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The role of mathematical modeling in designing and evaluating antimicrobial stewardship programs

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Opinion statement

Antimicrobial agent effectiveness continues to be threatened by the rise and spread of pathogen strains that exhibit drug resistance. This challenge is most acute in healthcare facilities where the well-established connection between resistance and sub-optimal antimicrobial use has prompted the creation of antimicrobial stewardship programs (ASPs). Mathematical models offer tremendous potential for serving as an alternative to controlled human experimentation for assessing the effectiveness of ASPs. Models can simulate controlled randomized experiments between groups of virtual patients, some treated with the ASP measure under investigation, and some without. By removing the limitations inherent in human experimentation, including health risks, study cohort size, possible number of replicates, and effective study duration, model simulations can provide valuable information to inform decisions regarding the design of new ASPs, as well as evaluation and

improvement of existing ASPs. To date, the potential of mathematical modeling methods in evaluating ASPs is largely untapped, and much work remains to be done to leverage this potential.

Introduction

Antimicrobials (AMs) have been widely used to treat bacterial infections since penicillin was commercialized and distributed to the public in 1945 ***(1)***. Historically, they have been so effective that, by the 1960s, experts believed that bacterial infections were rapidly becoming a thing of the past ***(2)***. However, prolonged exposure to AMs, coupled with natural selection, has permitted many bacteria species to sustain genetic mutations that possess increased resistance to the effects of AMs ***(3)***. Resistance was observed as early as 1942 to pre-penicillin AMs, and resistance to penicillin was observed as early as 1947 ***(3)***. Since then, antibiotic resistance (AR) has become a massive problem in health care settings, causing high rates of morbidity and mortality. The Centers for Disease Control and Prevention (CDC) reports that over 2 million people become infected with AR bacteria each year in the United States, and that tens of thousands die annually because of these infections ***(4)***. The majority of these deaths occur in health care settings ***(1)***. Moreover, the CDC suggests that options for treating gram-negative bacterial infections are becoming limited, as gram-negative bacteria are becoming more resistant to AMs and few new medicines are in the pipeline ***(5)***. Some scientists believe the situation is almost as critical for gram-positive bacteria ***(6, 7)***.

It is well documented that increased AR is highly correlated with increased AM exposure ***(3, 8, 9)***. In 2010, there were 833 prescriptions for AMs written per 1000 people in the US: a total of 258 million prescriptions ***(8)***. Many professionals assert that this prescription rate can be reduced significantly by addressing what are generally considered inappropriate uses of AMs, including prescription of AMs for viral infections or for other reasons when they are not needed, sub-optimal dosage or treatment duration, overuse of individual AM classes (e.g. broad spectrum agents), treatment with an ineffective AM, prescribing AMs primarily based on financial reasons, and ineffective use of strategies (like cycling) designed to reduce overexposure to specific AM classes ***(2, 8, 9)***.

Strategies to ameliorate the rise and spread of AR in healthcare settings are desperately needed. In response, hospitals and other healthcare facilities have introduced guidelines and policies focused on responsible use of AMs that fall under the term *antimicrobial stewardship programs (ASPs)*. A policy paper released by the Society for Healthcare Epidemiology of America, the Infectious Diseases Society of America, and the Pediatric Infectious Diseases Society in 2012 describes antimicrobial stewardship as "programs (that) optimize antimicrobial use to achieve the best clinical outcomes while minimizing adverse events and limiting selective pressures that drive the emergence of resistance and may also reduce excessive costs attributable to

suboptimal antimicrobial use" ***(10)***. In addition to healthcare facilities, individual clinicians also acknowledge the need for guidelines to aid in responsible use of AMs. For instance, doctors have recently reported the desire for more guidance on optimal prescription practices ***(2)***.

An ASP can be viewed as a collection of individual *antimicrobial stewardship measures (ASMs)* intended to guide clinicians at various decision points in the infection treatment process, with a primary goal of treatment success for the individual patients, and, as a secondary goal, a reduction in the incidence of infections involving AR pathogens ***(10)***. For the purpose of this discussion, we draw a distinction between ASMs and "infection prevention measures," the latter including factors like hand hygiene, environmental decontamination, contact precautions, and patient isolation. The present work focuses specifically on ASMs.

