the data, and then recoded it focusing on the types of negotiation and relevant strategies deployed in these negotiations, drawing from Strauss and Abbott. We found that healthcare professionals can negotiate their prescribing behaviours in several ways. Appropriateness can take both the patient's and professional's needs into consideration, especially in primary care, and as such is contextually mediated. Finally, appropriate prescribing depends on monitoring and audit mechanisms – particularly *who* does the monitoring, *where* it is done, and *when.* Our paper problematises 'appropriate' antibiotic prescribing since the term is a short-hand for a constellation of managed uncertainties. Therefore, this kind of disciplinary language is counter-productive and may, in the long-term, lead to relationship breakdowns between

policy makers and front-line antibiotic prescribing staff. The ethos surrounding the measurement and monitoring of 'appropriate' prescribing needs to recognise the environment of uncertainty underpinning the development of the guidelines, and the practice of prescribing antibiotics.

Introduction:

In recent years, the United Kingdom (UK) has been a global leader in developing policies to reduce the risk of antibiotic resistance. This risk has been conceptualised as both a risk to life, and a risk to the economic status quo.(296,365) Several policy changes have been made in order to mitigate these risks. The primary policy lever in the UK is focused on reducing the opportunities for resistance to develop, meaning that there needs to be less selective pressure on bacteria. This may be achieved by issuing fewer antibiotic prescriptions, since antibiotics preferentially select for the evolution of bacteria with resistance mechanisms. In practice, reducing antibiotic prescriptions tends to be conceptualised as equivalent to reducing inappropriate prescribing, because of the difficulties associated with defining and measuring the latter.(21,22) To that end, incentive payments called quality premiums have been attached to reducing antibiotic prescribing in primary and secondary care in England.(17)

The definition of what is considered 'appropriate' antibiotic prescribing has changed dramatically over time. While Alexander Fleming's prescient warnings of antimicrobial resistance are oft-cited in contemporary work in this area, they can be quoted out-of-context. Fleming correctly warned about the dangers of resistance, but only as a result of *taking an insufficient dose* of antibiotics. The discoverer of antibiotics wrote, in his 1945 Nobel Prize lecture: (366)

> *The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant. Here is a hypothetical illustration. Mr. X. has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies. Who is primarily responsible for Mrs. X's death? Why Mr. X whose negligent use of penicillin changed the nature of the microbe.* ***Moral: If you use penicillin, use enough.***

Newer guidelines target the over-prescription of antibiotics for self-limiting infections, and cite evidence of the often minimal impact of antibiotics on the duration of even more serious illness, such as bacterial bronchitis and pneumonia.(367–369) Current discourse, then, supersedes Fleming's *judicious use of sufficient dose,* and moves toward *judicious refusal to prescribe* antibiotics in the first instance. However, current antibiotic prescribing guidelines are not entirely evidence-based, at least in part because it is difficult to obtain ethical approval to undertake the trials needed to test conventional doses and durations of antibiotic courses. More broadly, though, postmodernist critiques of 'evidence-based medicine' centre on the fact that guidelines falsely promise an objective truth, or 'best' approach, when their creation is heavily mediated by social factors.(370,371) What is termed inappropriate prescribing is, in fact, better described as guideline-discordant prescribing. We wanted to know how health care professionals negotiate the interaction between guidelines, their professional judgments, and their patients' needs, within the context of these uncertainties in

UK primary and secondary care, and asked: is it ever possible for health care professionals to prescribe antibiotics appropriately?

Antibiotic prescribing practices in the UK : practice and theory

The last 25 years have been a time of great antibiotic prescribing change in the UK. While antibiotic prescribing used only to be the purview of doctors, now this practice is shared among doctors, dentists, nurses, pharmacists, physiotherapists, midwives and others. This trend of widening antibiotic prescribing practices has been occurring in Western European and Anglo-Saxon countries; Australia, Canada, Ireland, New Zealand, Sweden, the UK and the USA have had nurse prescribing for over a decade.(372) Pharmacist prescribers, however, are less common, though the UK, Canada, and New Zealand have introduced different modalities of this practice.(373) The UK has been at the vanguard of pharmacist prescribing, having introduced legislation supporting this in 2006.(374) Moreover, in recent years as AMR has become a priority policy focus in the Department of Health and Social Care (DHSC, previously the Department of Health), the number of economic incentives for so-called 'appropriate' prescribing has increased, alongside ancillary audit, monitoring and evaluation requirements.(375,376) This has resulted in GPs and hospital doctors being monitored by antimicrobial pharmacists and Clinical Commissioning Groups (CCGs) or equivalent medicines management officials.(377) In the UK, therefore, the approach to improving the use of antibiotics has become top-down, led from the centre, hierarchical, and governed by disciplinary and financial measures. These are tried and tested policy levers, but there remains a compliance gap between antibiotic prescribing guidance and real-world antibiotic prescribing.

This compliance gap has been shown to be socially mediated, complicated, and, crucially, negotiated.(378–381) Broom et al's work on the negotiations between pharmacists and doctors in Australia, where pharmacists could not prescribe, drew on Strauss' theory of negotiated order and Abbott's work on professional hierarchies.(77,78) Strauss developed his theory of negotiated order first to explain the ways in which individuals, on behalf of organisations, undertake the covert and overt tasks, and implement the rules, regulations, and requirements of their positions.(77) Negotiation occurs in a negotiation *context*, which is informed by previous negotiations that have been undertaken and the contexts where these have taken place, assimilated into an order. Abbott helps further to clarify the organisation of professions and professionals into power structures. If a profession is 'an occupational group with some special skill' then whatever framework is adopted to understand a profession – functional, structural, monopolist, or cultural, the goal is the acquisition of power due to the professionalization of that skill.(78) Overall, any professional claim to jurisdiction tends classically to also be a claim to exclusivity. This exclusivity is maintained, or developed, through training and accreditation. This is why these theories, taken together, are particularly relevant to the context of antibiotic prescribing, and efforts to audit, monitor, and oversee prescribing behaviours.

Strauss and Abbott's theoretical contributions have been deployed in concert to analyse other hospital contexts. For example, Allen turned to Strauss and Abbott in order to describe the negotiations undertaken to modify the day-to-day occupational responsibilities of nurses and doctors in the UK within the context of nurse educational reforms.(382) Incidentally, one area in which nurses were being encouraged to increase their skillset was the administration of intravenous antibiotics.

Our research draws on Strauss and Abbott to examine at interprofessional relationships in the United Kingdom. We wanted to determine whether pharmacists' ability to prescribe antibiotics influenced the extent to which Strauss' Negotiated Order could be called on to describe the interprofessional interactions, and whether Abbott's jurisdictional friction would be amplified with more professionals able to prescribe than in Broom et al's initial work in this arena. Second, we have extended our qualitative interviews beyond the four walls of the hospital to include similar negotiations taking place between professional groups in primary care. GPs, for instance, rely on hospital and laboratory staff for input related to diagnosis and prescribing of antibiotics. While care settings are important, and different enough to drive major differences in practice and antibiotic prescribing between sites, the direction of health policies in the UK and other high income countries is toward increasing integration of services, and innovation in health care delivery.(383,384) When facing an aging population and a decade of austerity following the Global Financial Crisis (GFC), the UK is aiming to push GPs into forming clusters, strengthen links between hospitals and community services, and integrate primary and secondary care services across the board.(385,386) It is fitting, therefore, to further develop an understanding of antibiotic prescribing behaviours across care settings.

Methods

Study design

We conducted a policy evaluation for the Department of Health and Social Care in the United Kingdom on the implementation of the UK Five-Year Antimicrobial Resistance Strategy 2013-18 (the Strategy). One part of the study comprised the study of six local health care settings across the United Kingdom. Case studies are useful tools for in-depth explorations of the *prescribing moment* and its context, as described by the prescribers.(387)

We selected six CCGs (or equivalent outside England) as local study sites. We chose one site in Wales, Northern Ireland, and Scotland, and three in England, including an urban site, a northern peri-urban site and a rural site.

We obtained host institution ethical approval and HRA approval.

Data collection

We conducted between 10 and 14 semi-structured interviews in each CCG or equivalent across primary and secondary care, and the CCG management between January 2017 and September 2018. Seventy-one one-on-one semi-structured interviews were completed. The interviews varied in length between 15 and 90 minutes. We selected our qualifying professionals purposively, and often on the advice of a local contact, either a member of the medicines management CCG teams, or the medical director of an NHS trust. We aimed to include finance directors from acute trusts; microbiologists; infectious disease consultants; junior doctors; nurse prescribers; ward nurses; consultant pharmacists; antimicrobial pharmacists; medicines management teams; chief executives of CCGs and acute trusts; professional education deliverers; GPs; public health officials; and infection prevention and control experts. We were able to interview all of these positions at least twice across the six case study sites. We interviewed a microbiologist, someone in a senior infection prevention and control (IPC) role, a nurse, a pharmacist, a GP, a non-microbiologist hospital doctor, and a non-executive member of the NHS acute trust board in each of the six sites.

Our six case study sites are named in the public domain (Betsi Cadwaladr, Blackburn with Darwen, Camden, Western Health and Social Care, Greater Glasgow and Clyde, and West Norfolk). These six sites were selected because they are composed of populations covering

the maximum variation of variables that may plausibly affect uptake of technology and AMR rates, as reported in the literature on AMR transmission: urban/rural, affluent/deprived, high/low HCAI rates, and high/low rates of antibiotic prescribing have all been posited in the literature to influence the emergence, transmission, and burden of AMR.(318–321) To that end, selection of unique sites in diverse contexts provided greater opportunities for learning. (315,316,322–324)

In this paper, we felt it more helpful to name the type of professional and anonymise the site rather than naming the site and grouping the professionals into larger categories to ensure anonymity. We therefore used random letters (ABSWXY) to describe each site in question.

Data analysis

We employed an interpretivist qualitative approach using both inductive and deductive logics.(388)

We approached the analysis by first thematically coding the data, and then recoding focusing on the types of negotiation mentioned specifically by Strauss: bargaining, consensus, collaboration, kick-backs, stability-instability, and order-disorder. We included a 'strategies' extension to the Straussian theory, as proposed by Maines and Charlton, which we adapted and used to capture when the interviewee was cognisant of their position within a negotiation, and explicitly listed strategies that they deployed in order to achieve their desired result.(389) In order to capture Abbott's work on professional jurisdictions, when there were examples of these negotiations occurring, we coded them as interprofessional, intraprofessional, or professional-patient, with a subgroup for patient proxies, such as relatives.(78)

Findings

Appropriateness is co-constructed among professionals

Healthcare professionals can negotiate their prescribing behaviours amongst each other due to diagnostic, prognostic, and treatment uncertainties inherent in the *prescribing moment.* Such negotiations appeared to be most successful when the Straussian conditions of compromise and consensus were met. In case study A, for example, doctors described the negotiation between surgeons, microbiologists, pharmacists, and infectious disease clinicians over time. There was an initially unsuccessful introduction of new guidelines to prescribe an antibiotic called gentamycin for patients who were suspected of having serious bloodstream infections. In spite of the guidance being predicated upon the best available evidence and compiled by experts in infectious diseases, microbiology, and pharmacy, the surgeons refused to prescribe gentamycin following a patient developing hearing loss, a known side-effect of that drug. Instead, surgeons would prescribe meropenem, a broad-spectrum antibiotic of last resort. One infectious disease consultant describes the process of compromise that was undertaken in this case in order to spare meropenem:

> *...so we introduced an antibiotic called aztreonam as an alternative to gentamycin, to try and prevent them prescribing […] meropenem. And, with a lot of very good work* ***from our antimicrobial pharmacist and our local micro biologist in that particular hospital, they switched away from these very broad spectrum antibiotics, to these narrow spectrum antibiotics***.

In this case, where a third antibiotic was introduced as a 'compromise' antibiotic following negotiations ending in consensus between engaged stakeholders, it is clear that initial views on what constituted an 'appropriate' antibiotic differed among professionals.

This compromise required engagement in questions of prescribing, which is not always a given. Many hospital clinicians in the six sites professed to defer to 'experts' in prescribing – normally infectious disease consultants or microbiologists, though occasionally doctors also cited antimicrobial pharmacists as examples of the experts that they would defer to. These clinicians' self-described deference is an example of Strauss's 'passive' negotiation whereby deferring to 'experts' and not engaging in decision-making can proliferate poor practise.

Due to resourcing constraints, it is unlikely that doctors can access advice about antibiotics at each prescribing moment. Therefore, doctors can reinforce their poor prescribing practices by apply what a microbiologist or pharmacist said about a previous patient, without always acknowledging the full difference between patients. This was reinforced in our data by hospital-based pharmacists and microbiologists alike. One microbiologist in Case Study X explained what they thought about prescribers' abnegation of responsibility in hospitals:

> *Where does the responsibility lie? […] fundamentally,* ***responsibility for all these demands should lie on the person interacting with the patient****. They should feel that they are responsible for this, whereas I think that, if there's a problem relating to resistant bugs on a certain ward, there's a belief that, oh, IPC and micro will sort that out, and I can tootle off and do something else.* ***Well, possibly, but it's still your patient; it's not mine. […] doctors must take ownership for the totality of care […]***

This microbiologist is voicing concerns about those who view professional jurisdictions as exclusive, or overly simplistic, and is advocating for more shared responsibility among professionals, as we saw in case study A.

In primary care, there is a similar mix of professionals interacting with respect to prescribing. However, the prescription moment is spatially and temporally more disparate from the interactions between the prescriber and other experts such as microbiologists or antimicrobial pharmacists. As such, there is a less well-developed understanding of what other professionals can offer to the prescribing moment. Moreover, patients tend not to be as acutely unwell. A GP in Case Study Y said about microbiologists' usefulness in antibiotic prescribing in the community:

> *I think we sometimes just see the lab as a, you know, they'll find the bug and you know, that's what they do, but* ***actually quite a bit of clinical thinking needs to go behind that, that's why microbiology is, you know, at least in part a clinical discipline.***

<u>Appropriateness takes the patient's and professional's needs into consideration</u>

Appropriate prescribing is also a negotiation between a patient and professional, especially in primary care. In this circumstance, delayed prescribing was widely used as a strategy to compromise with patients in the presence of diagnostic or prognostic uncertainties. This tool was often used in cases where patients were unwell and one of the following other conditions was met at the time of the consultation: the patient was about to travel for a holiday; it was a

Friday; or the patient was determined to receive an antibiotic, according to the perception of the GP.

> *…if we think, no actually I'm pretty sure this is viral we'll say to them* ***I really think this is viral****,* ***advise*** *about symptomatic treatment and maybe* ***say****, if you're no better in* ***three days****, let reception know and I will* ***let you have a prescription for an antibiotic at that stage.***

If prescribers have patients who present with a suspected – but not confirmed – diagnosis of a bacterial upper respiratory condition, and they believe – though do not know – that the patient can manage with self-care alone, the prescriber may negotiate these two uncertainties by issuing a delayed prescription.

This uncertainty can be also seen in particular in the categorising of patients perceived as too old, too young, or too systemically unwell not to receive antibiotics. This is not considered to be guideline-discordant, or 'inappropriate' prescribing. A patient's frailty is an independent indication for an antibiotic script. However, the fuzzy boundary between true prognostic uncertainty and a 'what-if' catch-all means that this particular exception is being used when relatively little uncertainty exists.

