So You Got Two Ologies? The Challenge of Empirically Modelling Medical Prescribing Behaviour and its Effect on Anti-Microbial Resistance as a Case Study

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Abstract. This paper reports the early stages of a funded project "Antimicrobial Resistance as a Social Dilemma: Approaches to Reducing Broad-Spectrum Antibiotic Use In Acute Medical Patients Internationally" to use ABM in understanding how the prescribing behaviour of professionals in "medical institutions" may affect the prevalence of Anti-Microbial Resistance (hereafter AMR), a situation in which standard treatments for infections fail. The first section explains the policy challenge of AMR and the research project strategy. The second section considers distinctive challenges raised by this kind of policy modelling. The third section presents preliminary results and the final section concludes.

1 The Policy Context

AMR is a current (and potentially catastrophic future) global problem in healthcare (http://www.bbc.co.uk/news/health-21702647). Formerly, the development of new antibiotics led medical professionals to believe that new treatment possibilities would always be available but, more recently, there has been a "drying up" of new medicines and a decline in the effectiveness of current ones. In a nutshell, AMR arises when bacteria are exposed to medicines that lack sufficient strength to kill them outright. (This may happen for many reasons: Failure to complete the course of treatment, mis-prescription, sub-standard drugs, the presence of asymptomatic conditions that are not intentionally being treated and so on.) The project on which this research is based is specifically organised around the problem that prescribing behaviour may constitute a social dilemma [1]. Ideally, medical professionals would use the results of
laboratory tests to accurately identify bacteria and thus prescribe the most effective and least "broad spectrum" antibiotic. (Narrow spectrum antibiotics are effective against one or a few conditions while broad spectrum ones have wide effectiveness.) In practice, medical good practice and the speed with which some conditions (like sepsis) develop make this strategy unfeasible (particularly where laboratory tests may be delayed or unreliable) with the result that medical professionals frequently begin by prescribing broad-spectrum antibiotics. These are rather likely to be effective against whatever ails the patient but at the cost of potentially creating resistance in other bacteria at the same time (which can then reproduce and spread in the population by a variety of mechanisms).

How do we manage a system in which the individual benefits to the particular patient (not dying) may be in conflict with the benefits to future patients (having effective treatments so they don’t die)? What would it be like to live in a world where currently routine surgery (including, for example, caesarian sections and appendectomies) was too risky because typical concomitant infections had become untreatable? There is also a wider context in which the use of antibiotics in animals is not limited to medical need — regular doses promote growth even in healthy animals — and not regulated with AMR in mind and where, in many countries, either deliberately or through inadequate enforcement, strong antibiotics can be bought "over the counter" without the intervention of relevant medical expertise serving a stewardship role [2]. This is another example of a global health problem. It doesn’t matter where AMR arises — and it is rather likely to arise at the "weakest links" in the global health system. Once it has arisen, it will spread.

This paper reflects on a variety of challenges that ABM faces in making a worthwhile contribution to this problem in the hope that these may serve as a case study of interest for other such projects.

2 The Policy Challenges

Part of the reason for presenting this model (even in its early stages) is that it throws up a number of interesting challenges of wider potential relevance. These can be divided into three broad classes.

