A Dynamic Theory of Antibiotic Resistance: Work in Progress

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Abstract

Many common bacterial pathogens have become increasingly resistant to the antibiotics used to treat them. Experts agree that the essential cause of the problem is the extensive and often unnecessary use of antibiotics, a practice that encourages the proliferation of resistant mutant strains of bacteria while suppressing the susceptible strains. However, it is not clear to what extent antibiotic use must be reduced to avoid or reverse an epidemic of antibiotic resistance, and how early the interventions must be made to be effective. To investigate these questions, we have developed a relatively simple system dynamics model that portrays changes over a period of years to three subsets of a bacterial population – antibiotic-susceptible, intermediately resistant, and highly resistant. The details and continuing refinement of this model largely reflect our growing knowledge of *Streptococcus pneumoniae*, a leading cause of illness and death worldwide. The paper presents the model’s structure and behavior, including its ability to reproduce time series from four different countries, and explores possible directions for further model development.

Over the past few decades and around the world, a wide variety of common bacterial pathogens have become increasingly resistant to the antibiotics used to treat them. As a consequence, the illness and death rates for some formerly well-controlled diseases, such as tuberculosis, are now climbing in worrisome fashion. In the United States, it is estimated that drug-resistant bacteria are now responsible for some 70% of the 90 thousand fatal hospital infections that occur annually (Bright 1999). Antibiotic resistance was estimated in 1993 to add $200 million a year to U.S. medical bills in the form of more expensive antibiotics, and over $30 billion a year when the costs of extended hospital care are included (Garrett 1994).

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Experts agree that the essential cause of the problem is the extensive and often unnecessary use of antibiotics, a practice that encourages resistant mutant strains of bacteria to proliferate while suppressing the susceptible strains. In the U.S., it has been estimated that one-third of the 150 million annual prescriptions for antibiotics are unnecessary (Levy 1998). Public policies that would help reduce such unnecessary use of antibiotics include educational campaigns and antibiotic use monitoring and control, as well as the development and dissemination of quick and accurate diagnostic tests. Of equal importance are policies that reduce the spread of infection, both because they limit the spread of already-resistant bacteria and because they reduce the need for antibiotic use. Such policies include vaccination and traditional hygiene and infection control measures such as the isolation of patients with drug-resistant infections (Neu 1992, Baquero et al. 1996, Okie 1997, Ekdahl et al. 1998, Levy 1998). Although the policy options are known, their relative effectiveness is not. In particular, it is not clear to what extent antibiotic use must be reduced to avoid or reverse an epidemic of antibiotic resistance, and how early the interventions must be made to be effective.

In the spring of 1998, the Infectious Disease Epidemiology and Surveillance Division of the Texas Department of Health (TDH), in partnership with the Strategic Decision Simulation Group (SDSG), assembled a group of experts to begin thinking systemically about the problem of antibiotic resistance and possible policy options at the state and national levels. The meeting

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2 An analysis of nationwide survey data on office visits compared actual prescribing behavior with established standards. This analysis suggests that 30% of the 23 million prescriptions for ear infections are unnecessary, 50% of the 13 million prescriptions for sore throat, 50% of the 13 million prescriptions for sinusitis, and 80% of the 16 million prescriptions for bronchitis (Okie 1997).

3 Hygiene and infection control measures are particularly important in settings where human-borne bacteria are plentiful, such as day-care centers and hospitals (Neu 1992, Levy 1998). Perhaps less obvious are recommendations to consumers to avoid uncooked meats and to wash fruits and vegetables thoroughly, and to farmers and ranchers to use techniques that may minimize infections and the use of antibiotics in their livestock and crops. The concern, yet to be demonstrated conclusively, is that antibiotic resistant bacteria may develop agriculturally and then be passed on to humans. More than 40% of the antibiotics used in the U.S. are for livestock, the great majority of this being low-dose usage which promotes animal growth but is also an ideal situation for the spread of resistance. One panel of experts has concluded that 40 to 80 percent of antibiotic use in livestock is unnecessary. Antibiotics are also widely used in aerosols sprayed on fruit trees, aerosols that can easily carry to other plants as well (Levy 1998, Bright 1999). Although the concern about agricultural-to-human passage of antibiotic resistance appeals to common sense, one piece of possibly contradictory evidence should be noted. In Denmark, the use of antibiotics in livestock is high and almost as great as that in Spain, which has five to six times the human population. Yet, the prevalence of antibiotic resistance in human pathogens in Denmark is much lower than that in Spain (Frimodt-Møller et al. 1997).
produced an integrative causal loop diagram, a version of which is presented in Figure 1. This
diagram identifies the basic dilemma associated with antibiotics, that is, the fact that they can
reduce illness for individuals in the short term, but if overused may become ineffective--
regionally, nationally, or even worldwide--due to bacterial resistance. Such a local-versus-global
dilemma has been described as a “tragedy of the commons” (Senge 1990). Figure 1 identifies
how various responses may eventually be tried as this problem becomes more apparent to
policymakers and pressure grows to do something about it.