In Case study A, an infectious disease consultant said of prescribers in her/his hospital:

> *But, it's like many areas, I think they identified themselves as slightly special, different patient group, maybe more complex. But, in fact, when you drill down into it, the majority of patients aren't, the majority of patients are like, you know,*

patients you have in this hospital, or hospital x, or hospital y. So, they were, kind of, exceptionalising themselves when, in fact, the majority of patients could be managed the same way, wherever they were.

This decision to prescribe even though the guidelines might contra-indicate is often associated with a concern about NHS acute trusts not supporting doctors; defensive medicine; and fears about being struck off.

A junior doctor in Case Study A said:

[…]the NHS is moving into a more of a litigation phase in how medicine is being practised. So, patients, and patients' families are becoming more and more interested in exactly what is being done and why it's being done. So, doctors are also practising more defensive medicines. So, discharges are taking longer and longer as well.

The concern about defensive medicine indicates that judgments – intra-personal negotiations – are being made in practitioners' minds about the relative risks of misjudging the balance of diagnostic, prognostic, and treatment uncertainties. If an antibiotic is prescribed unnecessarily, the immediate outcome is likely to be insignificant, and indirect. The practitioner is unlikely to face serious professional consequences, and the weight of one 'exceptional' and less defensible prescription is unlikely to wholly cause a hospital or a GP to lose their quality premium. However, the risk of misjudging the weights of these uncertainties in real-time is serious patient and thus professional harm.

Matters of hierarchy: hierarchy matters!

Another way in which our data have shown that appropriate prescribing is situational, and consequently not fixed, is the tension between prescribing behaviours and the top-down antibiotic prescription metrics, which are clarified in respondents' views of monitoring and evaluation.

Monitoring and audit is conducted in primary and secondary care, in combination with the relative weights of uncertainties for a given patient, feed into the decision taken by the health care professional at the prescribing moment. Auditors tend to be antimicrobial pharmacists and nurses, and their expanding role as expert-auditors influenced the views of prescribers in both primary and secondary care about their usefulness, albeit in different ways. Overall, when antibiotic prescribing monitoring was undertaken near the patient, at individual level, and in real time, it was more impactful and integrated into the existing organisational context than otherwise.

In primary care, pharmacists may monitor the prescribing undertaken by GPs and nurse prescribers. A pharmacist may sit within a practice, or may rotate between practices, in order to evaluate and feed back on the prescribing patterns of a particular clinic. Pharmacists tend to be funded external to the practice, for example, by the CCG. In this context, informants were mainly positive about this process, especially in resource-deprived settings such as case study sites W and B, where informants saw the pharmacists as an additional resource whose purpose was to help GPs with their workload. When pharmacists were seen as less directly helpful, however, opinions could also be more negative, dismissive, and sometimes even

gendered. In case study S, one GP, when asked about the role of an in-practice antimicrobial pharmacist paid for by the CCG who was reviewing doctors' antibiotic prescribing, said:

> *We've got a practice support pharmacist who encourages us to prescribe appropriately but it's mainly encouraging. She's a very useful, very clever girl, she is, but she doesn't tell us what to do, she advises.*

A GP in case study B was also sceptical of their CCG-funded pharmacist/auditor, opining that the role of the auditor was to save the local area money, not, in fact to improve prescribing at all.

These inter-professional hierarchies and jurisdictional frictions can compound poor practice, especially when there is an othering mentality underpinning prescribers' assumptions. When asked to describe the health care-acquired infection work happening in her/his hospital, much of which involves monitoring roles, the medical director of Case study B said s/he could not because it was led by the Director of Infection Prevention and Control. When asked to elaborate, s/he replied:

> *[…]infection prevention and control is nurse-led, whereas anti-microbial is a doctor thing and you can see from what I'm saying, I'm doing the doctor stuff.*

There is, however, a difference between key informants' views on pharmacists and nurse prescribers conducting auditing, and the monitoring itself. In general, monitoring activities that tended to be further removed in both time and space from the prescribing moment were viewed less favourably by our interviewees. An outlier was a commissioner in Case study A:

> *[Pharmacists] will usually visit practices on an annual basis and as part of that visit will give feedback about latest developments, about current kind of performance levels and tools to assist GPs in best prescribing. There's often, you know, very good continuity and it's the same person who tends to go back to that same practice year after year, and they know quite a lot about the history of the practice.*

This divergent quotation came from a commissioner whose responsibilities included commissioning community pharmacists to undertake prescribing feedback, but in general, when the feedback sessions were so rare (annually), our key informants were underwhelmed by, or even dismissive of, the impact they had.

Discussion

Overall, the appropriateness of any particular antibiotic therapy is co-constructed amongst professionals, between patient and professionals, and even intra-personally. Monitoring and audit mechanisms – particularly *who* does the monitoring, *where* it is done, and *when* – mediate our aggregate understanding of prescribing and its appropriateness. Consequently, appropriate prescribing for any given problem cannot readily be described as a binary state, or even as a spectrum between most and least appropriate, but rather as a constellation of managed uncertainties. The type and magnitude of these uncertainties influenced the negotiation context and consequently the interviewees' views of, and decision-making in, the prescription moment.

Most of our respondents found prescribing guidance useful. Rather like Porter and O'Halloran's responses to the postmodernist critiques of evidence-based practice,(370,371)

our respondents felt that guidance was necessary, but not sufficient, to describe antibiotic prescribing realities. In spite of their perceived usefulness, assigning an ‘appropriate’ or ‘inappropriate’ label to guideline concordance and antibiotic prescribing is necessarily power-laden, and exceptionalising is a key negotiation strategy for prescribers. However, over time, conditions are created for these exceptions to be rolled into social norms of prescribing behaviour, jurisdictional boundaries, and the like. And indeed, these ambiguities, Strauss argued, require negotiation, and negotiation in turn facilitates organisational work (389). This conception of organisational authority as stable – and rational – has been challenged by various scholars, including Stelling and Bucher, and Frieden, who used the weaknesses in this area in order to insist that the ideas underpinning the negotiation and distinct roles in a hierarchy are due, fundamentally, to social interactionism.(390,391) In spite of these critiques, negotiated order can operate at the meso-level to describe the negotiation process inherent in antibiotic prescribing. And, furthering the foundational work of Broom et al, Strauss and Abbott can be deployed to extend the analysis to encompass both primary and secondary care prescribing, and to work toward understanding the multiple boundaries of antibiotic prescribing between groups of professionals.

Our findings also demonstrated that GPs in resource-deprived settings were most positive about the contributions of antimicrobial pharmacists. This differed from the earlier work of Allen, which found that, whilst doctors held favourable views of nurses assuming some of their roles, such as the case of antibiotic administration, any work approaching diagnosis by nurses was more likely to be contested.(382) The disparity between our results and previous studies in this field demonstrates that meso-and macro-level constraints to best practice – such as resourcing concerns – can challenge Abbott’s assertions that there are fixed components to professional identities in work in health organisations.(78,392)

There are several limitations to our research, chief among them being that we have diverged from the ethnographic tradition of much of the previous research using the Theory of Negotiated Order, such as Allen's work in 1997. Ours lacks extensive observations, having been predicated upon one-off interviews, without field notes or long-term placements. This is a known limitation when using Strauss' theory. Reeves et al point to this as a reason for why our understanding of professional negotiation and relationships stays at the level of 'abstracted empiricism'.(392) However, what we have done is taken a broad look at the negotiation context. This has let us theorise about the multiple working organisations and professionals operating within this meso-level space across six divergent case study sites across the UK, but has not stretched to allow us to interrogate our analysis on the wards or in the clinics over time.

If the term 'appropriate' is to be used with respect to prescribing behaviours, then we assert that *appropriate* prescribing is more likely to occur with multiple professionals linked together in a well-understood hierarchy, with internal audit mechanisms that are patient-based, and with cooperative and consensus-led iterative adaptations to prescribing over the course of a patient's admission or visit. Whereas *reductions* in prescribing are likely to be achieved with financial incentives and behavioural interventions implemented following audit mechanisms.(17,21) This is not to say that these reductions are inappropriate, but in those (over)-prescription cases, these are likely to be contextually appropriate, or at least contextually mediated, given the uncertainties in the patient interaction, the constraints of the health services, and the negotiations undertaken with the patient, the medical community, and future monitoring and audit mechanisms.

To conclude, top-down policy-setting and centralised targets are named components of the UK's – and other countries' - AMR policy strategies for the next five years. However, this is setting up prescribers for failure because appropriateness is a constellation of mediated uncertainties. Where monitoring and audit needs to occur, these should be developmental, not disciplinary; these should be proximal to the patient in time; and these should be undertaken at the individual level before being aggregated.

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Declaration of Interest:
All Authors declare no interests

Impact, engagement, and dissemination

The early findings from this chapter were presented in a rapid-fire talk at the conference for the Society for Social Medicine in Cork, Ireland, in September 2019 (Appendix: Document 7). The abstract for the talk was, along with all peer-reviewed abstracts for the conference, published in a supplement of the Journal for Epidemiology and Community Health.

The analysis and interpretation comprised a sizeable part of a one-hour seminar I gave at LSHTM's Antimicrobial Resistance Centre on 3 November 2020.

Since then, the paper was submitted to Critical Public Health (January, 2021)

DISCUSSION

Preface

This research programme took as its starting point the interrogation of the evidence base forrapid diagnostic tests; continued by examining views of prescribers on their adoption (or non-adoption) in the UK; conducted a critical discourse analysis of the evidence submitted to the Health and Social Care committee on AMR in 2018; and concluded by problematising one of the crucial concepts – appropriateness - in AMR and antibiotic prescribing. I conducted four studies on these topics. The first study was a systematic review and meta-analysis of the clinical effectiveness of rapid diagnostic tests for bacterial identification and antibiotic susceptibility testing. The second, which was written up in chapter form, was a qualitative analysis of qualitative interview data in six case study sites across the UK with respect to key service users' views on rapid diagnostic tests in primary and secondary care. The third and fourth studies were a critical discourse analysis of the submissions to the parliamentary Health and Social Care Committee on AMR and a secondary analysis of the qualitative interviews problematising the concept of 'appropriateness' of antibiotic prescribing.

These latter two studies were informed by the key findings from early phases of the PhD that i) therapid diagnostic tests examined by the systematic review do not appear to be clinically effective (that is, they do not inform decisions about clinical care in any way that clearly is of clinical benefit to patients), and ii) care providers had serious questions about the usefulness of these tests, and whetherrapid diagnostic tests in care settings were contributing benefits, if they were indeed contributing to patient care at all. Studies three and four were more critical, therefore, of the dominant narratives of diagnostic technologies, and their findings suggested that iii) corporate interests in AMR behave similarly to other private interests in the Commercial Determinants of Health, but have not received the same research attention as it would have if it were unhealthy commodities industries and iv) that the concept of 'appropriate' antimicrobial prescribing is at the heart of why diagnostics seem to be such an enticing solution to the problem of AMR; namely, a push towards concepts like 'appropriate' prescribing shifts the burden away from structural, macro- or meso-level solutions, such as adequate resourcing, and onto the individual professional or patient.

This final chapter puts these findings in context. There are seven main sections:

1. Situating the systematic review within the context of studies 2, 3, and 4
2. Methodological contributions following on from the systematic review
3. Situating my work within the larger fields of Commercial Determinants of Health
4. Situating my work within the contemporary context of COVID-19
5. Meta-research findings and the elusive 'red thread'
6. Paper IV, and
7. Strengths, limitations, and areas for future research.

1. Situating the systematic review within the context of studies 2, 3, and 4

Overall, studies two, three, and four can help to contextualise and deepen the interpretation of the findings from the systematic review.

Mortality, length of stay, and turnaround time:

The meta-analyses of mortality and length of stay which I conducted in my first study suggested that any purported improvements due torapid diagnostic tests were only found in pre-post quasi-experimental and observational study designs and not in the RCTs. On turnaround time, papers reported many different segments of the bacteriological sampling pathway – creating the conditions where definitional heterogeneity precluded comparing even apples with apples.

However, upon completion of the qualitative interviews, it was clear that there were in any case very mixed views from clinicians (and health care workers more broadly) about the clinical benefits of such diagnostic technologies. When the qualitative analysis was restricted to the types of diagnostic technologies reviewed in the systematic review – primarily MALDI-TOF MS and real-time, quantitative PCR, the views of the microbiologist, pharmacist, and infectious disease experts on the whole was that the tests were only as helpful as funding for a 24-hour laboratory service would be. Moreover, these experts felt the tests were not helpful enough to warrant switching to an off-site centralised laboratory, which was one of the funding models that has been hypothesised as necessary for local non-teaching hospital laboratories to be able to afford these technologies. Only RITs and the MALDI-TOF mass spectrometer received largely positive comments, though in the case of the MALDI-TOF MS, this was not the case from sites that had experience using one. In the site that already had a MALDI-TOF mass spectrometer, either it was described as having been vastly less useful than hoped or, in the resource-constrained sites, the new technology represented a

significant investment in laboratory services that was perceived to be in addition to day-to-day costs or the block laboratory contract; a one-off 'top-up' in funding. To contextualise these findings further, we can also draw from the fourth study (on problematising appropriate prescribing), where monitoring and audit was viewed most favourably in resource-constrained settings. This occurred when the presence of an antimicrobial pharmacist or nurse prescriber in the GP practice was paid for centrally, and was not seen to be coming from the local-level funding pot. In this context, monitoring and audit was seen as positive not because of the actual activity of monitoring and audit, but because antimicrobial pharmacists, who often also saw acute uncomplicated upper respiratory tract patients, or conducted medicines reviews in primary care – both activities that would otherwise have to be undertaken by the core GP and nursing team – were seen as an additional, externally-funded resource to help manage the day-to-day running of the GP service.