Commonly-used ASMs include ***(10, 11)***:

A. *Institutional "default" treatment recommendations:*
    i. *Recommended treatment pathways* for commonly-encountered high-priority clinical syndromes (e.g. surgical prophylaxis, community-acquired pneumonia, urinary tract infections, and asymptomatic bacteriuria) are pathways that provide a foundation for the design of individual treatment protocols.
    ii. *Protocols for de-escalation of antimicrobial therapy* are standing recommendations advising clinicians on when to re-evaluate a patient's ongoing drug therapy. For instance, relevant lab tests may provide information to guide an efficient transition from therapy with a broad-spectrum AM to a targeted therapeutic protocol with a narrow-spectrum alternative.
    iii. *Protocols for discontinuation of antimicrobial therapy* are standing recommendations intended to help clinicians understand when relevant test results and other indicators suggest that antimicrobial treatment (AMT) may be safely discontinued.
B. *Formulary restriction and pre-authorization policies* are designed to control the use of specific therapeutic drugs, by requiring clinicians to obtain approval from a hospital ASP or other governing body before prescribing one of the restricted AMs. Restrictions are typically based on local infection and resistance patterns, as well as economic and other considerations.
C. *Targeted susceptibility reporting* refers to hospital antibiograms and other AM susceptibility information that are readily available to clinicians to inform their treatment decisions.
D. *Lab tests to identify causative pathogen(s) and associated antimicrobial resistance profile(s)* provide valuable information to clinicians as they seek to de-escalate a patient's ongoing AMT. De-escalation usually means switching from a broad-spectrum to a narrow-spectrum drug at a dosage and frequency sufficient to overcome the pathogen's demonstrated level-of-resistance to that drug.
E. *Prospective audits with feedback* from designated infectious disease-trained physicians and pharmacists are used to leverage the relevant expertise of these individuals to provide AM education

and advice on questions of AM prescription, including drug selection, use of restricted drugs, adjustment of initial therapies, and related matters.

A typical ASP will consist of some subset from this list of ASMs, coupled with a set of infection prevention measures. Note that we do not include *electronic clinical decision support* in our list of ASMs, despite its inclusion in a number of specific ASPs. From the perspective of "therapy decision points," this is not an ASM in its own right, but is actually a means to efficiently implement and facilitate many of the listed ASMs, principally by making relevant information and recommendations readily available to practicing clinicians.

Developing optimal ASPs is no small feat and testing the effectiveness of these programs with controlled epidemiological studies is nearly impossible in healthcare settings ***(6)***. Ideally, one would evaluate these ASMs through a controlled experimental investigation comparing outcomes in two groups of patients randomized between the current protocol and the ASM in question. However, cost, time, and ethical considerations make this evaluation strategy either impractical or impossible to implement with living patients ***(12)***. Mathematical modeling can augment standard epidemiological studies by providing the means to conduct simulations of these controlled experiments, simulating many replications in a short period of time, and involving only virtual patients. The benefits of these methods are vast: Individual ASMs, and combinations of ASMs, can be assessed without the cost of endangering real lives, thereby providing valuable information to ASPs and other healthcare professionals. Moreover, mathematical methods offer the potential to optimize ASPs without having to test each component ASM separately.

Here we review recent research publications (since 2012) that use mathematical models to investigate and assess specific ASMs. Most of these investigations utilize one of three principal model types:

- *SIR-type models:* The most commonly used mathematical models in infectious disease modeling are variants of the classical SIR model introduced by Kermack and McKendrick in 1927. These models simulate the spread of an infectious disease through a population by viewing the population as a finite number of homogeneous sub-populations. (Early SIR models used three sub-populations: Susceptible (to the infection), Infectious (capable of spreading the infection), and Recovered (from the infection), hence, the acronym "SIR" in the name.) The movement (reflecting changes in the disease state) of individuals between these sub-populations over time is typically modeled with a system of ordinary differential equations or, occasionally, stochastic transition (e.g. Markov) models. In the present context, SIR-type models are most often used to simulate interactions between groups of individuals (e.g. colonized and uncolonized patients) in a single hospital ward, an entire hospital, or a broader community. Some of these models treat patients and healthcare workers (HCWs) as separate populations, while other models make no such distinction.