The first class (which inspired the title of the paper) is the need to build a model which interfaces directly both with microbiology and with epidemiology (as well as the psychology and sociology that bear on medical decision making and the institutional structure of medical treatment). In order to understand the problem of AMR, it is not possible to “abstract out” either from the way that illnesses develop and present to the patient and the medical professional or from the way that these illnesses spread from person to person in the "wider world". This immediately presents a subsidiary problem (particularly for illness presentation) that might be called “model scaling”. The initial ABM of decision-making (mainly designed as a basis for discussion by various experts and research collaborators — and described in much more detail in [3]) is neither large nor hugely complicated but it is not at all clear to what extent it is possible both to abstract realistically from microbiology (such that the policies developed using the ABM stand some chance of actually being useful in the real world) and to ensure that the microbiological element of the model doesn’t become unfeasibly large in its own right (but see [4]). There are two specific aspects of microbiology that might give
rise to this challenge. The first is the process of mutation and transmission of resistance. In this process, completely new mechanisms of resistance (either for specific antibiotics or for a range of treatments operating in a similar way) can arise and, once they have arisen, can transfer from one kind of bacteria to another (resulting in the ultimate threat of multi-drug resistant bacteria). The second is the detail of the interplay between bacteria and antibiotics. For example, an antibiotic that is introduced into the body in sufficient doses to treat sepsis in an external wound effectively may then operate at a much lower dose in the gut and thus create potential for the development of AMR at that site (particularly since the gut is often a site of asymptomatic bacterial colonies). Furthermore, there is a cross over effect in that one thing that determines the more “traditional” (Darwinian) spread of AMR is whether or not particular mechanisms of resistance (or combinations of mechanisms) experience a significant “evolutionary survival penalty” in their reproductive cost. If the antibiotic is present and “challenging” the bacteria, it may be a resistant variant that comes to dominate the environment (with consequences for subsequent transmission) but if the antibiotic is absent, the non-resistant variant may be the one that has greater reproductive potential. It can be seen that if the ABM needs to represent individual bacteria (or even competing open ended populations of variant bacteria) at different sites in the body then the model needed as a “chassis” for understanding the impact of medical decision-making could become extremely challenging in its own right. (It would be frustrating to invest in such a model only to discover it had little effect on the policy outcomes but in a complex system, such a discovery is perfectly possible.) The attempt to address this problem is ongoing but has proceeded by stages. The initial ABM (discussed below) was designed to be concise and “not incompatible” with relevant reading and expert judgment. However, while it was possible to devise a coherent and “structurally plausible” ABM (one that did not abstract out from any clearly relevant processes like prescribing decisions or social transmission of disease), it was also clear that the model was not congruent with certain aspects of the intended problem under study (in particular the distinctive functioning of broad and narrow spectrum antibiotics in prescribing and the exact nature of the resulting social dilemma). However, the basic model proved sufficient both to sharpen thinking about the nature of this challenge and devise effective questions that allowed the elicitation of a stylised microbiology from an expert microbiologist. (It is surprising how reticent published academic research on AMR is regarding how this is actually supposed to occur.) This stylised model is currently being finalised and incorporated into the ABM.

The second challenge (which might be seen as an outgrowth of the first) is to build and interpret a model in which the diverse perceptions of different types of agents shape the evolving system. There is an explicit microbiology that researchers can “access” via their privileged position with respect to the ABM but the patient only knows that they “feel bad” and can articulate certain symptoms (like fever or diarrhoea). The medical professional can diagnose on the basis of those symptoms (though they may not be perfectly reliable indicators of the underlying condition and the patient may not be able to report them reliably) or can make use of laboratory testing (which “bypasses” the symptoms and attempts – but still somewhat fallibly – to identify the actual infecting agent). Back in the real world, notoriously, we only have data about patients who actually seek
treatment (unless they die which produces some data but not necessarily what is needed) and even if we know what they are suffering from, we may not know with any assurance where they got it. (This is a problem besetting models that attempt to adjudicate the different “causes” of hospital infections such as different classes of medical workers and poor hospital hygiene, see for example [5].) By its nature this problem cannot be “solved” but it is far better that the modeller be aware of it than not be.

As suggested in the discussion of results below, the best that can be hoped for is a model that sensibly “interfaces” with the sorts of data that are actually likely to be available at different levels of description such that they can then be used for calibration and/or validation as appropriate. For example, we can ask patients how they feel directly. We can ask medical professionals to diagnose based on different kinds of symptoms (which may be “invented” to explore counterfactual decision making). We can use laboratory research to check the connections between tests and symptoms.

To what extent is diarrhoea a reliable indicator or a particular illness? To what extent can it be made a more reliable indicator by asking subsidiary questions (short of testing) about that symptom? It seems that (based on this example) many policy models may have to engage with the fact that different actors do not simply disagree about a shared state of the world (as with economic preferences and many analytical models for example) but actually see the world in fundamentally different ways. (For an example of subjective and “objective” data in the slightly different context of wellbeing see [6]).