The challenge for policymakers is to identify the most effective types of responses and to
concentrate on these points of high leverage proactively rather than reactively, working with the
multiple interest groups affected by these policies to ensure their acceptance and success. In the
first phase of our work, we used causal loop diagrams to establish a stakeholder framework for
the multiple interest groups. In the second phase, we used simulation modeling to examine
specific policy options. The modeling process began in the summer of 1998, with Jack Homer
brought in to assist the TDH-SDSG team and direct the technical work. The initial models
considered the dynamics of both human and bacterial populations, with an approach to human
population dynamics much in line with prior system dynamics models of epidemics (Homer and
culminated in the writing of a white paper (TDH 1999) that was distributed for review by, among
others, the experts who took part in the original systems thinking exercise in 1998.

The initial modeling work helped to clarify the thinking of the team and, in particular,
caused us to focus on the difficult questions of how much and when antibiotic use must be
reduced to avoid or reverse an epidemic of resistance. Consequently, our more recent efforts
have focused on grounding the work more solidly in the scientific literature, collecting data not
available in the literature, and revising our model of bacterial population dynamics so that it
reflects this knowledge as much as possible. Because we are still only part way through this
necessarily iterative process (Homer 1996), we have subtitled this paper, “Work in Progress.”
Our purpose in this paper is to present what we have discovered so far, and to identify some of
the loose ends and open questions that remain.
Basics of antibiotic resistance

The literature on antibiotic resistance is vast; many books are entirely devoted to the subject (e.g., Levy 1992, Chadwick and Goode 1997) and infectious disease journals devote many pages to it. Although the basic concepts derive intuitively from population genetics, the details differ considerably by bacterial species and class of antibiotic, and the relationship between antibiotic use and antibiotic resistance is complex and a subject of some controversy.

Bacteria are ubiquitous in our environment and within our bodies; only a fraction are pathogenic. Infectious disease occurs when the immune system encounters a bacterial pathogen for which it is not prepared, perhaps due to a lack of previous exposure. The bacterial flora with which we coexist, known as commensals, are not only benign but often protect us from pathogenic bacteria by competing with them for niche turf and thereby preventing their proliferation (Levy 1998).

After gaining access to bacteria, antibiotics typically retard bacterial proliferation by interfering with the production of components needed to form new cells; specifically, they may inhibit bacterial cell wall synthesis, protein synthesis, folic acid synthesis, or DNA replication. The number of antibiotics on the market is large and includes more than 50 different variants of penicillin, 70 variants of cephalosporin, 12 tetracyclines, 9 macrolides, 8 aminoglycosides, and so forth. But bacteria evolve continuously and have developed responses, in the form of resistance genes, for every type of antibiotic in existence; indeed, at least three bacterial species have strains that are resistant to every antibiotic available (Neu 1992, Levy 1998).