- *In-host Population Models (IHPMs)*: IHPMs use ordinary differential equations to track the population of bacteria inside a person (host) as the bacteria interact with the in-host environment. The environment can include interactions with the immune system as well as with AMTs.
- *Agent Based Models (ABM)*: ABMs differ from both SIR-type models and IHPMs in that they simulate a collection of autonomous individuals (agents), rather than a finite set of homogeneous sub-populations. These agents are each given their own set of characteristics (e.g. infection state). The simulation proceeds through a sequence of interactions of agents with each other and with their environment. ABMs are particularly useful when the number of individuals is small (e.g. in a small hospital ward), or when individual differences are expected to be significant to the simulation. As the number of agents increases, ABMs become computationally expensive and are much less amenable to mathematical analysis when compared to either SIR-type models or IHPMs.

Although not within the scope of the present work, interested readers should note that some recent work on ASPs has also been done using statistical models (e.g. ARENA models) to evaluate ASMs. (See, e.g., ***(13-15)***.)

Models to Assess Antimicrobial Stewardship

Our literature search identified 18 papers, published since the beginning of 2012, that use mathematical models to assess the potential of ASMs to contribute to reductions in AR rates within hospitals. Table 1 collects basic facts about each.

Table 1. Key facts about each paper in the search results: first author; year of publication; pathogen studied; infection type; antimicrobial studied; and reference number. Abbreviations used: MRSA = methicillin-resistant *Staphylococcus aureus*; ICU = intensive care unit; VRE = vancomycin-resistant enterococci; MSSA = methicillin-susceptible *Staphylococcus aureus*.

First Author	Year	Pathogen	Infection type	Antimicrobial(s)	Ref #
Chamchod	2012	MRSA	Non-specific	Non-specific	***(16)***
Caudill	2013, 2015	MRSA	Pneumonia	Imipenem, oxacillin	***(17, 18)***
D'Agata	2012	Non-specific	Non-specific	Non-specific	***(19)***
Deeny	2015	Healthcare-acquired MRSA	None (screening)	Muporicin	***(20)***
Doan	2015	*A. baumannii*	Non-specific in ICU	Non-specific	***(21)***
Felton	2013	*P. aeruginosa*	Healthcare-acquired	Piperacillin-tazobactam	***(22)***

			pneumonia		
Geli	2012	Non-specific	Non-specific	Non-specific	***(23)***
Grima	2012	*C. difficile* and VRE	Non-specific	Non-specific	***(24)***
Hurford	2012	*P. aeruginosa*	Non-specific in ICU	Non-specific	***(25)***
Kardaś-Słoma	2013	MSSA and MRSA	Non-specific in ICU	Several non-specific classes, differing by activity vs. MSSA and MRSA	***(26)***
Obolski	2012	Non-specific	Non-specific	Two non-specific	***(27)***
Sypsa	2012	Carbapenemase-producing *K. pneumoniae*	Non-specific	Non-specific	***(28)***
Schultsz	2013	MRSA, ESBL-*Enterobacteriaceae*, *P. aeruginosa*, gentamicin-resistant *K. pneumoniae*, amikacin-resistant *Acinetobacter*	Non-specific in tetanus ICU	Ceftazidime, piperacillin-tazobactam, ciprofloxacin	***(29)***
Tan	2014	Carbapenem-resistant *A. baumannii*	None	Cefepime, ertapenem, imipenem, meropenem, piperacillin-tazobactam	***(30)***
Ternent	2015	Non-specific	Non-specific	Non-specific	***(31)***
Wiesch	2014	Non-specific	Non-specific	Two from unspecified classes	***(32)***
Yakob	2014	*C. difficile*	Gastrointestinal system, *C. difficile* infection	Non-specific	***(33)***

Antimicrobial Stewardship and Treatment Decision Points

Different ASMs target different decision points in an AMT protocol. It is instructive to organize the current ASM arsenal in terms of these decision points, i.e. the decisions made by the clinician during the progression of patient treatment from the initial decision to treat, through the discontinuation of therapy:

1. Will the patient receive AMT?
2. Details of the initial AMT plan:
    a. Choice of drug
    b. Mode of administration
    c. Dosage and frequency
3. Re-evaluation of therapy plan (for possible de-escalation):
    a. When to re-evaluate
    b. Re-evaluate choice of drug (e.g. switch from broad-spectrum to narrow-spectrum)
    c. Re-evaluate mode of administration (e.g. switch from parenteral to oral)
    d. Re-evaluate dosage and frequency
4. Discontinuation of AMT

In the context of "antimicrobial treatment decision points," ASMs can be viewed as aids to the practicing clinician at the different decision points. Table 2 lists each decision point, the supporting ASMs for each, and the modeling references that speak to each ASM.