(ii) Appropriateness of antibiotic prescription

With respect to appropriateness of antibiotic prescribing, it was found in the systematic review that there were too many endpoints in the included study to make a comparison between any single category of endpoints. Occasionally, the authors of included papers suggested in their discussion sections that diagnostic tests were (i) improving de-escalation (the process of switching from intravenous to oral antibiotics), (ii) increasing the speed and frequency with which patients were switched from broad to narrow spectrum antibiotics, and (iii) getting patients onto an 'appropriate' antibiotic sooner (the antibiotic that provided coverage against the bacterial infection of the patient). It was not possible to synthesise this outcome data across studies, and these data were also not readily able to be disaggregated by the various other components of the intervention. For example, in many of the pre-post quasi-experimental study designs, the introduction of the rapid diagnostic test also coincided with training for ward-based staff and laboratory staff on the types of information that the diagnostic could provide, and how to tailor antibiotics based on the results that were returned. In many cases, the introduction of the diagnostic test also coincided with major health services modifications, such as introducing a 24-hour laboratory. Bringing in the findings from my second study, one of the most frequently described relative advantages of diagnostic technologies in primary care was the ability to use these tests as a way to facilitate communication with patients. While communication with patients is unlikely to be as relevant in the secondary care context, there is certainly a case for assuming that any

communication and knowledge training that increased or facilitated the relationship between laboratory staff and ward-based prescribers would have been an important confounding variable when it comes to assessing the effectiveness of the diagnostic technology at improving care. This can be seen in a wide range of studies in the field of antimicrobial stewardship.(393–396) For example, it is known that intervention bundles can have interactive and multiplicative effects, and this has been demonstrated previously in quality improvement studies that assess the introduction of communication interventions in combination with changes to antibiotic prescribing guidelines, changes to audit and monitoring, other enabling or punitive stewardship interventions, or a combination of these.(23,397–401)

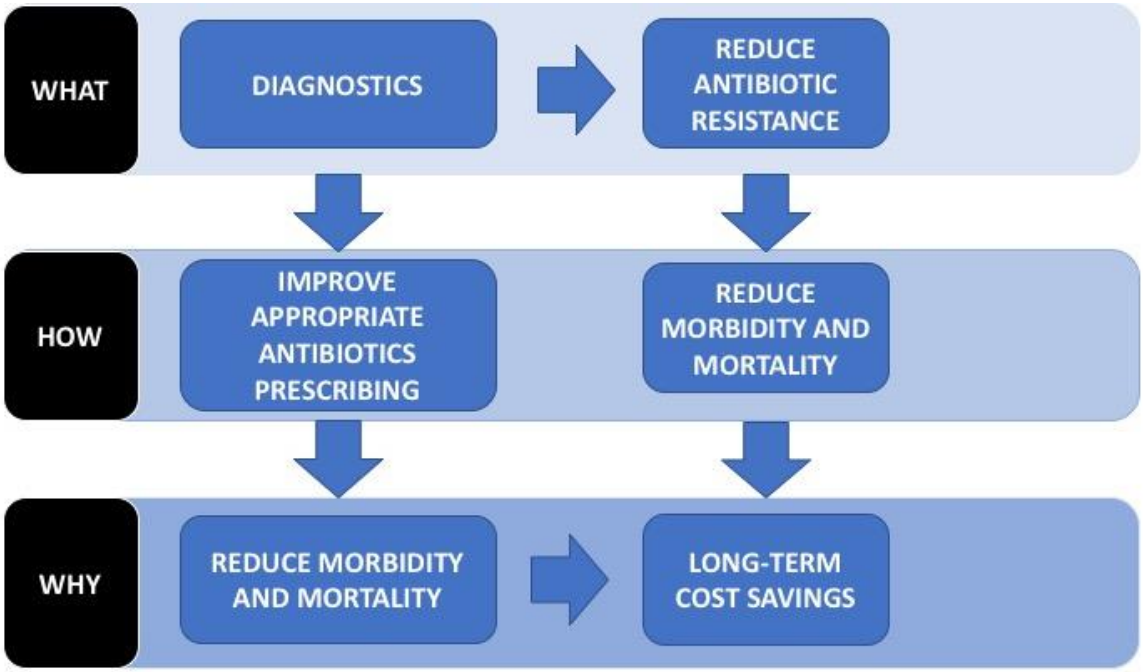
Of course, the fourth study problematising the concept of appropriate prescribing demonstrated that appropriateness is contextually mediated; and, in hospitals at least, dependent on compromise, negotiation, and other concepts that are rooted in meso-level organisational theories and in an understanding of professional jurisdictional tensions. These qualitative data informed my view of the systematic review findings on whether diagnostic tests reduced inappropriate prescribing. Or, more precisely, the analysis I presented in the fourth and final study has, cyclically, questioned whether 'dorapid diagnostic tests reduce 'inappropriate' prescribing' is even a sensible question. 'Appropriate' prescribing is, at best, of use in a limited and specific performance management way, when audit and monitoring is proximal in space and time to an individual patient's treatment. At worst, however, it has been used as a term to justify the adoption of technologies of limited use, as seen in the systematic review, and has allowed for the circumvention of the very real problems of underfunding of the NHS in favour of an alleged technological silver bullet. Of course, if diagnostic technology were truly a quick fix to AMR, it would not be without its allure. However, this seems not to be the case, across all four studies I conducted.

The context described in the fourth study is also relevant with respect to the wide-scale system-level policy changes being brought in in the UK and around the world. Many of the studies included in the systematic review were conducted between 2013 and 2017. At an international level, AMR was becoming increasingly prominent as a health topic of concern, as demonstrated by the resolutions tabled at the UN and G20, and the WHO's monitoring and evaluation exercise of evaluating countries' progress on developing AMR national action plans.(14–16) At a national level, the UK introduced multiple quality premiums in primary

and secondary care related to reducing prescribing, and in particular reducing prescribing of last-line antibiotics.(17–19) This was not an aberration; the USA, the Netherlands, France, Belgium, Canada, and Ireland – the countries contributing the largest proportion of studies to my systematic review - all introduced policies, task forces, or extended monitoring and audit activities in antimicrobial resistance within this time period.(402–405)

In the UK alone, antimicrobial pharmacists were brought in-post, quality premiums were introduced in primary and secondary care (as described in study four) antibiotic prescribing audit and monitoring processes were brought in to de-escalate and reduce antibiotic prescribing, and education on AMR was integrated into the national nursing and medical curricula.(273,274,276,377,406) GP practice and hospital prescribing rates across over sixty indicators were made publicly searchable in 2017 with PHE's "Fingertips" dashboard.(407) National and international policy were changing alongside the introduction of diagnostic technologies, within the context of increasing monitoring. Antimicrobial resistance was high on the political agenda because it was understood that, by reducing antibiotic resistance, and reducing morbidity and mortality due to it, there would be massive long-term cost savings (Figure 7).

Figure 14 Simplified logic model about the role of diagnostics in long-term cost savings for the health service



The UK government's policy guidance has been consistent throughout the last nine years, and the direction of travel has only been towards diagnostic testing. Increasing the uptake of diagnostics will, apparently, reduce antibiotic resistance; by employing diagnostic tests, health care workers will ensure patients are placed on the correct antibiotic therapy – or none whatsoever – sooner, meaning that patients should improve faster, reducing required treatment times, and ensuring that patients spend no more time than necessary on an antibiotic. This reduces antibiotic resistance by reducing all but the most necessary courses of antibiotics, thereby reducing the selective pressure on bacteria.

The problem with this logic is that this is not what my systematic review and meta-analysis found, and certainly not what was found when contextualised among the other three studies. Diagnostics are not a panacea, according to front-line workers. Microbiologists are more likely to want diagnostics than other prescribers, but not universally. Infection prevention and control nurses prefer the idea of some rapid diagnostics over others. RITs based in the ward were the most positively cited example of a diagnostic tests. Not all tests are created equal, and the high-level policy push for more and better diagnostics is being co-opted and contorted in the lobbying points in the corporate messaging, and in the policy direction taken by national government.

2. Methodological considerations following on from the systematic review

Overall, I demonstrated in my systematic review that some diagnostic tests can be combined in meta-analyses even if testing for different pathogens and/or bacteria because of their position *in the care pathway.* The main critique from my paper's peer reviewers at the first journals I submitted to (Lancet Infectious Diseases, Journal of Antimicrobial Chemotherapy) centred upon my meta-analysis and choices to aggregate diagnostic technologies. This made me reflect upon the problems I faced throughout the entire systematic review and meta-analysis process. Chief among them was a feeling that many of papers were falling out of the meta-analysis. That is to say, the full texts had been deemed relevant, and had been included in the 58 studies that had made the final systematic review. Those studies included at least one of my outcomes of interest. However, when it came to the final meta-analyses, even though I undertook ones on length of stay, mortality, and had planned to include meta-analyses of antibiotic stewardship outcomes and turnaround time outcomes, the first two categories with meta-analyses had fewer than 10 studies in them, and I could not meta-

analyse the antibiotic stewardship or turnaround time outcomes. I felt it necessary to systematically track what, after inclusion, was happening to all my included studies. I undertook this exercise drawing theoretically from descriptions of the purpose of the PRISMA diagram in systematic reviews, as follows.(408–410)

The PRISMA diagram is a reporting guideline for systematic reviews. It is a type of flow chart that includes a minimum set of data that allows readers to follow the journey of the papers through the systematic review title/abstract/full text screening process. In practice it does not always include information about why studies are excluded at each stage of screening, though it should. It also often includes a box showing the progression from all articles identified for inclusion in the overall narrative review to the subset of those that are also appropriate to include for meta-analysis. However, there is at the time of writing no current PRISMA reporting requirement to describe why studies are excluded from meta-analysis but included in narrative synthesis. The most recent guidance on the PRISMA flow diagrams specifically is from 2009, (the 2015 and 2020 updated guidance do not update this part of the guidance) and while it does include the recommendation to include the number of studies that are excluded from the quantitative synthesis, there is no requirement to report the reasons for exclusion from quantitative synthesis, though it is often included in any table that lists each study included in the narrative synthesis.(410) It is also usually reported in the results section of the paper. However, the particular reasons for exclusion are rarely *analysed* within reviews themselves, and even less frequently analysed in reviews of reviews.

There are many reasons why studies should be excluded from quantitative synthesis. They are non-trivial and likely to vary across fields. One major reason is poor study quality.(411) There are many other reasons why studies may be excluded from a meta-analysis, especially in areas where there is a paucity of evidence, or in newer fields. Moreover, the problems do not only derive from the exclusion of studies *per se*, but also about the fact that this leaves a much small pool of studies to work with as well as the need to statistically manipulate the included papers in order to aggregate them due to external or statistical heterogeneity.

I have demonstrated that a Sankey diagram can be used to categorise the problems inherent in meta-analyses in the field of rapid diagnostic test clinical effectiveness, which is vastly less populated than the field of diagnostic tests accuracy. If Sankey or similar flow diagrams are regularly adopted in systematic reviews in future, it will allow for the comparison of the types

of exclusion patterns in different sectors and for a more systematic analysis of the reasons for exclusion from meta-analysis. Antimicrobial resistance diagnostics studies, for example, appear to suffer strikingly from a wide variety of definitions across antimicrobial stewardship and turnaround time outcomes. This may be unusual for systematic reviews, or it may be perfectly common to suffer from such definitional heterogeneity. The point, however, is that it is not possible to assess *how* normal or abnormal this practice is without working toward transparent and comparable processes for reporting on such data.

A priori, it seems as if in this field each individual paper that reports on its own very specific and completely different antibiotic stewardship outcome of interest – and its own very specific turnaround time definition – may be trying to demonstrate an impact of the intervention in whatever way possible; I would suggest that what is urgently needed instead is the development and adoption of a set of standardised antibiotic stewardship outcomes that particular interventions could choose, in their protocols, to report on. However, I am aware that that recommendation is predicated upon my impressions of the field, rather than my ability to analyse the definitional heterogeneity in diagnostics research as compared with definitional heterogeneity in pharmaceuticals, or other hospital drug or diagnostic interventions. Nonetheless a move toward regularising reporting in this way could move the field of diagnostics reviews forward, with a view to minimising a known challenge and exposing the weaknesses inherent in the research.

So in the context of this research, and in the context of weak evidence to support the use of diagnostics – but a strong top-down pressure to continue expanding access to them as seen in the third study – I feel that the Sankey diagram is an important new methodological addition to systematic reviewing that, if adopted more widely would allow researchers to analyse the included studies in their reviews using a critical lens, and compare the outcome heterogeneity across disciplines.

There are also resonances with another field of research: the Commercial Determinants of Health. Lessons learned from the CDoH field demonstrate that an inability to group studies, draw parallels across contexts, and aggregate data benefits industry rather than patients.(123,412–414) Capturing the ways in which various fields measure outcomes and endpoints would be one way methodologically to advance future systematic review analyses, in particular in the field of CDoH.

3. Situating my work within the larger field of the Commercial Determinants of Health

Initially, antimicrobial resistance, diagnostics, and CDoH was thought to be somewhat of an incongruous fit for the dissertation. But by the end of it, I was finding common ground with CDoH researchers, experiencing common problems, often tied to risks of publishing findings perceived to be at odds with corporate interests, and commiserating with scientists, such as Jon Deeks, who was threatened with litigation following his calls for transparency in the case of certain COVID-19 rapid diagnostic tests. In spite of this, AMR still does not sit easily within the bounds of the burgeoning CDoH field. Indeed, recent definitions of CDoH frame the discipline as a non-communicable disease-based field *prima facie*. Two relevant reviews were published in 2020 on: (i) the definitions of the CDoH, and (ii) how CDoH are represented in conceptual frameworks.(132,133) In the former, Lacy-Vawdon and Livingston reviewed 33 papers that define CDoH, of which 19 provided no definition of the term, and in the remaining papers, three types of definition were described. These were: an incentives-based definition, introduced by West and Marteau, of "factors that influence health which stem from the profit motive"; a product and behavioural science-based definition, introduced by Kickbusch,(131) and the most definition of the three, of "strategies and approaches used by the private sector to promote products and choices that are detrimental to health"; and Kosinska and Ostlin's (415) friction definition, where CDoH is a relevant lens to describe 'a good or a service where there is an inherent tension between the commercial and the public health objective'. In none of these three definitions is there any reference to the natural history of any disease, communicable or non-communicable; rather, all three definitions focus on the systemic factors and competing interests leading to, or away from, health. And yet, in this review's background section, the authors situate CDoH as falling squarely within the broad topic field of non-communicable diseases (NCDs).

In Maani et al's review of 48 conceptual frameworks on Social Determinants of Health (SDoH), with a view to determining whether and how commercial determinants are incorporated into SDOH thinking, the authors also situate their review in the context of non-communicable diseases, describing CDoH as a term that is 'increasingly focussing attention upon the role of tobacco, alcohol, and food and beverage companies and others – as important drivers of non-communicable diseases (NDCs)'.(133) This is in spite of the fact that many of the 48 frameworks they mention in their paper highlight the continued relevance of communicable diseases within the SDOH framing. More broadly, the WHO definition of

SDoH - where many CDoH scholars are choosing to situate their research and frame the field - includes a global focus on the importance of early child development, urbanization, and health systems strengthening, all of which in turn have been described as crucial to the reduction in communicable disease transmission and burden in LMICs, and also the emergence and transmission of zoonotic diseases.(416)

I admire and respect the work of CDoH researchers; indeed, I hope to be considered one myself in due course. But this major oversight prompts me to interrogate why the majority of the CDoH community neglect to include within the definition and frameworks that they align themselves with a space for, at the very least, the possibility that these very same commercial drivers of poor health and inequalities may be relevant too to the fields of communicable diseases? Quite possibly, this stems from the context in which most CDoH research is currently being undertaken and methods being developed, namely high income countries. It is true that the global burden of diseases look quite different when disaggregated between high and low-middle income countries, (Figure 15) and if one's focus and academic training were predicated upon one's own country context (pre-COVID-19), it may have made sense to focus one's efforts on the non-communicable disease burden, so prevalent in high income countries, rather than focusing on a broader definition that requires only the presence of the public health/private sector friction, or a profit motive at odds with the health and wealth of a nation. This state of affairs may also have developed, understandably, due to the fact that UCIs are areas where corporations have succeeded in providing a good or service directly to consumers, that can, epidemiologically, be linked to poor health. However, corporations determine health not only by providing goods and services, but also by withholding them, by selling substandard goods – such as in the case of access to medicines and diagnostic tests, or by winning large public-sector contracts and underperforming. This is perhaps most obviously visible with COVID-19,(417,417–422) but this is not a new phenomenon. If the central components of the CDoH definitions are (i) the profit motive, (ii) a tension between public health and that very same profit motive, and (iii) optionally, a product or good, then another example, this time in LMICs, is late/delayed access to antiretroviral drugs (ARVs) and to triple therapy, due to patent protections leading to overwhelming burden of morbidity and mortality due to a communicable disease.(423)

Figure 15 Taken from Global Health Risks, (424) the ten greatest global health risks overall, and then disaggregated by low-, middle-, and high-income country status.