A bacterium may acquire a resistance gene by direct inheritance, by spontaneous mutation (which may produce a new resistance trait or strengthen an existing one), or by accepting genes from other bacteria in a process known as gene exchange. There are several possible pathways for gene exchange: plasmid conjugation, transformation, transduction, and transposon-mediated exchange (Neu 1992). Most gene exchange passes traits among members of a species (e.g., Streptococcus mitis), but transposon-mediated exchange may pass traits to members of a different species (e.g., Streptococcus pneumoniae.) As one leading researcher has stated (Levy

\[4\] Plasmids are tiny loops of DNA carried on the surface of bacteria that can help them survive various environmental hazards. Transposons are molecules that can enable a resistance gene to hop from one plasmid to another and become integrated with the receiving plasmid.
In terms of population genetics, antibiotics are said to put selective pressure on susceptible strains of bacteria, diminishing their ability to proliferate and thereby putting them at a reproductive disadvantage relative to resistant strains. Although antibiotics are used to fight pathogenic bacteria, they also tend to put selective pressure on commensal bacteria and encourage the spread of resistance traits among these benign flora. Because commensals coexist with their host and have long periods of time to evolve resistance traits (in contrast with pathogens, which are usually cleared in a matter of days or weeks), resistance typically develops among commensals before being passed to pathogenic intruders (Levy 1998, Austin 1997). Consequently, antibiotic resistance has been a particular problem with broad-spectrum antibiotics, such as third-generation cephalosporins, that are active against a wide variety of bacterial genera. Such antibiotics encourage the spread of resistance traits among multiple types of commensals and subsequently to their pathogenic cousins, and not only to the original intruder for which the drug is given (Levy 1998, Ballow and Schentag 1992, Frimodt-Møller et al. 1997).

While experts agree on a positive link between antibiotic use and resistance, the exact nature of this link is still under active discussion. Experience and epidemiological models suggest that resistance may emerge only when antibiotic use exceeds some threshold (Levy 1998, Austin 1997). Such a threshold may vary by hospital or community, because of differences in contact rates (as affected, for example, by the prevalence of day-care programs for young children), hygiene, and other factors affecting the spread of pathogens. In theory, the threshold may also be affected by such factors as patient compliance and duration of treatment. Unfortunately, no one yet knows how to determine the threshold, and most hospitals and communities lack the data that would be required to do so (Levy 1998).

If resistance has already emerged, the key question concerns the extent to which antibiotic use must be reduced to reverse the problem to an acceptable level, or even whether such a reversal is possible. Logically, reversal of resistance should be possible if susceptible strains, at a lower level of antibiotic use, can regain a natural reproductive edge over resistant strains. Furthermore, common sense suggests that since susceptible strains were dominant over resistant strains for the millennia preceding the advent of antibiotics, they must have some sort of a natural advantage. In fact, laboratory studies of *Escherichia coli* have shown that resistance
usually but not always imposes what is called a fitness cost, expressed, for example, as 5% per generation (Levin et al. 1997). This fitness cost has been explained as being the result of resistant strains having to divert some of their limited energy from reproduction to maintaining their antibiotic resistance traits (Levy 1998).

Outside the laboratory, it has been demonstrated that stringent restrictions on the use of cephalosporins in a hospital can, in a year’s time, reverse even high levels of antibiotic resistance (Ballow and Schentage 1992, Rahal et al. 1998). Perhaps more instructive for society at large is the case of Finland, where macrolide (mainly erythromycin) consumption was reduced by more than 40% after outpatient usage guidelines were issued at the end of 1991, in response to the emergence of resistance in group A Streptococcus. Interestingly, even after the reduction in usage, resistance continued to climb from a value of 13% in 1990 to a peak of 19% in 1993, before starting a decline that by 1996 left resistance at under 9% (Seppälä et al. 1997). A similar story is reported from Iceland, where a national campaign to reduce antibiotic use has been successful at bringing down penicillin resistance in Streptococcus pneumoniae, which had prior to the campaign climbed from 2% in the late 1980s to 20% in 1992 (Okie 1997).

But the news about the reversability of resistance is not uniformly good. Samples of E. coli taken from a day-care center in Atlanta were found to be resistant to streptomycin even though that antibiotic has been rarely used in the last thirty years. Lab studies confirmed that these streptomycin-resistant E. coli had virtually no fitness cost relative to susceptibles. Other lab studies involving the coevolution of resistant and susceptible species indicate that the fitness cost of resistance can decline over time through adaptation, specifically through the development of so-called compensatory mutations. In such cases, even the radical reduction of antibiotic use may do little or nothing to reverse resistance (Levin 1997, Morell 1997).