Table 2. Clinical decision points (Column 1) during the course of AMT for an individual patient, and the specific ASMs (Column 2, corresponding to the numbering in the ASM list given above) that support each decision point. Column 3 lists references (since 2012) that use mathematical models to investigate the effectiveness of each ASM in reducing the emergence and spread of AR.

Decision Point	**Supporting ASMs**	**Modeling References**
1. Will the patient receive antimicrobial treatment?	A.i.	***(16, 19-21, 24-26, 28, 30, 31, 33)***
2. Initial therapy plan:		
a. Choice of drug	A.i.,B, C	***(25, 27, 29, 32)***
b. mode of administration	A.i.	***(22)***
c. dosage and frequency	A.i., C	none
3. Re-evaluation of therapy plan (for possible de-escalation):		
a. When to re-evaluate	A.ii., D, E	***(17, 18)***
b. Re-evaluate choice of drug	A.ii., B, C	***(17, 18)***
c. Re-evaluate mode of administration	A.ii., D, E	***(22)***

d. Re-evaluate dosage and frequency	A.ii., C	none
4. Discontinuation of antimicrobial therapy	A.iii., D	***(16, 21, 23, 25, 26, 28, 30)***

In what follows, we revisit each treatment decision point from Table 2, and discuss the relevant search results that address ASMs related to that decision point. For each reference, the key assumptions built into the model, the model type, and the outcomes predicted from the modeling study are summarized.

Will the patient receive antimicrobial treatment?

Eleven of the search results investigated factors that may inform this decision point. Of these, two ***(16, 20)*** simulate the impact of patient screening (upon admission) for MRSA, two ***(24, 31)*** investigate the impact of specific non-AM treatment options, and five ***(19, 21, 25, 26, 33)*** consider consequences of a non-specific reduction in the AM prescription rate. The remaining two ***(28, 30)*** consider an overall reduction in the hospital-wide consumption of AMs, without specifying particular actions that would bring about such a reduction.

Ten of these eleven studies assess ASMs in terms of pathogen prevalence, either discussing AR strains in particular ***(16, 19, 20, 24-26, 28, 30)***, or pathogen prevalence independent of resistance-level ***(21, 33)***. The remaining work ***(31)*** focuses on assessing effectiveness through successful clearance (within a single host) of an infection due to a pathogen population that features a mix of resistance-levels.

Key points on each of these 11 works:

- Chamchod and Ruan ***(16)***:
    - *Key assumptions:* AM treatment does not fully clear the pathogen. Patients with prior AM exposure progress from the colonized state to the infected state at a faster rate than those without prior treatment. Patients with prior AM exposure are more likely to become contaminated via HCW contact than those without prior treatment.
    - *Model type:* Ward-level SIR-type model of patients and HCWs.
    - *Model predictions: M*ethicillin-resistant *Staphylococcus aureus* (MRSA) infection is more prevalent among those patients with prior AM exposure than among those without treatment.
- D'Agata et al. ***(19)***:
    - *Key assumptions:* Only patients undergoing AMT may acquire colonization with multi-drug resistant organisms (MDRO).
    - *Model type:* Ward-level SIR-type model of patients without HCWs modeled directly.