	Risk factor	Deaths (millions)	Percentage of total		Risk factor	Deaths (millions)	Percentage of total
	World				*Low-income countries*[a]		
1	High blood pressure	7.5	12.8	1	Childhood underweight	2.0	7.8
2	Tobacco use	5.1	8.7	2	High blood pressure	2.0	7.5
3	High blood glucose	3.4	5.8	3	Unsafe sex	1.7	6.6
4	Physical inactivity	3.2	5.5	4	Unsafe water, sanitation, hygiene	1.6	6.1
5	Overweight and obesity	2.8	4.8	5	High blood glucose	1.3	4.9
6	High cholesterol	2.6	4.5	6	Indoor smoke from solid fuels	1.3	4.8
7	Unsafe sex	2.4	4.0	7	Tobacco use	1.0	3.9
8	Alcohol use	2.3	3.8	8	Physical inactivity	1.0	3.8
9	Childhood underweight	2.2	3.8	9	Suboptimal breastfeeding	1.0	3.7
10	Indoor smoke from solid fuels	2.0	3.3	10	High cholesterol	0.9	3.4
	Middle-income countries[a]				*High-income countries*[a]		
1	High blood pressure	4.2	17.2	1	Tobacco use	1.5	17.9
2	Tobacco use	2.6	10.8	2	High blood pressure	1.4	16.8
3	Overweight and obesity	1.6	6.7	3	Overweight and obesity	0.7	8.4
4	Physical inactivity	1.6	6.6	4	Physical inactivity	0.6	7.7
5	Alcohol use	1.6	6.4	5	High blood glucose	0.6	7.0
6	High blood glucose	1.5	6.3	6	High cholesterol	0.5	5.8
7	High cholesterol	1.3	5.2	7	Low fruit and vegetable intake	0.2	2.5
8	Low fruit and vegetable intake	0.9	3.9	8	Urban outdoor air pollution	0.2	2.5
9	Indoor smoke from solid fuels	0.7	2.8	9	Alcohol use	0.1	1.6
10	Urban outdoor air pollution	0.7	2.8	10	Occupational risks	0.1	1.1

[a] Countries grouped by gross national income per capita – low income (US$ 825 or less), high income (US$ 10 066 or more).

CDoH, definitionally, then, is far more tied to the tactics used by industries, than the specific diseases caused by (or denied using) these tactics. I feel that the importance of being able to view these tactics across a wide range of contexts cannot be overstated.

Even if infectious diseases were, before COVID-19, on the decline, they cause dramatic and inequitably distributed burdens of disease; in high income countries and low-middle income countries alike, infectious diseases are more likely to affect the lowest socioeconomic quartiles of society; and once infected, people who are the most deprived in a society are also likely to be sicker for longer, and to have more severe complications and higher mortality risks.(425–428) I have shown in my dissertation that multinational pharmaceutical companies and medical diagnostics companies lobby for UK NHS funding, and adopt many of the same industry playbook tactics as have been described above including, in addition to lobbying, the

adoption of marketing approaching, sponsoring conferences and journals, funding favourable science and scientists while discrediting unfavourable science – and threatening experts with legal action. These are all tactics that are well-known in CDoH research.(132,133,350)

Most fundamentally, though, it should be irrelevant to CDoH research whether communicable or non-communicable diseases cause a greater burden of deaths in a particular environment; this argument strikes me as exactly the type of reasoning that benefits all private industry involvement in public health; as the public health community divides itself between social and commercial determinants, infectious and non-infectious diseases, and then further subdivides within each of those categories (I myself have progressively whittled the scope of this dissertation down from infectious diseases, to bacterial infectious diseases, to resistant bacterial infectious diseases, to diagnostics that can be used to identify resistant bacterial infectious diseases, and so am of course not immune to this argument), then industries can exploit these divisions in order to pander to the technocracy in each specific niche; they can lobby governments and co-opt public sector funds for corporate subsidies. I therefore advocate strongly for a definition of CDoH that does not include at its core a non-communicable disease criterion, nor indeed any type of disease criterion; the tactics themselves, and their impact on health outcomes, is surely enough to define the field, and will have the added benefit of allowing researchers from a wider cross-section of health research to compare their findings and contribute to developing methods to fight against the negative effects of corporate interests in health research.

4. Situating my work within the contemporary context of COVID-19

Inevitably, mention of COVID-19 has crept into this dissertation. This is because it was, ultimately, this global pandemic that laid bare how: diagnostics were a "wild-west" compared with other more highly regulated health interventions; the UK government immediately turned to the private sector to scale up private superlabs for COVID-19 testing; and similarly, the UK government contracted out NHS test-and-trace largely without including public health practitioners in the process.(420) Here is a real-world, real-time case study that demonstrates how rapid, novel diagnostics systems and processes are implemented by the UK government in times of health crisis. The problems that the COVID-19 diagnostics roll-out have faced echo many that arose in this thesis, including concerns about real-world test

performance, private contracting and outsourcing, and dissent from the UK medical and public health communities.(420,421,429–432). An example of this is that negative rapid diagnostic test results provided *de facto* travel passports for students, anyone still travelling internationally, and others, including essential workers who were being tested for much of the pandemic, even as the lateral flow tests were deemed not fit for purpose for asymptomatic screening.(433,434)

Diagnostic antibody and antigen testing for COVID-19 were suddenly front-page news from March 2020 onwards. Both the US and UK governments mentioned these tests early on as important tools in their COVID-19 lockdown strategy. The UK even ordered 3.5 million of one type of test, which was later deemed 'wildly inaccurate' and had to be discarded.(429) Secretary of State for Health Matt Hancock has ordered millions of tests from nine other companies; at the time of writing there remains uncertainty about their effectiveness.(431)

There are serious concerns that the regulatory process for diagnostic testing is being weakened, not strengthened, at this time. The WHO issued advice in the form of a scientific brief on the use of antibody tests on 08 April (a week after the 3.5 million tests were discarded in the UK), recommending that these tests only be used in research and disease surveillance, and only when the tests are validated.(435) The WHO has issued stronger guidance against rapid immunodiagnostic tests to detect proteins from the COVID-19 virus in respiratory, sputum, or blood samples, saying that these tests must go through the normal validation process before the tests can be used.(435) They recommend that these tests should not be used 'for clinical decision-making, until evidence supporting use for specific indications is available'.(435)

The overreliance of the government on as-yet-undiscovered technological solutions is markedly similar in the COVID-19 pandemic to the work I have undertaken in the last three years. And it is not simply in the reliance on untested diagnostics. It is also in the rapprochement between government and the private sector, without involving the extant public health community in the solution. This was seen most obviously in the United States in the early days of the pandemic. The US government extolled the importance of antigen testing. President Donald Trump declared a national emergency due to COVID-19 on 13 March, 2020.(436) In this address, Trump brought up to the podium the CEOs or other senior representatives of rapid diagnostic testing companies who were providing, or who had

pledged to provide, diagnostic tests. The companies in question were: Labcorp, Quest diagnostics, and Becton Dickinson (Figure 10).

Figure 16 Clockwise from top left, screenshots of CEOs of Becton Dickinson, Labcorp, and Quest Diagnostics with President Trump during his declaration of a national emergency, on 13 March 2020

The next day, the share prices of these three diagnostics companies increased substantially, alongside the share prices of the other CEOs congregated with Trump in that press conference, on the worst day for the S&P index in more than 30 years.(437) The shares of Google also rose, based on President Trump's assertion that Google were involved in a nation-wide effort to provide 1.5 million weekly tests that Trump promised in the same speech. However, Google later clarified that they were not involved in any such project.(438)

To be absolutely clear: I am not asserting that the government has to provide, or even should provide, all diagnostic testing for any infectious disease outbreak, or even that the government should only rely on public sector or arm's length bodies for development, commissioning, administration, and interpretation of test results. However, the government promotion of private sector-led diagnostics as an important solution in the COVID-19 crisis, one requiring less regulation in the face of such serious procurement and validation challenges, in concert with a largely uncritical position about the benefits of diagnostic testing is highly relevant to the work I have been undertaking.(430) Moreover, there are

important questions to be asked about why, in nearly all circumstances, the private sector was the *primary* port of call in the COVID-19 diagnostics quandary. NHS labs were returning results faster than privately contracted ones, and to a higher standard, and 44 laboratories remained 'underused' during the first pandemic wave due to rapid scale-up of private outsourcing.(420)

Overall, the question about diagnostics as a CDoH problem over the course of the pandemic is also a question about equity. If we believe that the diagnostics being (over)promoted by political and interested parties are helpful, then it stands to reason that we should be ensuring equitable access to these diagnostics. If, on the other hand, we pause and consider the multiple causes for concern we have about the clinical effectiveness of the diagnostic tests that we have for AMR, for COVID-19, and for any number of other diseases, then the question is still about equity, but a different kind altogether: shareholder or private equity. Why, if we have serious doubts about the abilities of diagnostics to provide an approximation of certainty – which is their aim – are senior figures in government providing free marketing and insufficiently scrutinised contracts to private sector contractors within a low-regulation and accountability context? The role of neoliberalism in producing these problems has been addressed elsewhere, both generally, and in relation to AMR, and so has, of course, a critique thereof.(439–444) I wrote an opinion piece for the BMJ expanding on the points above to describe the role of neoliberalism in the UK's COVID-19 response, due to be released in January 2021.

5. Final reflections: meta-research learnings and the elusive 'red-thread'

As well as my methodological reflections, disciplinary reflections, and reflections on the links with COVID-19, I have also reflected on the process of engaging with the topic of AMR, in academia. I have found that, perhaps due to the interdisciplinarity, the critical lens, and the commercial interests in this field, the process of writing and submitting papers, and having them accepted by journals, was different to publication processes I have been involved in previously.

In attempting to aggregate clinical effectiveness data from different diagnostic tests, I have interrogated whether an indirect meta-analytical comparison could be undertaken. While I

believe the decisions I took in the meta-analysis were in the interest of increasing methodological rigour, and consistent with methodological guidance and widespread practice as described in Chapter 1, they were not considered to be so by some reviewers when they were submitted for peer-review. The primary reason for rejection of my review paper from three journals, where it was sent out for peer-review (Lancet Infectious Diseases, CID, and BMJ Open) was due to the aggregate nature of the analysis. Two reviewers (JAC; Lancet Infectious Diseases) were concerned about the findings given their *a priori* understanding of the evidence base. This was a harder critique to accept; reviewers pointed to individual studies that demonstrated the clinical effectiveness of diagnostics in their critiques – in effect, they were cherry-picking positive findings, in order to reject the findings of the first reliable, comprehensive systematic review of the entire evidence base. I undertook a modification of the systematic review chapter following these rejections. I had to think more about my audience before resubmission, and concede that infectious disease practitioners may not find this methodologically experimental systematic review practically useful because they do not consider the tests to be similar enough to aggregate, because they perform slightly different functions in the laboratory, and for different diseases/pathogens. However the health services lens of the care pathway was a useful framework for me to use (or adhere to) whenever I needed to remind myself why we should be being critical of the tests in the first instance.

The bias in favour of diagnostics does seem to be widespread. In one case, as described in the Introduction (and again in the paper that follows), my systematic review was offered publication, but not as an original research paper, but rather as a debate piece, which of course it was not. It was explained that the journal would run it alongside the 'opposing view', or, in other words, the pro-diagnostics opinion, giving these equal weighting, due to the 'controversial' nature of my null findings.

This was not the first time that I had found it difficult to publish findings or even opinions about proprietary technologies. I wrote an editorial for the BMJ which was published, but without an entire paragraph, which the editor explained was a minor tweak due to the legal advice they had taken. Upon speaking with colleagues in CDoH research, I found that this was a very common experience. I therefore wrote an analysis piece - submitted to BMJ, reviewed, given 'revise and resubmit' status, and now resubmitted and under review again – on publication bias within the publication process, which I present as another important finding from this doctorate, below.

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

SECTION A – Student Details

Student ID Number	402062	**Title**	Ms
First Name(s)	Rebecca		
Surname/Family Name	Glover		
Thesis Title	Antimicrobial resistance in the United Kingdom: a mixed-methods dissertation on diagnostics, discourse, and decision-making		
Primary Supervisor	Mark Petticrew		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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Where was the work published?			
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Where is the work intended to be published?	British Medical Journal
Please list the paper's authors in the intended authorship order:	Rebecca E Glover, May CI van Schalkwyk, Nason Maani

Stage of publication	**Undergoing revision**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	REG conceived the idea, and led on drafting, editing, analysis, and reviewing MCIvS also conceived the idea, and was involved in drafting, editing, analysis, and reviewing NM was involved in drafting, editing, and analysis, and reviewing

SECTION E

Student Signature	Rebecca Glover
Date	29 December 2020

Supervisor Signature	Mark Pelliccer
Date	31.12.20

Paper IV: Scholarship stewardship or Litigation mitigation? Defensive editorial bias in Commercial Determinants of Health research

Under review: BMJ Analysis December 2020

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Introduction

There is a growing understanding that Commercial Determinants of Health (CDoH) can impact on population health, and research into the strategies that industries use to undermine public health is of profound importance.(79,133,445–447) However, research in this area may be hampered due to unique professional challenges.(448,449) The power of corporate actors in areas such as tobacco, alcohol, processed food, and gambling has been shown not just to influence health directly through the promotion of unhealthy products, but also through funding research to cast doubt and contest independent evidence that threatens profits. In this analysis, we review the direct mechanisms of influencing the academic literature, and introduce a framework to analyse the indirect mechanisms of editorial bias in the academic publication pathway. In order to mitigate the risks of 'defensive editing' – making editorial decisions with an eye to libel risk – we propose a set of recommendations (Box 1) to develop safeguards for CDoH research.

Industry influence on research

For decades, harmful product industries have dedicated considerable resources to influencing and manipulating research, with the aim of managing carefully what is known, and what remains unknown, about the harms of their products and corporate practices. Industry-funded studies and those with author conflicts of interest are more likely to deliver results and/or conclusions favourable to the sponsors' interests. This is perhaps best evidenced by the tobacco industry.(82,450–457) Alongside the classic examples of industries publishing favourable trial results and suppressing unfavourable ones,(458) there are also cases where industry influence has taken the form of **industry-led publication bias;** proponents have created industry-funded academic journals, positioned themselves within non-industry funded journals as editors, and funded journal supplements.(459) Many of the tactics adopted by the tobacco industry are also used by other industries when profits and population health are in conflict.(129,459–462) Industry manipulation of research can therefore bias the evidence base, and consequently which policy and treatment decisions are made, with implications for health. Silencing or obscuring established facts, fuelling controversy and spreading doubt and denial about potential hazards posed by a product are all tactics that have been deployed in the past. Additionally, industry funding can bias research through influencing research agendas (i.e. what questions are asked), as well as through shaping the design and conduct of

research (e.g. through choice of comparator) and, of particular relevance to this analysis, through influencing how findings are reported and disseminated through direct action – power and influence through corporate agency - or indirectly through the actions others take to pre-empt industry strategy – structural power and influence.