**Case study: Beta-lactam resistance in Streptococcus pneumoniae**

The modeling work with the Texas Department of Health has, from the beginning, focused on a single problem: the growing resistance of pathogenic S. pneumoniae, commonly known as pneumococcus, to the broad class of antibiotics known as beta-lactams, which include the penicillins, the cephalosporins, and the carbapenems. Because the mechanics of antibiotic resistance can differ so widely by bacterial species and class of antibiotic, it has been helpful to
have had this kind of focus, though it may possibly limit the applicability of our model to other cases of antibiotic resistance.

Worldwide, pneumococci are the leading cause of community-acquired pneumonia, as well as the leading bacterial pathogen in children and adolescents. In the U.S. alone, pneumococci cause each year an estimated three thousand cases of meningitis, 50 thousand cases of bacteremia, 500 thousand cases of pneumonia, and seven million cases of otitis media (middle ear infections) (CDC 1996). Deaths from invasive pneumococcal disease exceed 40 thousand per year in the U.S. (Long 1999). Worldwide, an estimated 1.2 million children die annually from pneumococcal disease (FitzGerald 2000).

Pneumococci were first identified by Louis Pasteur in 1881 and subsequently shown to be the most common cause of lobar pneumonia. Some ninety different capsular serotypes of pneumococci have been identified, though only a small subset of those are prevalent pathogens, with some variation in the distribution of serotypes by country and continent. Pneumococci colonize the nasopharynxes of 15 to 60 percent of individuals at any given time; the carriage rate has been shown to depend on age of the individual, season, crowding, and the prevalence of influenza and other viral infections that may compromise immunity. Most people are colonized for weeks to months and remain asymptomatic. Disease, when it occurs, usually follows rapidly upon the acquisition of a serotype new to the individual, rather than after prolonged carriage. For example, about 15% of young children who acquire a new serotype become ill, most commonly with otitis media (Long 1999).

Efforts to develop a pneumococcal vaccine began in 1911, but waned with the advent of penicillin in the 1940s. Interest picked up again in the 1960s, leading to a first vaccine licensed in 1977, and the current 23-valent vaccine (active against 23 of the most common serotypes) licensed in 1983 (Long 1999). This pneumococcal polysaccharide vaccine (PPV) is recommended primarily for the elderly, among whom only 27% had been vaccinated in the U.S. as of 1993 (CDC 1996). A new 7-valent pneumococcal conjugate vaccine (PCV) is effective in young children and recommended for all children under the age of two (FitzGerald 2000).

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5 One study found the mean duration of pneumococcal carriage in disease cases to be 36 days, with a range of 3 to 267 days, and the mean duration of carriage in non-disease cases to be 26 days, with a range of 4 to 192 days (Ekdahl et al. 1997).
The first case of antibiotic resistant pneumococci was reported in Australia in 1967, followed by reports from New Guinea in 1969 and South Africa in 1977 (CDC 1996). Evidence suggests that resistance often emerges first in oral viridans group streptococci commensals, such as *S. mitis* and *S. oralis*, after which it may be transferred to colonizing pneumococci (Koornhof *et al.* 1992, Reichmann *et al.* 1997). Pneumococci do not acquire resistance genes by plasmid conjugation (involving direct contact with other living bacteria), as many other species do, but instead by absorbing long, free-floating strands of bacterial DNA (of deceased pneumococci or streptococci) from their host environment.

Multidrug resistant strains of pneumococci emerged in the 1980s. By the end of the decade in Hungary, 70% of children with pneumococcal illness carried strains resistant to five different classes of antibiotics. By the 1990s, drug resistant pneumococci had turned up all over the world, some resistant to as many as six different classes of antibiotics (Neu 1992, Garrett 1994).

**Data on pneumococcal resistance to penicillin**

There have been many reports on the prevalence of antibiotic resistant pneumococcal infections, but such reporting is far from universal and the full extent of the problem is not known (CDC 1996). In the U.S., for example, it is a reportable condition in only some states, and national surveys by the Centers for Disease Control and Prevention (CDC) and by others are published only irregularly. What is known is that there is great variation in prevalence by geographical region and by age of individual, and that prevalence is capable of changing quickly in any particular location (Cetron *et al.* 1996, CDC 1996, CDC 1999).