    - *Model predictions:* Increasing the percentage of patients receiving AMs from 0% to 100% will increase MDRO-prevalence by only ~8%, from ~22% to ~30%.
- Deeney et al. ***(20)***:
    - *Key assumptions:* MRSA spread by direct contact between patients with no HCW-facilitated spread.
    - *Model type:* Ward-level ABM of patients without HCWs.
    - *Model predictions:* When compared to the strategy of "mupirocin treatment for clinical MRSA infections only," the "screen all patients and treat, with mupirocin, those who test positive for MRSA" strategy leads to a long-term decrease in incidence of mupirocin-resistant MRSA, while the "treat all patients prophylactically with mupirocin" strategy leads to a long-term increase in incidence of mupirocin-resistant MRSA.
- Doan et al. ***(21)***:
    - *Key assumptions:* There is no distinction between AR and non-AR *A. baumannii* strains. Infection can be spread by the local environment. AM treatment within last 30 days increases the likelihood that a patient will become colonized. AMT within the last 30 days implies that both colonized and infected patients are more infectious.
    - *Model type:* Ward-level SIR-type model of patients without HCWs in an intensive care unit (ICU).
    - *Model predictions:* A 61% reduction in length of AMT duration for *A. baumannii* ICU patients will result in ~14% decrease in prevalence of colonization and infection. A reduction in the rate of AM prescriptions will produce no significant change in prevalence of colonization and infection.
- Grima et al. ***(24)***:
    - *Key assumptions:* Vancomycin-resistant *enterococci* (VRE) patients on AMs are more likely to contaminate HCWs than VRE patients who are not on AMs. VRE-colonized patients are under contact precautions.
    - *Model type:* Ward-level SIR-type model of patients and HCWs.
    - *Model predictions:* Use of non-AMTs, such as fecal donor installation therapy, in 50% of *C. difficile* patients will result in an 18% reduction in prevalence of VRE colonization compared with AM use only.
- Hurford et al. ***(25)***:
    - *Key assumptions:* No multidrug-resistant strains of *P. aeruginosa* (PA). Under AMT, resistance emerges at a constant rate over time.
    - *Model type:* Ward-level SIR model of patients without HCWs in an ICU.
    - *Model predictions:* AMs for fewer patients will result in a lower number of patients colonized with *PA*.
- Kardaś-Słoma et al. ***(26)***:

    - *Key assumptions:* There is no distinction between colonized individuals and infected ones. The different AM "classes" differ only in their activity-level against MRSA. Within the hospital, infection is spread only through HCW contact.
    - *Model type:* Ward-level ABM of patients, without HCWs, in an ICU, linked to an SIR-type model of colonization within the local community.
    - *Model predictions:* A 10% reduction in overall AM use may result in outcomes ranging from a 69% decrease to a 52% increase in MRSA frequency in the ICU (and 37% decrease to a 46% increase in the community), depending on which AM classes are reduced.
- Sypsa et al. ***(28)***:
    - *Key assumptions:* Once patients are colonized, they remain colonized for the duration of their hospital stay. The duration of HCW contamination is one hour.
    - *Model type:* Ward-level SIR-type model of patients and HCWs.
    - *Model predictions:* In situations where 50% compliance with hand hygiene guidelines is required to control HCW-facilitated carbapenemase-producing *Klebsiella pneumoniae* (CPKP) transmission, a 40% reduction in antibiotic use could result in CPKP control with hand hygiene compliance as low as 40%.
- Tan et al. ***(30)***:
    - *Key assumptions:* The fraction of *A. baumannii* isolates that are carbapenem-resistant depends only on the total volume of AM used; in particular, it is independent of both ward-level and in-host dynamics.
    - *Model type:* A single ordinary differential equation modeling the proportion (over time) of *A. baumannii* isolates hospital-wide that are non-susceptible to either imipenem or meropenem. (Total AM consumption in the hospital enters as a constant in the differential equation.)
    - *Model predictions:* The number of defined daily doses (DDD) of ertapenem (hospital-wide) correlates with prevalence of carbapenem-resistant *A. baumannii*.
- Ternent et al. ***(31)***:
    - *Key assumptions:* The AM concentration inside the host remains constant over time. The anti-virulence drug increases the effectiveness of the immune response in clearing the pathogen. The transfer of AR genes via plasmids is modeled as "direct contact" in a well-mixed pathogen population.
    - *Model type:* IHPM of interactions between pathogen, immune cells, AM, and anti-virulence drug.
    - *Model predictions:* A two-phase treatment consisting of an anti-virulence drug, followed by an AM may result in clearance of a pathogen population, even when that population features a mix of AR levels.
- Yakob et al. ***(33)***:

- *Key assumptions:* Patients colonized with *C. difficile* are more likely to progress to *C. difficile.* infection if they were recently treated with AMs.
- *Model type:* Ward-level SIR-type model of patients, without HCWs.
- *Model predictions:* The rate of AM prescription has little effect on the rate of *C. difficile* infection, when bundled with either gut microflora support, hygiene and sanitation improvements, or shorter patient hospital stays.