An appreciation of the considerable power that corporations wield has, in part, catalysed the growing recognition of the need to research the CDoH. Corporate power comes in many forms, including the manipulation of research and influence of policy environments.(463) Industries, and those funded by them, exercise power to manipulate research; these mechanisms can be direct or indirect, overt or covert, conscious or subconscious, but detailing these methods does not provide a comprehensive picture; industries also try to prevent publication of, and ask for retractions for, articles featuring undesirable findings. This will be detailed further below. Structural power may exist in addition to corporate agency; those involved in knowledge production – academics and journal editors - act in anticipation of what they perceive industry may do with their agency.(447) This introduces what we term **defensive publication bias** into the evidence base – a pre-emptive self-censoring, on the part of academics, reviewers, and editors throughout the publication process, and can occur in two underexplored ways: presenting a debate or false balance in the publication process when the research and evidence base do not support the need for doing so; and redacting commercially threatening data. These two defensive publication tactics are further exacerbated by industry responses to the redacted articles, as demonstrated later in our analysis. These are strategies that may come from understandable attempts to avoid litigation, but risk leading to bias, and contributing to building and maintaining an evidence base favourable to industry while important findings from a public health perspective remain silenced or distorted. Here we introduce some examples of such practices, consider their implications, and set out a series of recommendations on how to address these issues and further understand potential impacts. Here we use our own redacted examples of article rejections in our experience trying to publish articles with data not favourable to industry. The redactions were undertaken by the authors in order to protect themselves.

False balance

False balance refers to the creation of a perception that there is an academic debate by presenting two sides of an argument equally, when a scientific consensus has already been established. This approach has been critiqued particularly in the context of climate change science and vaccine 'debates' in recent years.(464,465) In academic journals, this can occur when editors send a paper for review, but choose a selection of reviewers perceived as "pro" and "anti" industry partnership or other industry activities. When reviews are then returned in line with those stances, and the editor rejects or revises the submission because of the existence of two opposing views, then this is one way where false balance can lead to a distorted evidence base.

> "The topic is potentially interesting and possibly even novel, however, I suspect that the format as a systematic review is not going to work. May I suggest a resubmission as a "For debate. These articles should air contentious issues or discuss controversies so as to stimulate discussion in the Journal on any given topic on [REDACTED]. Articles should be as clear and concise as possible, consist of [REDACTED].
>
> The role of [REDACTED] is potentially such a topic and a lot of their material (especially their [REDACTED] would support a debate. However, space would preclude a full systematic review type approach."

Figure 17 An editor describing why they would prefer that the 'controversial' (problematic for industry) findings of a systematic review and meta-analysis be presented as an opinion, in a 'debate' article, rather than an original research article.

Figure 17 contains a redacted email received by an author containing an excerpt from a journal editor who deems the findings of a systematic review and meta-analysis on a particular product 'controversial'. The meta-analysis demonstrated that proprietary medical technologies were not improving clinical outcomes for patients. Though there were no methodological or statistical concerns raised in the response to the article submission, the editor suggested publishing the findings of the systematic review and meta-analysis in the form of a 'debate' opinion piece, and commission a pro-medical technology piece to publish alongside of it, thereby giving the impression of debate and minimising original research findings by promoting false balance. Such discussion would conventionally likely happen *after* the review was published had it not been for the controversial content of the research.

Redacting commercially sensitive data

This type of publication bias can take many forms. First, editors may reject a paper without review because of the fear of controversial findings. The publication of the study might be delayed, because of data that is considered to be sensitive, or controversial. The study may even be published, but with particular data redacted.

An example of this can be seen in Figure 18, about a piece that was subsequently published without the data in question.

> "It is a great piece and a really interesting discussion. Thanks for thinking of [REDACTED] for this article.
>
> The only really substantial change that I have made is to take out a section in the middle which highlights specific things that [REDACTED] companies have done. I think I would probably need to run that all by a lawyer because [REDACTED] companies are quick to complain (and threaten legal action.) I think that actually all the fundamental points that you want to make, are encompassed in the more general discussions about [REDACTED] involvement without singling out specific companies."

Figure 18 An editor explains how likely legal action meant that redactions were required before publication.

While sometimes essential, redacting commercially sensitive data due to the risk of libel suits or other risks privileges industries. This risk does not exist for scholars who publish analyses in other areas of public health concern, e.g. where the likely harm-causing agent is a microorganism. There is, consequently, a higher threshold for studies stemming from research on corporate activity.

Situating these defensive publication biases within a context of coordinated rebuttal campaigns and threats of litigation

Commercial actors can undermine the reputation of independent researchers and their work. This will be familiar to those working in CDoH, and there are examples from climate change, tobacco, and many other areas.(466) Peer-reviewed studies that are critical of corporate activity are often followed by actual or implied threats of legal action, requests for retractions, or letters to the editor. In some cases, emails to researchers or their employers are sent that threaten 'loss of reputation'. It has been hard for us to access private exchanges between corporations, editors and researchers, but one such example that was shown to us was a document by an industry body alleging that a research paper constituted "reputational damage". Since reputational damage may be one of the legal requirements for a libel suit, this thinly veiled language had the effect of the editor of a journal discussing the possibility of a retraction with the authors, though there has been some protections in the UK against libel for peer-reviewed journals. Ultimately, of the six pages of alleged inaccuracies listed by

the corporate body, all but one were demonstrated to be false accusations of inaccuracy. The minor misquote was corrected in an erratum by the editor, which is not uncommon in academic literature, but it is conceivable that the weight of this disproportionate response may bias the editor in favour of an unduly cautious approach in future editorial decisions surrounding CDoH research, not unlike the phenomenon of regulatory chill, which refers to government or policy maker reluctance to proceed with health policies/regulations in the face of industry challenges and threats of legal action.(467)

Not all post-publication rejoinders from industry are delivered in private. In some cases, rebuttals from industry, or industry-funded organisations, are in the public domain, such as in the trade press, or in the form of letters to the editor, or on social media sites such as twitter. While we do not wish to imply that discussion in the academic literature is not beneficial, such industry-led rejoinders deserve closer scrutiny, since they can frame academic research as 'biased', or 'opinion', without offering reasonable justifications for such assertions. While researchers are typically offered the right to respond, this does not prevent such industry organisations from selectively citing their unevidenced – but published – letters as proof of rebuttal.(468,469) This type of activity fits into a broader pattern of selective citation and misrepresentation of the evidence base to generate doubt.

Discussion

Corporate actors have a long history of directly influencing the evidence base in their favour. This is precisely why more CDoH research is needed. In addition, there are also editorial biases that risk the transparent and comprehensive production of knowledge in this field. If

Box 1: PAPER recommendations

Publicly available database of letters to editors threatening legal action

Audits of whether the submissions pertaining to commercial organisations are treated differently to other types of research

Peer-reviewed research could build an 'information commons'

Expertise: "Commercial determinants of health" should be a field of specialism.

Round-tables, seminars, meetings, and joint efforts to co-create a toolkit for all involved in working in CDoH research

these three editorial biases and the litigious environment surrounding academics and journal

editors are not managed, CDoH research will be stymied through a fear of nuisance rebuttals, libel claims, and personal and professional reputational damage. Researchers and journal editors alike may continue to undertake decisions that fundamentally bias the evidence base in favour of the industries we seek to hold to account. To catalyse an agenda to tackle these issues, we propose five recommendations, helpfully termed **PAPER**, summarised in box 1, and elaborated further below.

In Box 1, we recommend that there should be a database of redacted libel letters, not dissimilar to growing trends in publishing peer reviews. Similarly, an research initiative to establish a "corporate permeation index" acknowledged that there was not enough data in the public domain about lobbying to calculate accurate estimates of the burden of this behaviour.(470) However, one 2014 paper recommended making all threats of libel against any journal or author (with personal information redacted), publicly available, to establish a searchable record.(471) This database would allow for systematic analysis of the scope and magnitude of the problem. Qualitative analysis should also be undertaken, using in-depth interviews with journal editors on this topic.

Second, journals should commission audits to determine if the submissions pertaining to commercial organisations are treated differently to other types of research, with summary reports being publicly available. This may not be feasible for smaller journals in all cases either due to budgetary or resourcing constraints. However, for journals within a large publishing company, this could be undertaken by the parent company level. Monitoring and evaluation audits could be undertaken on a small sample of random submissions across the parent publisher's portfolio to keep costs down, and the results of these could be made publicly available.

Third, peer-reviewed research could build upon the call for an 'information commons'– a space for the publication of research of public interest - ensuring alternative and independent voices are heard and encouraged to exist.(472)

Fourth, academics, journal editors, funders, publishers, and can work together to develop a framework for assessing acceptable and unacceptable litigation risk so that peer reviewers and academics feel confident that assessment of such work is transparent and structured.

Finally, this is a challenging field, but we need to recognise the corporate influence on health in the treatment and selection of journal articles. "Commercial Determinants of Health"

should be able to be selected upon submission of a journal article as a specialist field. This recommendation is caveated; we advocate for inclusion of this as a topic selection in journals, but *we are not* advocating for a separate journal on the Commercial Determinants of Health; exposure to commercial products may have harmful or beneficial effects, and it is important that analyses of these are conceptualised as part of mainstream epidemiological or health research given the cross-cutting nature of the field.

Irrespective of issues related to data availability, a few key issues appear clear. First, editorial biases are likely to exist in CDoH research. Second, due to these biases, there is a risk that potential publications on CDoH are less likely to be accepted than research in other domains due to the nature of their content not the quality or importance of the research. Third, the defensive publication examples such as the ones listed above are not consistent with the committee on publication ethics (COPE) code of conduct, which includes the pledge to "preclude business needs from compromising intellectual and ethical standards".(473) Though the risk of litigation may have pushed some academics to pre-emptively censor themselves, and some journal editors to pre-emptively reject articles or remove data that is commercially sensitive – akin to defensive medicine – more can be done structurally to develop a healthier publication environment for this type of research. A key role of scientific research is to bear witness to the forces shaping the world, whatever they be. We cannot afford to allow contributions to health and wellbeing to remain in the shadows.

Key points:

- Researchers and journal editors involved in the production and dissemination of research on Commercial Determinants of Health face heightened risks, including litigation, loss of reputation, and difficulty publishing in this area.
- Concerns about 'litigation mitigation' - nuisance libel suits - can lead to the delay, suppression, and minimising of Commercial Determinants of Health research in a way that benefits industry and undermines this burgeoning field.
- These practices affect the state of the evidence base and are consequently a serious public health issue.

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Competing Interests

None to declare

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Limitations, strengths, and future research

Limitations

There are numerous limitations, both within and among the various strands of this dissertation. I have discussed many of the methodological limitations within the various chapters. However, a weakness of the entire programme of research is that I did not decide on a single unit of analysis to keep as consistent throughout the various strands.

If I had better understood at the beginning of the research programme that a possible outcome might be that the commercial involvement in the portrayal of diagnostics as technological silver bullets would be a recurrent problem, I might have asked more about these involvements, and conflicts of interests more broadly, in my qualitative interviews. I might have focused my questions less on the technical supposedly value-neutral aspects of clinical effectiveness, and chosen to ask more questions about the financial relationship between diagnostics companies and the hospital laboratories, trusts, or CCGs if I had decided that a local level lens was indeed the correct choice. (Incidentally I did enquire early on about the prospect of accessing contracts between the diagnostics companies and NHS laboratories but these were private and not subject to FOI requests due to the unique purchasing arrangements of these tests.) There are some benefits to having undertaken the work as I did as well, which is that I gleaned some insight about the same topic at various strata. And as most of the capacity that diagnostics companies have to push their products comes from national-level laws and guidelines, it did seem reasonable at the time to pursue this avenue.

I also did not make provision for going back to conduct future interviews with my same interviewees. I made some attempt to mitigate this limitation by planning to send the thesis back to some of my more engaged interviewees – those who asked to be updated as to the final results –to solicit feedback about whether my qualitative analysis and discussion sections felt relevant or familiar to their lived experiences. However, the write-up occurred during the middle of a global viral pandemic and my interviewees were front-line NHS staff, and I felt that it might be inappropriate to follow-up with them in this way.

Another source of methodological concern was the decision to include CCG-level (or equivalent) case studies for two qualitative studies, and to analyse national-level policy documents in the absence of local-level policy documentary analysis means that comparing

across studies is more difficult than if I had limited the governmental or administrative level of my analysis to either a single tier, or a single cross-section. However, local-level policy and documentary analysis is notoriously difficult; this can be mitigated against using observation and longitudinal interview practices. This may be something we attempt in PIRU, as we have recently embarked on our evaluation of the UK's 2019-2024 AMR strategy, and we have recommended to DHSC that we return to the same case study sites in which we conducted research throughout 2018.

Strengths

But my research also has many strengths as a dissertation. Despite the above limitations, it shows the development of a programme of research, each stage of which genuinely informed the next stage. The individual elements were conducted rigorously and produced genuinely new findings and as such add to their specific evidence bases. The research as a whole also contributes not just new evidence but new thinking, in particular about infectious diseases and the industries involved in treating them as a CDoH problem; and in how to critically appraise evidence(s)- especially in the midst of a public health crisis. Finally, methodologically, it contributes both to systematic review methods and also to mixed methods research processes, and throughout the dissertation I have developed into a researcher able to engage with my discipline(s), and academic discourse, both narrowly, within the field of AMR, and conceptually, to make connections between this and the ideas and positions held within the field of the Commercial Determinants of Health.

More broadly, what I have done is effectively what health services research, and public health do as new(er) disciplines. They borrow from the most appropriate disciplines and methods in order to conduct research on a particular, often knotty, topic. It uses a variety of ways of getting hold of the issues, and contributes – hopefully – to different audiences. Which, in an applied field like health, is of course essential.

Future research

My PhD evaluated the clinical impact of rapid diagnostics for AMR, and analysed the impact of the narrative of an AMR 'crisis' on the proposed policy solutions. The pharmaceutical and medical diagnostics industries are able to co-opt this narrative to misrepresent the scope of

interventions likely to be effective. Extensions of this research would be to conduct (i) citation analysis to map the evidence used by industry (ii) media / document analysis to trace industry narratives in public discourse, (iii) qualitative interviews with stakeholders and experts in industry influence research, such as the SPECTRUM consortium (UKPRI funded) and (iv) social media analysis to compare industry messaging to that of public health organisations. These methods have previously been developed in studies of the unhealthy commodities industries and would be transferable and appropriate, given the findings of this research. Applying the methods I developed to improve PRISMA reporting, namely the Sankey diagram, to other systematic review in UCIs, is another avenue of future research; this way we could move toward a standardised understanding of heterogeneity across disciplines. To conclude, the field of CDoH research seems, at the least, a useful area to learn and apply lessons about industry playbooks in order to help critically analyse the discourse around crises, AMR, and government-and industry-led siphoning off of public sector funds. CDoH may also act as a crucial lens through which to understand the hegemony of private sector-led solutions to AMR.