Despite the lack of universal reporting, most of what has been published is consistent in reporting on the prevalence of penicillin resistant pneumococci (PRP), and researchers all generally use the same accepted standards for determining whether a pneumococcal isolate should be considered susceptible, intermediately resistant, or highly resistant to penicillin.7

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7 The National Committee for Clinical Laboratory Standards (NCCLS) recommends an initial screening for PRP by the oxacillin disk technique, which is highly sensitive and specific and detects almost all isolates with any resistance to penicillin or other beta-lactams. Isolates found to be non-susceptible by this method should then be subjected to quantitative testing of minimum inhibitory concentration (MIC),
Researchers often sample or survey multiple hospitals and medical centers, rather than just one. Also, the analysis often focuses on invasive pathogenic isolates drawn from normally sterile areas (e.g., blood, cerebrospinal fluid, pleural fluid, and middle ear fluid), rather than on noninvasive isolates that may comprise a mix of pathogenic and nonpathogenic pneumococci.

Time series on PRP for the United States, Spain, South Africa, and Hungary are presented in Figures 2, 3, 4, and 5, respectively. These are the most extensive time series we have found, each covering at least 11 years. Despite a few gaps and inconsistencies, the data lead to some useful conclusions or working hypotheses about the dynamics of PRP on a national level:

♦ PRP may grow in a ten-year period, from a low level of 10% or less to a high level of 30% or more (Spain), but need not grow to that extent (U.S., South Africa).

♦ Even after rapid growth, PRP tends to plateau without climbing inexorably to 100% (Spain, Hungary).

♦ Growth in PRP may at times reverse substantially and in a short period of time (Spain, South Africa, Hungary).

♦ Growth in high resistance occurs only when intermediate resistance is already significant, e.g., greater than 10% (U.S., Spain).

♦ High resistance may plateau even while intermediate resistance continues to grow (Spain).

The fact that total PRP may plateau at levels well below 100% is of particular interest. Some epidemiological models have suggested that such stable coexistence of susceptible and

using accepted breakpoints for specific antibiotics. For penicillin, the breakpoints are Susceptible: \(<0.06\) µg/mL; Intermediately resistant: \(1.0\) µg/mL; Highly resistant: \(>2.0\) µg/mL (CDC 1996).

8 A seven-year time series from France for the years 1984-1990 shows growth in total resistance from less than 1% to 12% and growth in high resistance from 0% to 6% (Geslin et al. 1992).

9 First, the U.S. time series has a gap during 1988-1991 when no national hospital surveys were done. Second, the U.S. series was culled from multiple articles representing the work of two different research groups with some changes over time in the hospitals they surveyed, so that some data are not strictly comparable. Third, high resistance per se was reported for the U.S. and Spain (and in Spain, only through 1989), but not for South Africa and Hungary. Fourth, in the case of Hungary, the sample includes both invasive and noninvasive isolates, mixed together in the data without identification, whereas in the other three countries the sample includes only invasive isolates. The Spanish authors (Fenoll et al. 1998) also present resistance data for noninvasive isolates for 1983-1996, not presented here. These noninvasive isolates are consistently more resistant than the invasive ones, with total PRP in the range of 50-60% throughout the period studied.
resistant strains in a population should be possible only if the rate of spontaneous mutation is relatively high, or if antibiotic consumption lies in a rather narrow band around the critical level for emergence (Austin et al. 1997). On the first point, we are not aware of any evidence suggesting a high rate of spontaneous mutation for pneumococci. On the second point, we are not aware of any argument for why a nation’s antibiotic consumption should naturally settle near the critical point, let alone two nations as different as Spain and Hungary.