The final challenge (and one that is less specific to the AMR model but is nonetheless interesting) is to make effective use of different sources of data to end up with something that is actually suitable to make a policy contribution. One can of course build the model using expert opinion alone (and this may have rhetorical advantages in getting “implementation buy in”) but a model that simply reproduces particular prejudices may do more harm than good (see [7] for a recent general introduction to this approach). How do we draw a boundary between scientific knowledge that can be “objectively” incorporated into the model (whether the experts are comfortable with it or not) and knowledge that is only effectively accessible via experts (and filtered through their potential prejudices)? Some relevant examples, showing the problematic link between funded research and practical science have already been suggested. Firstly, it may be that any benefits of a project to improve prescribing for humans is “swamped” by the effects of animal use and/or free market availability of antibiotics. Even if it becomes clear that market aspects are the problem, a lack of political will and the limited feasibility of effective regulation in some countries means that it almost certainly will not be dealt with. Secondly, it is surprisingly hard to establish conclusively from the literature what the evidence base is for the claim that prescribing behaviour creates or speeds up the development of AMR. While it is fairly plausible (and supported by qualitative interviews with relevant medical professionals) that there is a potential social dilemma in play, one simple but fundamental reason why prescribing might not be susceptible to change is because medical professionals simply don’t share the characterisation of the problem put forward by the researchers. Thus there is not only a technical problem of making the ABM both empirically convincing and suitable for exploring practical policy but a contextual problem of making sure it is solving the right problem and cannot simply
be dismissed by experts as enshrining a particular arbitrary view that they
do not share. We now turn to seeing how some of these issues play out in
the current form of the model.

3 Some Preliminary Results

As already suggested, the aims of this model were, firstly, to produce
something quickly that worked and could then be a basis for collaborator
and expert discussion and, secondly, to create something approximately
“structurally valid” for future development. By the latter we mean that
while particular elements of the model were simplified (for example,
medical professionals always have access to exactly the right antibiotic for
any given illness), there were no aspects of the domain (at least based on
our judgment of the literature and considerable expert discussion) that was
deliberately excluded. Pursuit of this aim is less common than might be
supposed. To take just one example, McPhie-Knowles [8] opens her
discussion of a food safety ABM by discussing the implications of “the
increasing complexity of the food supply chain” but her model contains no
such supply chain and even the shops and restaurants she does represent
are not “correlated” in sharing suppliers (as might be expected if supply
chains were in operation). The first ABM thus serves as a “chassis” for
later versions (although, as previously suggested, the stylised
microbiology of the initial version has already been found wanting and is
in the process of being superseded.)

A good illustration of this “structural validity” approach is the
treatment of medical professionals in the model. The research project deals
with hospitals and, as such, will need to take account of institutional
structures and things like the possibility of cross infection (see for
example [9]). The simple model involves what are effectively “single
hander” GP practices so it retains the structural aspects of patients
deciding they are ill and needing treatment (and then going to a medical
professional and receiving it) but does not, at this stage, deal with the
“bureaucratic detail” of that process (and to be fair, in the UK at least,
much illness is dealt with effectively on the basis of single GP visits
followed by dispensing via a chemist/pharmacist.) A similar principle of
simplification without elimination was the aspiration of the model as a
whole.

The model has three core elements: The treatment process, the
illnesses and the social context. The latter is probably the simplest to
describe. Agents move around at random (another simplification from
moving around purposively that nonetheless retains the “structural
importance” of movement and social contact) and may thus infect each
other with any illnesses they have (probabilistically and on the assumption
that all illnesses are based on mere contact rather than, say, sexual activity
— again an intended attempt at “structural validity” in regard to
transmission). If they decide they are ill, they will move immediately to a
patch (the simulation is written in NetLogo and the code is available from
the corresponding author) that has a medical professional on it. (These are
a small fraction of the total population.) The medical professional will
look at their symptoms (there are no laboratory tests at present though they
will be implemented very shortly) and then decide what treatment to
prescribe. The patient will then, 100% reliably, participate in the treatment
and will usually recover (for reasons that are just about to be explained).
As suggested above, in a sense, the illnesses need to be the most complicated part of the whole ABM. The mechanism of illness presentation is designed to be, in a stylised way, a reflection of how illness appears to work simultaneously from the perspective of the microbiologist, the patient and the medical professional. The key concept in the stylised representation is that of “illness level” (which might represent the quantity of bacteria in the body for example and thus be calibrated at least approximately). When first infected a patient has a very low illness level and no symptoms (but they will be contagious). As the illness level rises, symptoms appear, at which point the patient is in a position to seek medical treatment. If they don’t do so, or if the treatment doesn’t work, their illness level continues to rise until they develop symptoms that either carry a risk of death (like convulsions) or directly result in death (like heart failure). Illness level is a simple “point total” that is incremented stochastically in each tick with two thresholds (for symptoms appearing and risk of death). Furthermore, illness level can be decremented either by “natural resistance” or by treatment. (Part of the issue about AMR in “popular medicine” is to discourage patients from seeking antibiotics for viral conditions that often present in very similar ways. Giving antibiotics for a virus is a pure social harm because they will do the patient no good and can only increase the risk of AMR.) This process thus matches, in a stylised way, the progress of many illnesses. Patients are contagious before they know they are ill. They become ill and seek treatment. Once they receive appropriate treatment, they will usually recover at least while antibiotics continue to work. (Of course, these stylised diseases are still very abstract. Parasites may need to be treated differently, as will sexually transmitted diseases and some illnesses require operations or other kinds of interventions than medication.)