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APPENDIX

Document 1: PROSPERO protocol

A systematic review protocol on using rapid diagnostic tests for antimicrobial resistance in hospitals: the effect on clinical outcomes and antibiotic prescribing, as well as on acceptability and feasibility

Rebecca E. Glover, Mustafa Al-Haboubi, Elizabeth Eastmure, Elizabeth Holdsworth, Mark Petticrew, Nicholas Mays

Citation

Rebecca E. Glover, Mustafa Al-Haboubi, Elizabeth Eastmure, Elizabeth Holdsworth, Mark Petticrew, Nicholas Mays. A systematic review protocol on using rapid diagnostic tests for antimicrobial resistance in hospitals: the effect on clinical outcomes and antibiotic prescribing, as well as on acceptability and feasibility. PROSPERO 2017 CRD42017060566 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017060566

Review question

1. Do rapid diagnostic tests (RDTs) for antimicrobial resistance change clinical outcomes or antibiotic prescribing for admitted hospital patients, compared to non-RDT best practice?
a. Do RDTs for antimicrobial resistance change clinical outcomes or antibiotic prescribing for high-risk patient subgroups, compared to non-RDT best practice?
b. What is the acceptability of using RDTs for AMR detection in hospitals among hospital staff?
c. What is the acceptability of using RDTs for AMR detection in hospitals among patients?
d. What are the barriers to implementing RDTs for AMR detection in hospitals and their laboratories?

Searches

We will search through the following databases: PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, PROSPERO, Global Health, Web of Science, The New York Academy of Grey Literature, Open Grey, Scopus.
We will conduct hand searching, expert consultation, and reference searches to provide supplemental coverage to ensure that the search strategy has not missed key literature. We will make an effort to search for unpublished studies by contacting authors, searching grey literature databases, and a selection of proceedings from key conferences.
We have used MeSH terms in the development of our main search string where appropriate, and have consulted a systematic review specialist librarian in the development of the main search strategy. Search terms will be tailored to specific databases.
We will include papers in all languages but will only run searches in English
We have no publication period restrictions.
The search strings used are available in full from the authors.

Types of study to be included

For questions 1 and 1a: Any observational epidemiological studies (cohort, case-control, cross-sectional, ecological, and longitudinal), or interventional studies (RCTs, cluster-randomised trials). However, we do not expect interventional studies in this domain.For questions 1b-d: Observational studies, ethnographic studies, qualitative research.

Condition or domain being studied

Changes in clinical outcomes or antibiotic prescribing due to using rapid diagnostic tests that show whether resistance to at least one antibiotic is present. Also, the acceptability and feasibility of using such rapid diagnostic tests in hospitals.

Participants/population

For 1 and 1a:
Inclusion criteria:
Adults and children admitted to and treated in secondary care or within a hospital setting.
Studies assessing rapid diagnostic tests for antibiotic resistance that include quantitative data on at least one

clinical outcome or antibiotic prescribing outcome will be included (morbidity, mortality, days on IV antibiotics, broad-to-narrow spectrum antibiotics, etc.)
Exclusion criteria:
Studies evaluating rapid diagnostic tests that do not report on at least one clinical or antibiotic prescribing outcome in a hospital setting.
Studies evaluating rapid diagnostic tests used to determine clinical diagnosis rather than the presence/absence of antibiotic resistance.
Studies looking at rapid diagnostic tests for tuberculosis or any slow growing bacteria.
Studies examining rapid diagnostic tests used for patients who are not admitted to hospital at any time during their stay.
For 1b-d:
Patients and staff admitted to or working in hospitals and secondary care.
Studies including any data on acceptability or feasibility will be included (opinions, preferences, attitudes, behaviour, adherence, use in decision-making, etc.)
Exclusion criteria:
Studies set in primary care.
Studies not looking at bacterial resistance.
Studies looking at the acceptability/feasibility of using a rapid diagnostic test for clinical diagnosis rather than the presence/absence of antibiotic resistance.
Studies looking at tests for tuberculosis.

Intervention(s), exposure(s)

For questions 1 and 1a:
We are interested in the change in clinical or antibiotic prescribing outcomes that might be associated with an introduction of RDTs into the hospital.
For questions b-d:
Any opinions, views, experiences, attitudes, feelings, knowledge, perception, belief, or understanding, or any expression about the phenomenon of interest; ease/challenges/benefits/approval/disapproval of RDTs for AMR.
Excluded for all:
RDTs that diagnose a clinical illness without any antibiotic sensitivity testing.
Studies examining minor improvements to classical techniques, i.e. automation of culture-based methodologies may shorten time to identification of bacteria, but if the microbiological technique is the same as before the intervention, then we will exclude the test in our analysis.

Comparator(s)/control

For questions 1-1a:
Hospital best practice without RDT, i.e. culture media and/or antimicrobial sensitivity testing, as appropriate.

Main outcome(s)

For questions 1-1a:
1) Clinical outcomes including but not limited to: 30-day all-cause mortality; reduction in morbidity/mortality; bed days averted; infections averted.
2) Antibiotic prescribing outcomes including but not limited to a change in: decision to treat, duration of treatment, defined daily dose (DDD), route, quantity, time-to-correct treatment, and change from broad spectrum to narrow spectrum antibiotics.
For questions 1b-d:
Beliefs, feelings, perceptions, ideas, opinions.

Additional outcome(s)

For questions 1-1a:
Costs, drug resistance, sensitivity, specificity, PPV, NPV, NNT, turn-around-time, adverse events, and any other relevant outcome to the capacity and quality of the rapid diagnostic test in question.
For questions b-d:
None.

* Measures of effect

Data extraction (selection and coding)

Titles and/or abstracts of studies retrieved using the search strategies will be screened by two reviewers to identify studies that may meet the inclusion criteria (below). The full text articles for the included abstracts will be retrieved and assessed by two reviewers to see whether the full text meets the eligibility criteria. Any disagreements over eligibility will be resolved through a discussion with a third reviewer.

Two review authors will then independently extract data using piloted and agreed data extraction templates. The reviewers will use summary tables to describe the characteristics of the included papers, including title, year, authors, the population studied, setting, exclusion criteria, diagnostic criteria, type of diagnostic, technology of diagnostic, specifications of diagnostic (PPV, NPV, sensitivity, specificity, antibiotic resistance detected), and primary and secondary outcome measures. Where there are differences in the data extracted between review authors, they discrepancies will be resolved through discussion. Where the two reviewers are unable to resolve any discrepancies, a third reviewer will arbitrate.

We will present the inclusion and exclusion of papers found using the search strategy in a PRISMA flow diagram.

Risk of bias (quality) assessment

All included primary studies will be independently assessed by two reviewers for bias using the appropriate risk of bias tool, depending on the type of study (i.e. the Cochrane 'risk of bias' assessment tool for randomised control trials, the appropriate CASP criteria for qualitative research, diagnostic studies, cohort studies, case-control studies, etc.). Quality assessment will be performed by both reviewers using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria which examines the following domains:

• Study design
• Risk of bias
• Inconsistency
• Indirectness
• Imprecision

GRADE will only apply to the quantitative studies.

Two review authors will independently rate the quality of included studies. Discrepancies will be resolved through discussion. Continued disagreement will be arbitrated by a third reviewer.

Strategy for data synthesis

For questions 1-1a:

We will investigate the included studies for methodological/statistical heterogeneity using I^2 and Q-statistics. If the data are heterogeneous, we will conduct a narrative synthesis of the findings from the included studies, structured around the primary outcome measurements. If the data are sufficiently homogeneous, we will conduct meta-analyses of effect sizes of the specified outcomes. We would calculate the overall pooled odds or risk ratio with 95% confidence intervals for our two primary outcome categories (clinical outcomes and antibiotic prescribing) to determine the possible difference in effect between using and not using rapid diagnostic tests for antibiotic resistance. We will calculate two-sided P-values. We will also assess publication bias.

For question b-d:

We will conduct a qualitative synthesis of identified studies.

Analysis of subgroups or subsets

Sub-groups: The placement/position of the test (point-of-care vs lab-based; kind of ward (i.e. ICU), and turn-around-time), the number of resistance targets on the test, or the test performance. If appropriate, we will also conduct a subgroup analysis of commercial vs in-house tests. However, it is expected that there will be high heterogeneity of study designs and outcomes and subgroup analysis may not occur, in favour of qualitative and descriptive analysis.

For questions b-d:

Not applicable: These analyses involve synthesis of qualitative data, and while subgroup analyses may be undertaken, it is not correct to identify these in advance of the study.

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Type and method of review
Systematic review

Anticipated or actual start date
03 April 2017

Anticipated completion date
31 December 2018

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The systematic review was funded by the Department of Health.

Conflicts of interest
None known

Language
English

Country
England

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Anti-Bacterial Agents; Anti-Infective Agents; Diagnostic Tests, Routine; Drug Utilization; Hospitals; Humans

Date of registration in PROSPERO
31 March 2017

Date of first submission
24 January 2018

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

31 March 2017
29 September 2017
25 January 2018

Document 2: Key areas gap analysis

LEGEND

(green)	>=1 systematic review found
(yellow)	tangential or inconclusive evidence
(orange)	not appropriate for systematic review
white	no evidence found on first (rapid) search

Key Area	Action	subactions	target population?	systematic review	Date	Source	evidence?	comments	Action	Comment
				EVIDENCE						
1: improving infection prevention and control practices	Embedding strong infection prevention practices and control of cross-infection in all educational programmes for healthcare workers and veterinary teams	Embedding strong infection prevention practices in all educational programmes for healthcare workers	Human	Yes	2008	http://www.ncbi.nlm.nih.gov/pubmedhealth	Risk ratios ranged from 0 to 1.20 (26 studies). A statistically significant decrease in infection rates after intervention was reported in 21 studies.	26 studies included, on 3 HCAIs (VAP, CRBSIs, CAUTIs). educational interventions comprised lectures, classes, video presentations, posters, questionnaires, fact sheets and practical demonstrations. RELEVANCE TO UK AMR STRATEGY KEY AREA/ ACTION: Showed that education is important in improving AMR IPC practices, The evidence is largely based on pre-post intervention work in intensive care units and should therefore be treated cautiously. Moreover, there were only 26 studies included from the 50 year search period that met the criteria of a) including an education intervention, and b) including an HCAI rate.	Further work	
		Embedding control of cross-infection in all educational programmes for healthcare workers	human						Veterinary consultation	
		Embedding strong infection prevention practices for veterinary teams	Animal						Veterinary consultation	
		Embedding control of cross-infection in all educational programmes for veterinary teams	Animal						Veterinary consultation	
	Ensuring adherence to evidence-based guidelines for preventing healthcare associated infections and clinical best practice for infections caused by managing multi-drug resistant organisms	Ensuring adherence to evidence-based guidelines for preventing HCAIs	Unclear	Yes	2013	http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006559.pub2/full	very low to low GRADE	The review includes 13 studies that assessed the effectiveness of interventions to improve health care providers' adherence to guidelines. The studies included RCTs, before-and-after studies, and non-RCTs.The evidence is referred to as very low to low GRADE, and the only strong recommendation that follows is that interventions that combine education with others tend to be more effective. RELEVANCE TO UK AMR STRATEGY KEY AREA/ACTION: This review shows that there is a (sparse) evidence base for improving adherence to AMR guidelines. However, the evidence suggesting effectiveness of such interventions is very low.	No further work	
		Ensuring clinical best practice for infections caused by managing multi-drug resistant organisms	Unclear						No further work	
	Encouraging and supporting animal keepers to improve bio-security and husbandry practices to minimise disease occurrence; for example, through appropriate housing design and good disinfection procedures	Encouraging appropriate housing design	Animal		2013	http://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-13-799	Vaccination and improved farming and feeding practices including dietary manipulation (e.g. probiotics and sodium chlorate feed additives [26]), cohorting of animals and dry bedding and soil solarization reduce STEC carriage and fecal shedding in animals, and hence the risk of STEC transmission to humans.	No conclusive evidence for the role of antibiotics as a risk factor for increased carriage of STEC; nor as a protective factor! RELEVANCE TO UK AMR STRATEGY KEY AREA/ACTION: The tone of this piece is crucial to the UK AMR debate, as vets and public health officials often find themselves on opposing sides of the debate. This is review represents a degree of evidence that contradicts the recommendation in the UK AMR strategy and therefore needs to be examined further, certainly with the help of a vet.	Veterinary consultation	
		encouraging good disinfection procedures	Animal						Veterinary consultation	
	Encouraging appropriate use of best practice in disease control, for example through isolation of sick animals, testing of new stock prior to mixing, use of vaccines, and disease eradication programmes	Encouraging best practice in the isolation of sick animals	Animal						Veterinary consultation	
		Encouraging best practice in the testing of new stock before mixing	Animal						Veterinary consultation	
		Encouraging best practice in the use of human vaccines	Human	Yes	1) 2014 2) 2013	1) http://www.cochrane.org/CD001269/ARI_vaccines-to-prevent-influenza-in-healthy-adults 2) http://www.cochrane.org/CD000422/ARI_vaccination-for-preventing-pneumococcal-infection-in-adults	1) modest, significant effect 2) strong evidence of protective effect	1) This paper shows the benefit of using human influenza vaccines in healthy adults. It reports on 116 studies, 90 of which compared the effect of influenza vaccine with placebo or no intervention. Live and dead vaccines give similar effectiveness, with approximately 45 doses needed to prevent 1 ILI. However, this effect size was significant. Evidence quality was moderate, with the cohort studies, 20% of the total, exhibiting a high risk of bias. Just under 10% were of sound methodology. 2) Pneumococcal vaccine for preventing invasive pneumococcal disease is found, in this Cochrane review, to be effective at preventing disease in otherwise healthy adults. There were 25 included studies, of which 18 were RCTs involving over 60,000 participants. No evidence to support claim that the vaccine prevents pneumonia. RELEVANCE TO UK AMR STRATEGY KEY AREA/ACTION: While these are specific examples of effective vaccine programmes, what they do show (and especially true in the case of the Pneumococcal vaccine) is that vaccines are effective at preventing diseases which have sequelae that are regularly treated with antibiotics. Moreover, these vaccines prevent diseases that might place the patient in contact with health care services. Indirectly, then, vaccines - even against viruses - can play a role in decreasing the demand for antibiotics.	No further work	
		Encouraging best practice in the use of animal vaccines	Animal							
		Encouraging best practice in disease eradication programmes	Animal						No further work	
	Sharing intelligence on emerging issues in human and animal health; as well as making better use of early warning systems to trigger appropriate containment measures at a national and global level to limit the spread of AMR	Sharing intelligence on emerging issues in human health	Human						No further work	
		Sharing intelligence on emerging issues in animal health	Animal						No further work	
		Making better use of early warning systems to trigger appropriate containment measures at a national level to limit the spread of AMR	Unclear		1) 2014 2) 2007	1) http://ecdc.europa.eu/en/publications/Publications/CPE-systematic-review-effectiveness-infection-control-measures-to-prevent-transmission-2014.pdf 2) http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005529.pub2/abstract	1) There is no evidence of infection control measures to specifically prevent the transmission of CPE during cross-border transfer. There is some evidence of measures that can be used to reduce regional transfer. 2) In the second paper, a Cochrane review of early warning systems for the prevention of intensive care deaths - a tangential field - only 2 studies were applicable. One UK study, and one Australian study. Any evidence was therefore inconclusive. However, of the two studies, both were good quality RCTs. One found insufficient evidence to demonstrate that EWSs in hospitals decreased mortality, and the other found that EWSs in hospitals did decrease mortality.	This paper is only concerned with CPE, a subset of the AMR problem. However, it is a pressing one in hospitals and the community in the UK. RELEVANCE TO UK AMR STRATEGY KEY AREA/ACTION: While these studies do not provide sufficient evidence to form the evidence base of the recommendations, they hint that there is some (minimal) evidence accrued to substantiate thinking about/including these recommendations. Context is key, however.	Further work	
		Making better use of early warning systems to trigger appropriate containment measures at a global level to limit the spread of AMR	Unclear						Further work	
	Cost-effective use of licensed vaccines to reduce the incidence of infections as well as promotion of the development of new vaccines, including those against multi-drug resistant organisms	cost-effective use of licensed vaccines to reduce the incidence of infection	Unclear	Yes					Further work	
		Promotion of the development of new vaccines, including those against multi-drug resistant organisms	Unclear	N/A		http://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-13-799	Study showed some vaccines prevented animal carriage of HUS-causing STEC and also its transmission. This is due to reduced E. coli faecal shedding. Probiotics and farm hygiene also had an effect; they decreased E. coli faecal loads.	There were 18 animal and 6 human studies included in this review. This review does not, strictly speaking, directly relate to AMR, but rather to E. coli more broadly. What it does show is that bacterial disease on farms can be decreased (both for individual animals and also with respect to transmission) with vaccines. There is no evidence to suggest that this would be different for resistant E.coli but conversely, a cursory scan did not turn up evidence to support this theory either.	Further work	