Initial therapy plan – choice of drug:

Four of the search results investigate factors that may inform this decision point. Three ***(27, 29, 32)*** of the four study the impact of specific AM-selection strategies, such as cycling and mixing, while the fourth ***(25)*** focuses on the reduction of a specific category (anti-Pseudomonals) of AMs. Two of these ***(25, 29)*** assess ASMs in terms of prevalence of resistant strains of the pathogen in question. The remaining two ***(27, 32)*** focus specifically on prevalence of multidrug-resistant pathogens.

Key points on each of these four works:

- Hurford et al. ***(25)***:
  - *Key assumptions:* No multidrug-resistant strains of *P. aeruginosa*. Under AMT, resistance emerges at a constant rate over time.
  - *Model type:* Ward-level SIR model of patients, without HCWs in an ICU.
  - *Model predictions:* Reducing both the total number of AM prescriptions and the number of anti-Pseudomonal prescriptions will result in a lower number of patients colonized with AR *P. aeruginosa*.
- Obolski and Hadany ***(27)***:
  - *Key assumptions:* Resistance to an AM is complete (i.e. the AM has no effect on pathogens resistant to it). Available AM-selection options are cycling, mixing, or combining, each with two AMs from which to choose. AM-induced stress favors survival of resistant mutants only in patients where resistant strains already dominate.
  - *Model type:* Ward-level SIR-type model of patients without HCWs.
  - *Model predictions:* Selection of AMs via a "combining" strategy performs slightly better than either cycling or mixing with respect to minimizing singly-resistant infections, but performs worse than either cycling or mixing with respect to minimizing doubly-resistant infections.
- Schultsz et al. ***(29)***:
  - *Key assumptions:* Colonized patients remain colonized for the duration of their hospital stay. Cultures are 100% accurate. AM selection is made from a menu of three: ceftazidime, piperacillin/tazobactam, and ciprofloxacin.
  - *Model type:* Ward-level Markov SIR-type model of patients, without HCWs, in an ICU.

    - *Model predictions:* An AM mixing strategy involving a 53% decrease in ceftazidime usage and a 7.2-fold and 4.5-fold increase in usage of piperacillin/tazobactam and ciprofloxacin, respectively, may result in a large (nearly 70%) reduction in MRSA prevalence, but little-to-no reduction in prevalence of any of the four gram-negative pathogens included in the study.
- zur Wiesch et al. ***(32)***:
    - *Key assumptions:* Two broad-spectrum AMs (with no potential cross-resistance) are available to prescribe. Resistance to an AM is complete (i.e. the AM has no effect on pathogens resistant to it). Patients become susceptible to infection because of previous AMT.
    - *Model type:* Ward-level SIR-type model of patients without HCWs.
    - *Model predictions:* Adjustable cycling (i.e. initial AM selection via cycling protocol, but changing it when patient progresses from asymptomatic to symptomatic infection) works better than non-adjustable cycling in reducing prevalence of multidrug-resistance.

Initial therapy plan – mode of administration:

One of the search results ***(22)*** investigates factors that may inform this decision point. The authors used a model of *Pseudomonas*-piperacillin/tazobactam interactions within a single host to compare the effectiveness of two different administration methods - bolus injection and intermittent infusion - with effectiveness measured both in terms of total *Pseudomonas* load and the load of piperacillin-resistant *Pseudomonas*. Key points on this work:

- Felton et al. ***(22)***:
    - *Key assumptions:* Resistance to an AM is complete (i.e. the AM has no effect on pathogens resistant to it).
    - *Model type:* IHPM of interactions between pathogen and AM.
    - *Model predictions:* Bolus regimens are equivalent to intermittent infusion in terms of both the antibacterial effect of piperacillin/tazobactam on *Pseudomonas* and the emergence of piperacillin/tazobactam-resistant strains of *Pseudomonas*.

Initial therapy plan – dosage and frequency:

None of the search results investigate this decision point.

When to re-evaluate:

One team of researchers investigates factors that may inform this decision point ***(17, 18)***. The authors use a model that combines ward-level interactions with in-host pathogen dynamics to compare timing differences between both pathogen identification testing and resistance profile analysis, both of which inform the timing of the clinician's re-evaluation of the initial treatment plan. They compare four re-evaluation strategies,

differing in the initiation time for pathogen-identification testing and minimum inhibitory concentration (MIC)-profiling, and use maximum pathogen load to assess outcomes.