The final complication, for a stage in the model that has not yet quite been reached, is that the disease is represented as a bit string of arbitrary “properties” (which determine which antibiotics work) and also determine the symptoms. This is again plausible in a stylised way and allows relevant phenomena to be represented elegantly in the model. (For example, a virus and a bacterial infection can both present with fever and wheezing so a laboratory test may be needed to avoid inappropriate antibiotic prescription). Thus the model is designed to respect the social dilemma at the core of the proposed research. Treatment can be based on symptoms alone or can use laboratory testing that identifies the actual bacteria involved. At the same time, the simulated medical professional faces the real challenge that the decision may be time critical with the consequence that the patient might, albeit rarely, die.

The final element, which is the other “ology” in the title of the paper, is the way that the medical professional decides, based on the symptoms, what treatment to offer. This element is particularly simplified at present with assumptions of infallibility and free availability of antibiotics (that match any particular “bit string” of illness). This is the area of the model that will be most developed in later versions (but is also necessarily postponed by the research design of the project involving the need to achieve qualitative interviews with relevant medical professionals).

The ABM is designed to model a fixed geographical area (which could be thought of as Iphoria or Staphordshire) and, based on this view, is initialised by a relatively small number of agents (a vector) infected
with the two illnesses commonly explored (one of which is a bacterium that needs antibiotic treatment and the other of which is a virus that will typically get better through natural resistance). The existence of disease “flare ups” is easier to justify when thinking of bounded geographical areas as the process by which diseases continue to mutate and diffuse on a global scale would be much more challenging to model.

There is only really space to discuss one result in this paper and this is somewhat in the nature of a baseline (though it still raises some interesting issues). Given the assumed severity, contagiousness and so on of the illnesses, how dangerous would they be if no medical intervention occurred at all? Conversely, even if medical treatment were “perfect” (in a way that can be defined within the model) would there still be fatalities? Figure 1 shows the answer to this pair of “bracketing” questions.

![Fig. 1. Death tolls with no medical intervention and “perfect” intervention](image)

These results come from a population of 500 agents and it is therefore clear that, without medical intervention, the bacteria specified are extremely dangerous. There were ten runs in each simulation condition and the three bars show the lowest and highest death tolls along with the mean for all ten runs to give a sense of stochastic variation. (In fact, it happens that nobody dies of the virus because it is strongly controlled by natural resistance.) Perfect treatment is defined as a situation where everyone seeks treatment as soon as they display symptoms, the medical professional can tell the virus from the bacteria with complete certainty and they treat immediately with exactly the needed antibiotic (which the patient takes without fail) for the particular bacteria (which involves a perfect bit string match). Importantly, even with perfect treatment there is a death toll though it is clearly very much smaller than without treatment.

It is a commonplace that ABM may produce thought provoking or counter-intuitive results and even this simple model appears to do so (though it should be noted that both terms have a strong subjective element and should thus be treated with caution). Firstly, it draws attention to the “voluntaristic” nature of medical help seeking in the system defined. Except in the event of communicable diseases that are very rare in the UK (it was interesting to see notices at surgeries during the Ebola outbreak
telling potential patients to go away and phone in) treatment must be sought. This means that, even if a patient seeks help as soon as they have symptoms and treatment is immediate and perfect, they may still be unlucky and die because their illness level happens to build up very fast stochastically even while the medicine is taking effect. In many countries, where treatment is expensive and difficult to access physically, illnesses may not present until they have become much more serious with a concomitant effect on death rates even assuming “optimal” treatment at the point of presentation.

The second point could almost be classed as rhetorical but is still important. There is a very strong medical culture of saving life at all costs (which creates issues with things like approved euthanasia for example). Apart from “driving” the social dilemma of AMR – patients here and now take precedence over the many patients “yet to come” (a general issue with broadly “utilitarian” reasoning), this practice also leads to the view that the best outcome is “no death”. This model suggests that this outcome is simply not attainable (and shows exactly why not in a particular kind of health system) but also shows that doing “something” is already hugely better than not intervening at all. Other preliminary experiments (not reported here) tend to show that while changes in prescribing behaviour do impact on lives saved to a small extent, most of the value added comes from deciding to intervene in the first place.