Key Area	Action	subactions	target population?	systematic review	Date	Source	evidence?	comments	Action
4: developing new drugs, treatments, and diagnostics	Encouraging innovation and providing an impetus for improved collaborative action to develop rapid diagnostics and new treatments and vaccines	Encouraging innovation and providing an impetus for improved collaborative action to develop rapid **diagnostics**	Human	N/A	2007	http://www.ncbi.nlm.nih.gov/pubmedhealth	Rapid diagnostic assays can be highly specific and provide time-saving diagnoses	This systematic review includes 87 articles of variable qualities and finds enough evidence to suggest that RDTs for Salmonella, Campylobacter and E. coli O157 are highly accurate, especially when the test uses PCR. However, this article mainly references stool assays, and a limited number at that. RELEVANCE FOR THE UK AMR STRATEGY KEY AREA/ACTION: The review, while extolling the technical virtues of a limited number of RDTs, finds insufficient evidence to suggest that tests are either cost-effective or provide additional health gains. RDTs that test for multiple pathogens simultaneously were not evaluated in this review and are therefore a potentially promising source of investment in future.	Further work
		Encouraging innovation and providing an impetus for improved collaborative action to develop new **treatments**	Human						No further work
		Encouraging innovation and providing an impetus for improved collaborative action to develop **vaccines**	Human						Further work
	supporting innovation through development of the scientific infrstructure, for example, through BIS 'Strategy for UK life Sciences'	Supporting innovation through development of the scientific infrstructure, for example, through BIS 'Strategy for UK life Sciences'	Unclear	N/A		https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf	While not a review of any kind, the document linked to in this section includes a series of case studies that demonstrate the effects of partnerships in the life sciences, and tangible outcomes that have been the product of investment and PPPs.	RELEVANCE FOR THE UK AMR STRATEGY KEY AREA/ACTION: This document provides concrete examples of where financial support in collaboration with public, academic, and private ventures have led to improved health and life sciences outcomes in the UK context.	No further work
	Addressing the commercial viability issues that are hampering investment in antibiotic development, assessing the relative merits of possible incentives to stimulate research and development in new antibiotics and other products, and fast-track priority review arrangements for new antimicrobials	Addressing the commercial viability issues that are hampering investment in antibiotic development,	Unclear		2016	http://www.ncbi.nlm.nih.gov/pmc/articles/P	The complex analysis does not allow for traditional effect size calculations. However, multiple viable solutions are identified based on modern economic theory. Due to the many market failures in this area, it is understandably a priority for policymakers and researchers alike. This taxonomy of economic theories, while useful, does not constitute imperical evidence for or against any theory. Such evidence is sorely lacking.	47 push, pull, and hybrid nterventions identified to incentivise antibiotic development RELEVANCE FOR THE UK AMR STRATEGY KEY AREA/ACTION: this is highly relevant for the UK AMR strategy. Some, though not most, of these combinations are recommended in the O'Neill report, and the strategy itself vaguely emphasises the importance of PPPs. However, there are many other theories that come to the fore in this piece. This is a part of the strategy that I would recommend looking at in more detail.	Further work
		Assessing the relative merits of possible incentives to stimulate research and development in new antibiotics and other products	Unclear			SEE ABOVE			Further work
		Fast-track priority review arrangements for new antimicrobials	Unclear					Not evaluable	No further work
	Building international partnerships and coalitions to influence change at the national, European, and international level by influencing initiatives like IMI, to facilitate more efficient discovery and development of medicines, vaccines, and diagnostics	Building international partnerships to influence change at the national, and international, level to facilitate more efficient discovery of **medicines**	Unclear					consider looking at the linked document re: BIS for case studies pointing to effective partnerships.	No further work
		Building international partnerships to influence change at the national, and international, level to facilitate more efficient discovery of **vaccines**	Unclear						No further work
		Building international partnerships to influence change at the national, and international, level to facilitate more efficient discovery of **diagnostics**	Unclear						No further work
	Opening up the research agenda, encouraging life sciences companies and academics to work with and share information about targets (pre-competitive phase) and being innovative about the clinical research process to optimise effectiveness and efficiency (shorter time, less costly and fewer late-stage failures) whilst providing safety safeguards	Opening up the research agenda	Human					Inappropriate for evaluation as a part of this task. This is because of the broadness of the recommendation.	No further work
		Encouraging life sciences companies and academics to work with and share information about targets (pre-competitive phase)	Human					Inappropriate for formal evaluation as a part of this task. This is due to the fact that 'evidence' in this arena would be likely to be anecdotal, or based on case studies.	No further work
		Being innovative about the clinical research process to optimise effectiveness and efficiency (shorter time, less costly and fewer late-stage failures) whilst providing safety safeguards	Human			SEE the 2016 article from above. Also, please note the redundancies re: 'innovation' throughout step 4.			No further work

Key Area	Action	subactions	target population?	systematic review	Date	Source	evidence?	comments	Action
6: better identification and prioritisation of AMR research needs	Ensuring funding of high-quality and relevant AMR projects in response to the NIHR themed call announced as part of a co-ordinated response to the publication of the 'CMO's Annual Report'. This call covers all aspects of translational, clinical, and public health research that could contribute to a reduction in the spread or occurrence of AMR, through new developments or changes in practice.	Ensuring funding of high-quality and relevant AMR projects in response to the NIHR themed call announced as part of a co-ordinated response to the publication of the 'CMO's Annual Report'. This call covers all aspects of translational, clinical, and public health research that could contribute to a reduction in the spread or occurrence of AMR, through new developments or changes in practice.	Unclear					Not appropriate for evaluation as a part of this task.this is because 'ensuring funding' is a broad remit comprising translational, clinical, and public health research. An evaluation would have to demonstrate that research in at least one of these areas has proven useful or effective at changing policy, which is a foregone conclusion. One example would be vaccination regimen recommendations made by mathematical and economic modellers at LSHTM/PHE, and the subsequent adoption of those recommendations.	No further work
	NIHR plans to fund a 'Health Protection Research Unit on AMR/HCAI' from April 2014. An open competition inviting universities in partnership with PHE is already underway	Fund an HPRU	Human					Action completed. Not appropriate for evaluation as a part of this task.	No further work
	Ensuring that research funders continue to collaborate so that both research needs continue to be identified as the evidence base evolves and key priorities continue to be funded	Ensuring that research funders continue to collaborate so that research needs continue to be identified **as the evidence base evolves**	Unclear					Difficult to evaluate the effect of collaboration between research funders	No further work
		Ensuring that research funders continue to collaborate so that **key priorities continue to be funded.**	Unclear					Difficult to evaluate the effect of collaboration between research funders	No further work
	Identifying, through expert advice from the ARHAI and DARC, emerging AMR research needs in humans and animals	Identifying, through expert advice from the ARHAI and DARC, emerging AMR research needs in humans	Human					Not appropriate for evaluation as a part of this task. This is because 'identifying research needs' is effectively a research question, based upon the initial steps of the scientific method, a methodology which would necessarily be used to evaluate itself, in this case. (in other words, an auto-evaluation of the scientific method is far and away beyond the scope of this task!)	No further work
		Identifying, through expert advice from the ARHAI and DARC, emerging AMR research needs in animals	Animal					Not appropriate for evaluation as a part of this task.	No further work
	Forging stronger partnerships around investigating the mechanisms leading to AMR with a view to identify potential new targets for drugs and vaccines	Forging stronger partnerships around investigating the mechanisms leading to AMR with a view to identify potential new targets for drugs	Unclear					consider looking at the linked document re: BIS for case studies pointing to effective partnerships.	No further work
		Forging stronger partnerships around investigating the mechanisms leading to AMR with a view to identify potential new targets for vaccines	Unclear						No further work

Document 3: Table used to create the Sankey Diagram

Table associated with Sankey Diagram. From left to right is the outcome of interest, the count of papers who report on that, whether they were included or excluded in meta-analysis and why, the count of those papers, whether subgroup or statistical variation further divided the papers, the count of each subgroup or statistical choice, and the consequences for meta-analysis.

Outcome of interest	Count (of papers)	Include or exclude	Count (include or exclude)	Subgroup or statistical variation	Count (subgroup)	Consequence for meta-analysis
Length of stay	25	Excluded subgroup	12	n/a	n/a	Not enough to aggregate
		Include RCT	3	Mean/SD	2	Statistical variation*
				Median/IQR	1	Statistical variation*
		Include quasi-experimental	10	Mean/SD	7	Statistical variation*
				Median/IQR	3	Statistical variation*
Mortality	21	Excluded subgroup	3	n/a	n/a	Not enough to aggregate
		Include mortality outcomes	22	30-day	8	Different endpoints*
				In-hospital	7	Different endpoints*
				28-day	4	Different endpoints**
				7-day	1	Different endpoints**
				14-day	2	Different endpoints**
Stewardship	17	Exclude	17	Antimicrobial stewardship outcomes	30	Different endpoints**
Turnaround time	19	Exclude	19	definitions	36	Heterogeneous definitions***

*leading to small meta-analyses and large confidence intervals
**Not enough of the same endpoint to aggregate
***Not enough of the same concept to aggregate

Document 4 : Qualitative interview participants by case study site, job description, and location

Number	Participants	Job description	Location
1.	West Norfolk	Senior manager-clinical	Primary and Community Care
2.	West Norfolk	Senior Manager-clinical	Primary and Community Care
3.	West Norfolk	Senior manager-clinical	Primary and Community Care
4.	West Norfolk	Nurse practitioner	Primary and Community Care
5.	West Norfolk	Nurse	Primary and Community Care
6.	West Norfolk	Nurse	Primary and Community Care
7.	West Norfolk	Nurse	Primary and Community Care
8.	West Norfolk	GP	Primary and Community Care
9.	West Norfolk	Nurse	Primary and community care
10.	West Norfolk	Senior manager-clinical	hospital
11.	West Norfolk	Senior manager-clinical	Hospital
12.	West Norfolk	Senior manager-clinical	hospital
13.	West Norfolk	Senior manager-non-clinical	hospital
14.	West Norfolk	Pharmacist	Hospital
15.	West Norfolk	Junior doctor	Hospital
16.	West Norfolk	Pharmacist	Hospital
17.	Blackburn with Darwen	GP	Primary and community care
18.	Blackburn with Darwen	Nurse Prescriber	Primary and community care
19.	Blackburn with Darwen	Nurse	Primary and community care
20.	Blackburn with Darwen	Pharmacist	Primary and community care
21.	Blackburn with Darwen	Senior manager-clinical	Primary and community care
22.	Blackburn with Darwen	Senior manager-clinical	Primary and community care

23.	Blackburn with Darwen	Senior manager-clinical	Hospital
24.	Blackburn with Darwen	Microbiologist	Hospital
25.	Blackburn with Darwen	Senior manager-non-clinical	Hospital
26.	Blackburn with Darwen	Doctor (consultant)	Hospital
27.	Blackburn with Darwen	Doctor (consultant)	Hospital
28.	Blackburn with Darwen	Nurse prescriber	Hospital
29.	Betsi Cadwaladr	GP	Primary and community care
30.	Betsi Cadwaladr	GP	Primary and community care
31.	Betsi Cadwaladr	Nurse prescriber	Primary and community care
32.	Betsi Cadwaladr	Pharmacist	Primary and community care
33.	Betsi Cadwaladr	Senior manager-clinical	Primary and community care
34.	Betsi Cadwaladr	Doctor (consultant)	Hospital
35.	Betsi Cadwaladr	Pharmacist	Hospital
36.	Betsi Cadwaladr	Nurse	Hospital
37.	Betsi Cadwaladr	Scientist	Hospital
38.	Betsi Cadwaladr	Junior Doctor	Hospital
39.	Camden	Pharmacist	Hospital
40.	Camden	Microbiologist	Hospital
41.	Camden	Nurse	Primary and community care
42.	Camden	Senior manager – clinical	Hospital
43.	Camden	Nurse	Primary and community care
44.	Camden	Doctor (consultant)	Hopsital
45.	Camden	Nurse	Hospital
46.	Camden	Senior manager – clinical	Primary and community care
47.	Camden	Pharmacist	Primary and community care
48.	Greater Glasgow and Clyde	Doctor (Consultant)	Hospital
49.	Greater Glasgow and Clyde	Pharmacist	Hospital
50.	Greater Glasgow and Clyde	GP	Primary and community care
51.	Greater Glasgow and Clyde	Doctor (Consultant)	Hospital/ Primary and community care

52.	Greater Glasgow and Clyde	Doctor (Consultant)	Hospital
53.	Greater Glasgow and Clyde	GP	Primary and community care
54.	Greater Glasgow and Clyde	Pharmacist	Primary and community care
55.	Greater Glasgow and Clyde	Senior manager - clincial	Hospital
56.	Greater Glasgow and Clyde	Pharmacist	Hospital/Primary and community care
57.	Greater Glasgow and Clyde	Doctor (Consultant)	Hospital
58.	Greater Glasgow and Clyde	GP	Primary and community care
59.	Western Health and Social Care	Pharmacist	Hospital
60.	Western Health and Social Care	Senior manager – clinical	Hospital
61.	Western Health and Social Care	Senior manager – clinical	Hospital
62.	Western Health and Social Care	Nurse	Hospital
63.	Western Health and Social Care	Doctor (consultant)	Hospital
64.	Western Health and Social Care	Nurse	Primary and community care
65.	Western Health and Social Care	Dentist	Primary and community care
66.	Western Health and Social Care	GP	Primary and community care
67.	Western Health and Social Care	Pharmacist	Primary and community care
68.	Western Health and Social Care	Midwife	Primary and community care
69.	Western Health and Social Care	Doctor (consultant)	Hospital
70.	Western Health and Social Care	GP	Primary and community care
71.	Western Health and Social Care	Pharmacist	Primary and community care

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EDITORIALS

Subscription model for antibiotic development

An unlikely answer to the global crisis in antibiotic resistance

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In July 2019 the National Institute for Health and Care Excellence (NICE), NHS Improvement, and NHS England announced that they will trial a "subscription model" when paying for new classes of antibiotics.[1] This incentive for antibiotic research and development decouples payments to drug companies from the volume of antibiotics sold, to help encourage new products to market.