- Caudill and Lawson ***(17, 18)***:
    - *Key assumptions:* Causative pathogen is a strain of *Staphylococcus. aureus* with high resistance to imipenem and intermediate resistance to oxacillin. Results of both the pathogen-identification testing and the MIC-profiling become available 24 hours after test initiation. Initial treatment with imipenem (broad spectrum), until pathogen is identified, after which switch to repeated 1000 mg doses of oxacillin (narrow spectrum), until oxacillin-MIC is identified, after which switch to repeated 2500 mg doses of oxacillin.
    - *Model type:* Ward-level ABM of interactions between patients and HCWs, linked to an IHPM (one for each patient and each HCW) of interactions between pathogen, immune response, and AM.
    - *Model predictions:* Initiation of pathogen-identification at the time of initial pneumonia diagnosis has the greatest effect on maximum pathogen load in this setting. This effect is enhanced by initiation of resistance analysis at the same time.

Re- evaluate choice of drug:

From our search results, two papers ***(17, 18)***, both by the same authors, addressed this decision point. For details, see the analysis under the previous decision point.

Re- evaluate mode of administration:

The analysis in Felton et al. ***(22)***, detailed under *Initial therapy plan – mode of administration*, above, applies equally to this decision point and is the only paper in this review to address it.

Re- evaluate dosage and frequency:

None of the search results investigate this decision point.

Discontinuation of antimicrobial therapy:

Seven of the search results address aspects that apply to this decision point. Four of these ***(16, 21, 23, 25)*** specifically address time-duration of AMT, while the other three ***(26, 28, 30)*** consider only a non-specific reduction in overall AM consumption. Of these seven papers, all except Geli et al. ***(23)*** are detailed under "*Will the patient receive antimicrobial treatment?*" above, and will not be repeated here, with the exception of Hurford et al. ***(25)***, because it includes model predictions that apply to this decision point, but not the previous one.

- Geli et al. ***(23)***:
    - *Key assumptions:* Sensitive bacteria mutate to become resistant bacteria at a fixed deterministic rate. The resistant bacteria population grows at the same rate as the sensitive population, but is assumed to die at a faster rate. The AM concentration is constant throughout the treatment period. Both strains of pathogen are killed by the AM, but at different rates.
    - *Model type:* IHPM of interactions between susceptible pathogen, resistant pathogen, and immune response.
    - *Model predictions:* Risk for development of resistant pathogens, as a function of AM use, differs between commensal and non-commensal bacteria. For commensals, risk is greatest for long treatment durations. For non-commensals, risk is greatest for intermediate treatment durations.
- Hurford et al. ***(25)***:
    - *Key assumptions:* See previous analysis.
    - *Model type:* See previous analysis.
    - *Model predictions:* Shorter duration of AMTs will result in a lower number of patients colonized with the resistant strain of *P. aeruginosa*.

Conclusions

Antimicrobial resistance will likely remain as a significant health crisis for the foreseeable future. Given the mounting evidence connecting AM resistance to AM use, overuse, and misuse, there is little question that we must wisely utilize our AM arsenal. Antimicrobial stewardship programs are central to this effort, and yet, recent reports indicate that fewer than half of the acute health care facilities in the U.S. currently have ASPs ***(34)***. As more of these facilities work to design and implement ASPs, they must choose which available ASMs are most likely to be effective within their institution and local community. Mathematical models can provide a practical and economical tool for simulating controlled experiments to predict the impact of ASMs, without putting humans at risk while providing valuable input to clinicians as they work to optimally choose the best drug, mode and timing of administration, and treatment duration.

As the small number of search results here illustrates, recent work that leverages the advantages of mathematical modeling in ASP development and assessment is limited. Fully two-thirds of our search results investigate the impact of an overall reduction in AMs, although only four consider distinctions between different AM classes. By contrast, few or none of these studies address ASMs related to the other therapy decision points (Table 2).

Many open questions remain about how to best optimize ASPs. High priority points-of-focus for future modeling investigations should include:

- Minimization of the time duration between the start of the initial therapy protocol, the re-evaluation and de-escalation of therapy (e.g. from broad-spectrum to narrow-spectrum antimicrobials), and the discontinuation of therapy.
- The effects of incomplete compliance with ASP guidelines.
- Accounting for acute care facilities within the larger community network.

Results from mathematical modeling studies that holistically analyze the decision points delineated in Table 2 could have a marked effect in helping to reduce the problem of antimicrobial resistance in healthcare settings.

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