This leads to a final interesting point that concerns the importance of things not discussed in the model. Although, cross infection was deliberately ruled out in the model, obliged ill people to co-locate for treatment (either at a GP or in a hospital) is not an obviously advantageous strategy (both in terms of direct symptomatic infection and the possibility of transfer of bacteria with AMR) and it is interesting that the old model of “house calls” may have had medical advantages despite its apparent lack of “technical efficiency”. In many countries, the cost and difficulty of seeking treatment has a profound effect on likely outcomes but, in fact, the same may be true (at least in specific circumstances) in the UK. Here the issue is not the great majority of cases successfully “fielded” by GP practices (which operate a vital and cost effective “triaging” system) but the speed of response that can be achieved for the relatively few people who are much iller than the initial contact would suggest. Given even a stylised disease process, effective wait time (and the ability to negotiate it in the light of new information) may become a crucial element of health outcomes. This is true whether the waiting occurs at home, under treatment, in A&E, pending referral to a consultant or somewhere else. Even the stylised illness model suggests why this may be so.

4 Discussion and Conclusions

It has been remarked that peer review gives a wholly unrealistic sense of the degree of “finish” to be found in the research process. The main “result” of this research in progress has arguably been to “throw away” a significant part of the existing ABM dealing with microbiology! Nonetheless, it is clear that engaging with real research problems, even in the early stages, generates insights that unlikely to be developed by cogitation alone. In this section I consider what this project has achieved and where it needs to go now.
As already suggested, the rapid development of a “chassis” ABM (which is nonetheless broadly “structurally valid”), based on an overview of existing literature and expert judgment, really does clarify thinking and provide a much better basis for focused discussion (particularly in collaborative research involving non-modellers). Without building the first model, it would not have been clear how incompatible it was with the idea of broad and narrow spectrum prescribing (despite its other many advantages) or exactly what questions to ask an expert to work out the relevant microbiological mechanisms for this. (As anecdotal support for an earlier claim, however, it is interesting how much experts disagree on the strengths and weaknesses of a model and how it would be most productive to develop it further. This situation, which I have observed in other projects, suggests that expert views must be treated with caution. Perhaps experts themselves need calibration and validation!)

Secondly, even the chassis model (as often claimed) throws up interesting and unexpected issues (about the role of “wait time” and the limited added value of particular interventions as opposed to intervention in general). If nothing else, this paper can be seen as another case study to support that broad claim about the virtues of ABM.

Thirdly, real problems create real challenges (which may not be the things that ABM is typically preoccupied with). The challenge of building models that “respect” (are empirically compatible with) the differing perspectives of microbiologist, patient and medical professional is not one that I have seen discussed in the literature and, interestingly, one that was discovered to be relevant to a rather different project at almost exactly the same time: Does it matter in effectively modelling people’s attempts to avoid counterfeit drugs that the researchers, like the patients, cannot really get reliable information about the prevalence of such drugs? Thus, this paper encourages a focus on ABM challenges that arise from definite problems rather than the preoccupations of the method itself.

The final implication is one that is not fully realised but can already be sketched. It is not worthwhile to devise a methodology for ABM [10] unless it can actually be implemented. This project has been an attempt to put such a methodology to the test with associated benefits and pitfalls. Before data is collected (but while data collection is being designed) one or more “version 0” models should attempt to synthesise existing theories, establish face validity with experts and collaborators, achieve broad “structural validity” and get a sense of the feasibility of calibration and validation from existing data. Does what is already known even approximately permit the ABM strategy for establishing a “good” model? (It is now our regular experience that one needs to “fight for” validation data in ABM research and ensure that it exists, or can be collected, right from the outset of any project. The issue of rigorous research design – [11, 12] – generally seems to me to be neglected in ABM relative to other methods like statistics or qualitative interviewing. This would be a concrete example.) The data collection process is designed to simultaneously improve structural validity, calibration and validation using “gaps” identified in existing research as a framework. (This approach must necessarily be open ended and it should not be presumed that any single research project is capable of completing it, only contributing usefully to it.) In parallel, existing policy interventions and expert judgment must be used to ensure that the resulting ABM (once it has shown sufficient quality to be credible to policy makers) is
“compatible with” the kinds of policies that are feasible and/or of interest. (Of course, there is no requirement that the model is used only to investigate such policies but to be credible it should at least be able to do that.) This project is thus part of a wider agenda to make a methodology of ABM workable in practice for policy relevant problems.

References