The model will use a health technology assessment process to identify a base "value" that the NHS would pay to pharmaceutical companies annually, regardless of how many prescriptions are issued. There may also be a small cost for each prescription, but the details of this new incentive have yet to be announced. The scheme's relation to existing means of valuing antibiotics and to related strategies for infection control requires scrutiny.

Global problem

Antibiotic resistance is recognised as a major global problem. Only one antibiotic in a new class, teixobactin, has been discovered in the past 30 years, and it was developed by a company spun out of a university research group.[2 3] Policy makers will aim to protect any new antibiotic by prescribing it for only the most severely drug resistant infections, which the industry says discourages antibiotic research.

Unfortunately, even if this subscription model and other pull incentives facilitate the identification of new classes of antibiotic, resistant bacterial isolates will eventually emerge.This is the normal result of evolution given underlying mutations, drug selective pressures, and number of doses given. Teixobactin claims to be evolution proof in the laboratory,[2] but these are small experiments compared with the real world experiment that occurs when antibiotics are taken on a global scale.

Although we welcome the news that the UK government will be investing in tackling antimicrobial resistance, and while the pharmaceutical sector may be a key partner in systemic approaches to managing the risk of antibiotic failure, tied investment in a particular pricing or incentive strategy poses considerable risks to public finances and policy goals.

Complex response

Revitalising the antibiotic pipeline is only one component of the complex response necessary to tackle antibiotic resistance. We must take care that innovations in pricing and incentive strategies do not sideline cheaper and potentially more effective opportunities to tackle systemic antibiotic failure. The subscription model aims to pay a fair price, but it is not clear how value will be assigned to any new antibiotics since their effectiveness in reducing antimicrobial resistance can be measured only retrospectively, after sustained use.

We should also be drawing on innovations in other treatment regimens for infectious diseases. For tuberculosis and HIV, monotherapy would be out of the question, and yet we persist in adhering to a single antibiotic course in many clinical settings.[4] Investing in local surveillance may also reap dividends by allowing us to optimise and tailor current treatment options—for example, by allowing local knowledge to modify prescribing guidelines.

Perverse incentives

If the incentive is successful, patients with a multidrug resistant bacterial infection will benefit from new treatment options. From the perspective of industry, however, this fund may be most useful for already discovered compounds that are known to be effective but were never released because of economic considerations. This might result in new releases but relatively lower investment in new compounds. Creating incentives based on a societal "value" calculation could lead to perverse incentives in the future, with companies holding back innovations in the hope that perceived value will increase as antimicrobial resistance rates get worse.

The dominant discourse around antimicrobial resistance draws heavily on liberal and behavioural economic models: by nudging companies to invest and urging individuals not to demand antibiotics and doctors to restrict prescription.[5 6] But structural and social solutions, such as improving sick pay entitlements for workers, reducing poverty, and providing longer appointment times with better resourced primary care, can also contribute to

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reducing infections, antibiotic use, and antibiotic resistance in the long term.[5-8] Unfortunately, these options are not a major part of the policy discourse.

This new payment model might boost drug discovery but it may also siphon away funds from known effective public health, social, and structural interventions; encourage distortions in global pharmaceutical regulatory markets; and create no long term meaningful change in the antimicrobial resistance framework. An international and interdisciplinary approach will be required if this policy is to be successful.

Understanding how this policy option came to dominate discourse is crucial. In a political context that supports market approaches in antimicrobial resistance, incentives can act as a means of capturing public resources for private gain. We must evaluate the subscription model throughout the policy cycle to avoid any risk of moving from an incentive scheme for new antibiotics towards a broader taxpayer funded grant state for big multinational drug companies.

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Document 6: The benefits and risks of public awareness campaigns: World Antibiotic Awareness Week in Context

The benefits and risks of public awareness campaigns: World Antibiotic Awareness Week in context

November 18, 2019

WAAW presents an opportunity for us all—around the world—to reflect on our relationships with antibiotics, now and into the future

Every element of health seems to have a day, week, or month dedicated to raising awareness. This is not necessarily bad; awareness campaigns can have a lasting impact for patients, professionals, and the public—and the longer and more intensive they are, the more likely it is that they work. [1] Mass media public health campaigns can raise awareness of the ills of tobacco and increase people's intention to quit smoking—although they seem not to increase the number who successfully manage to quit, according to the biggest review to date on this topic. [2] The same review found some evidence that sexual health public awareness campaigns effectively increased condom use. [2] This is not limited to strictly public health campaigns either; mass media coverage of climate change in Japan—linked to national campaigns—has increased the public's understanding of, and concerns about, the same issue. [3]

Antibiotic resistance mass awareness campaigns are relatively new compared to many of these examples. The first World Antibiotic Awareness Week (WAAW) was launched by WHO in November 2015, centred upon European Antibiotic Awareness Day (EAAD), which is in its 12th year. The stated mission of WAAW was ambitious: to raise awareness about AMR, to halt its emergence and spread, and to encourage best practice by professionals and the public. Each year, WHO compiles a selection of posters and videos in different languages on their website. The scale and energy of implementation of WAAW activities then relies on national governments and local health organisations and their (already overworked) staff.

This year, NHS England has marked WAAW by sending a letter to commissioners and providers asking them to "engage" with WAAW (18-24 November) and EAAD (18th November), and to "register" their WAAW-compliant activities. It also exhorts staff to check their local antibiotic guidelines and seek additional training for antibiotic prescribing. On top of all of this, the "keep antibiotics working" campaignwill run again for the month of November—readers may recall the advertisement with singing and dancing antibiotic tablets.

What work do these campaigns do?

It is unclear what impact, if any, these types of social marketing campaigns have in the field of antibiotic resistance. A 2010 review found that they can have some positive benefits, when done properly, over time, with a multifaceted campaign that targets both professionals and the public. [1] In this way, the English campaign gets it right. However, many of the key messages—such as "finish your antibiotic prescription"—are scientifically debatable, which can undermine public trust. [1, 4] The ways antibiotics and microbes are described in public media are understood to be confusing not only in scientific complexity, but in locating responsibility for action. [5] In different settings, knowledge of AMR does not translate directly to intended action—for example increasing use of particular antibiotics. [6, 7] Raising AMR awareness has also been shown to lead to negative consequences such as stigma of minority groups. [8, 9]

Given these challenges, the AMR community has welcomed a recent report from the Wellcome Trust, "Reframing Resistance," which aims to support communication "based on the best available empirical evidence." [10] Premised on an aspiration for a universal set of AMR messages that can work across settings, the report sits uncomfortably with evidence that information needs vary across contexts; a 2018 review of awareness raising interventions across different target populations found success varied markedly. [11] The same message that will draw attention from policy makers may not resonate with the public and care providers around the world. Indeed, Wellcome's testing of the "antibiotic apocalypse" narrative across settings showed it to be at best confusing and at worst actively detrimental to the relationship between experts and members of the public. It is interesting, therefore, to recommend a universal communication message of AMR

as “undermining modern medicine” together with a logic that raising public consciousness will result in political pressure to act, a context-bound assumption that is unlikely to hold across political settings.

It is true that campaigns can marshal support. An evaluation of European countries involved in EAAD found that the majority of governments allocated funds to EAAD activities, and media attention increased on the topic while the campaign was running. [12] However, in the context of overworked public health staff, the exhortations to “engage” may be causing other health priorities to fall by the wayside, all for the sake of a campaign that is likely to be only marginally beneficial, if at all.

Co-opting of public health awareness campaigns

Mass media awareness campaigns are, at their core, public health interventions. As such, they should be as evidence-based as other public heath interventions, and wherever possible, the potential negative consequences should be evaluated, and understood.[13] Potential costs are that the involvement of industry may cloud the messaging, create trust issues with the public, and may even result in distortion or misrepresentation of the science. This has been shown for alcohol, tobacco, high fat sugar and salt foods, and baby formula in the past. This also happens with pharmaceutical companies who push so-called “disease awareness campaigns.” [14]

In AMR, it is often said that the pharmaceutical and diagnostics industries are part of the solution. [15] However, as in all sectors, industries’ interests and incentives do not necessarily align with those in public health. WAAW offers companies the potential to highlight their particular products, and the opportunity to reframe the AMR discussion in terms that will benefit their corporate strategies, a clear conflict of interest that should be considered before offering industry a seat at the public health table. Corporate social responsibility (CSR) is one vehicle through which this potential can be realised. There is now a thin line between industry activities in informing the public (as part of WAAW), and pushing particular diagnostic tests or reframing the funding landscape as an impossible barrier for the private sector to overcome. This is not simply an abstract ethical comment—there are actual harms engendered. Capturing public money for industry led solutions and introducing early technologies that are under-evaluated or whose value is overstated are activities that capture public funding and investment that could be put to better use. There is also the question of crowding and skewing the policy agenda, such that policy support for industry-led or industry designed solutions come to be seen as preferable to public health systems strengthening and reform.

Solutions

WAAW presents an opportunity for us all—around the world—to reflect on our relationships with antibiotics, now and into the future. As WAAW grows, we can make deliberate choices about AMR messaging tailored for different groups, in an evidence-based way, as with other public health interventions. One-size-fits-all messaging can confuse, and actively harm, our AMR efforts internationally. For policy makers, global level apocalyptic narratives may be required to out-compete other threats to health and security. For members of the public however, if we wish to engage curiosity and critical reflection rather than feed a “risk society”, different messages are required. Either way, WAAW campaigners are not responsible for industry’s use or misuse of messaging. Industries operating in AMR do not have the same agenda or bottom line as governmental and inter-governmental organisations. Without oversight of these industries, there is a risk of mission capture when collaborating with, and accepting funding from, organisations whose interests are to increase market share, push for deregulation, and, if possible, acquire public funds and policy space to subsidise investments and reap shareholder profit. For WAAW to be successful, and a means towards a public health end, is such a close relationship with the private sector required, ethical or effective? While the popularity of a public private partnership approach makes it seem inevitable that industry needs to be “at the table,” the public sector should not be cast as naïve for taking their regulatory role seriously; by being wary of offering industry a seat at the table, public health experts can prevent attempts to co-opt public awareness in order to capture and divert public funds.

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Document 7: Abstracts from 2019 and 2020 conference presentations at the Society for Social Medicine, published in the Journal of Epidemiology and Community Health

2019: Why do some GPs and practice nurses in the UK continue to prescribe antibiotics inappropriately? A qualitative analysis of health professionals' antibiotic prescribing in primary care in the NHS

FREE

RE Glover,
A Fraser

Background Antibiotic prescribing in primary care has decreased over the last five years. Nevertheless, this remains an area of concern as antibiotic resistance rates continue to increase. Some prescribers continue to prescribe inappropriately – i.e. in contradiction of clinical guidelines. This qualitative study undertakes thematic analysis to determine the attitudes and perceptions of these professionals about inappropriate prescribing.

Methods We draw on data from our evaluation of the UK's five-year antimicrobial resistance strategy, undertaken from 2015–18 funded by the Department of Health and Social Care. We conducted 73 semi-structured interviews across six case study sites at the CCG level or equivalent in each of the four nations in the UK. Relevant informants in each trust were theoretically sampled in order to capture a mix of professionals in each case study site (including GPs, nurse prescribers, antimicrobial pharmacists, medicines management trust professionals, microbiologists, hospital doctors with opinions on primary care, and commissioners with oversight roles). Analysis was undertaken drawing on inductive and deductive logics.

Results In primary care, antibiotics have a symbolic potency that is constructed and mediated through the interactions of the prescriber and the patient. These interactions produce a negotiated understanding between both parties in relation to the significance and symbolism of an antibiotic prescription. Our analysis highlights how decisions to prescribe an antibiotic may be influenced by the context of competing pressures extrinsic to the patient-provider relationship, including time, risk, and responsibility. In certain circumstances this may lead to the inappropriate prescription of an antibiotic script.

Influenced by the theory of negotiated order,[1] we explore how different approaches towards antibiotic-seeking behaviour by patients are interpreted by prescribers. We highlight how extrinsic factors may influence co-produced care, and consequently impact upon a patient or provider's agency, including: (1) rapid diagnostics, which aim to reduce uncertainty in a consultation; and (2) disruptions to medical hierarchies, such as attaching an antimicrobial pharmacist to a GP practice in order to monitor the appropriateness of antibiotic prescriptions.

Conclusion How providers negotiate their patients' antibiotic-seeking behaviour is linked to temporal factors, professional experience, perceptions of risk, and culturally mediated understandings of 'appropriateness'. Future efforts to reduce antibiotic prescribing in community settings may be achievable by pulling on extrinsic levers, rather than sacrificing the patient-provider relationship.

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2020: Stakeholder narratives of 'problems' and 'solutions': analysing the 2018 Health and social care committee antimicrobial resistance submissions in the United Kingdom

RE Glover
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Background Antimicrobial resistance (AMR) is an area of global policy attention. Antibiotic resistance is often characterised as a 'wicked problem', because it (i) affects, and requires simultaneous action by, public, private, and third sector stakeholders, (ii) requires local, regional, national, and supranational buy-in (and implementation of strategic change) across low, middle, and high-income countries, and (iii) spans human, animal, and environmental health. The corollary to AMR being described as a wicked problem is that 'crisis' narratives have been adopted by public health policymakers and practitioners to marshal resources, attention, and public engagement. This AMR narrative has been co-opted at times, in order to privilege solutions promoted by and involving the private sector; with the co-optation of these solutions comes the risk of sequestering public sector funds to subsidise private sector work – in particular, in the pharmaceutical and medical diagnostics industries.

Methods There were 72 written submissions made to the 2018 'Antimicrobial resistance' House of Commons Health and Social Care Committee. The sectors represented in these submissions were industry, trade associations, non-governmental organisations, professional associations, academia, government, public private partnerships, and homeopathy proponents. We accessed these documents and extracted relevant data according to the theoretically-informed critical discourse analysis (CDA) framework that we developed. Once this was complete, two researchers collaboratively coded the findings. A third researcher randomly coded a sample of the documents in order to determine reliability.

We identified the dominant and biosecurity narratives that were used by the various actors who submitted evidence. We then compared the narratives, framing, and language used by the private sector with public and third sectors, and academia. We subsequently analysed the three main promoted 'remedies' to the AMR problem and categorised them within a 'market paradox' framework.

Discussion We found that, irrespective of sector, the submissions presented the problem of AMR similarly. The solutions, however, diverged dramatically. The relevant industries use particular discursive strategies to achieve their aims, including the development of market paradoxical positions; on the one hand, asking for subsidies and incentives, but on the other hand explaining that regulation would be detrimental to 'innovation'. We expand on these paradoxes, and catalogue the tactics used to achieve them discursively, including: obfuscating funding sources, stake inoculation, and lobbying for influence. Learnings from the unhealthy commodities industry allowed us to critically appraise the framing of industries involved in AMR.

Conclusion Overall, our CDA demonstrates that commercial interests deploying the crisis narratives do so in order to lobby heavily for self-serving solutions, namely deregulation and public subsidies. Discursive choices shaped by a technocratic-industry complex are redefining the pathways to success, monitoring, and decision-making in the global AMR arena.

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Document 7: Ethical approvals for qualitative research

Action Required	Status	Review Reference	Date Modified
No	Favourable (Fast-Track)	14569 /RR/11538	31/10/2018 17:11

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