There may be a more compelling reason for why PRP can settle at levels below 100%. It seems that among pneumococci, some common serotypes develop resistance much more frequently than others, reflecting widely differing propensities to absorb resistance genes from the host environment. Figures 6 and 7 show the serotype distributions of PRP for the U.S. and Spain, respectively, based on aggregations of data covering 1979 and most of the 1980s. In these figures, each line segment on the graph represents the incremental contribution of a single serotype (or, in a few cases, the combined contribution of multiple miscellaneous or unidentified serotypes), in terms of the total number of isolates (x-axis) and the number of resistant isolates (y-axis) in the sample. In the U.S. data, PRP averages only 5.0% overall, with a range of 0% to 38% for individual serotypes. In the Spanish data, PRP averages 27.8% overall, with a range of 0% to 89% for individual serotypes. The strongly bowed-out rather than linear curves in Figures 6 and 7 reflect the skewed distribution of resistance among the serotypes. It is evident that, in both cases, a small number of serotypes are responsible for the majority of resistant isolates. Moreover, the specific serotypes that account for most of the resistance in the U.S. data also account for most of the resistance in the Spanish data. Taking the two data sets together, it appears that an increase in total PRP primarily reflects increasing resistance within a subset of serotypes, rather than increasing resistance among all serotypes. Even if the more resistance-

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10 The U.S. data for Figure 6 come from 19 hospitals submitting 5,469 isolates to the CDC over the period 1979-1987 (Spika et al. 1991). The Spanish data for Figure 7 come from 26 hospitals submitting 2,197 isolates to the Centro Nacional de Microbiología over the period 1979-1989 (Fenoll et al. 1991).

11 In the U.S. data, four of the common serotypes (each with over 100 isolates in the sample) account for 36% of total isolates but 72% of resistant isolates. These serotypes, in descending order of resistance (from 38% down to 5%), are #19A, #14, #23F, and #6B. In the Spanish data, five of the common serotypes (each with over 100 isolates) account for 36% of total isolates but 84% of resistant isolates. These serotypes, in descending order of resistance (from 89% down to 41%), are #23, #6, #9, #14, and #19. (Lettered sub-variants were not identified in the article from Spain.) The resistance of serotype #9 is only 2% in the U.S. data, making this the only common serotype to have relatively low resistance in the U.S. data but relatively high resistance in the Spanish data.
prone serotypes eventually became 100% resistant, many of the less resistance-prone serotypes would still have much lower levels of resistance. This could explain why total PRP might settle at something considerably below 100%.

Next, one might ask why, in the Spanish time series data (Figure 3), the level of high PRP appears to plateau at around 15% in the late 1980s, even as intermediate PRP continues to climb. One hypothesis is that there are differing serotype propensities for high PRP just as there are for PRP generally. In particular, if an even smaller number of serotypes have the propensity to become highly resistant to penicillin (e.g., through the acquisition of even stronger resistance genes) than have the propensity to become intermediately resistant, this might explain a relatively low plateau for high PRP. Unfortunately, the Spanish data do not identify rates of high PRP by serotype, and we have not yet located any other data that would help clarify this matter.

The PRP time series data presented here all reflect relatively large samples taken from multiple locations throughout each country, and in that sense they are the best data we have found on national PRP patterns. But we cannot ignore other data that may indicate possibilities not apparent in these time series. In particular, smaller sample, non-longitudinal data from Hungary (Marton 1992) and Asia (Lee et al. 1995, Song et al. 1999) indicate the possibility of very high percentages of both total PRP and high PRP per se. The highest percentages are from Korea, where we have data from two periods of time. For 1991-1993, one hospital (131 isolates) experienced total PRP of 70% and high PRP of 33%, while for 1996-1997, two medical centers (177 isolates) experienced total PRP of 80% and high PRP of 55%.

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12 High PRP levels per se are not presented for the 1990s in the Spanish data (Fenoll et al. 1998).

13 For Hungary, a sample from 1988-1989 (135 isolates) exhibited total PRP of 58% and high PRP of 35%. For Asia, samples are from 1996-1997, and reflect 996 invasive isolates from 14 medical centers in 11 countries. After Korea, the highest PRP percentages are for Japan (65% total, 27% high), Vietnam (61% total, 33% high), and Thailand (58% total, 22% high). These are followed by Sri Lanka and Taiwan (about 40% total PRP), Indonesia and Singapore (about 20%), and Malaysia, India and China (10% or less).
Data on beta-lactam antibiotic use

As stated previously, our modeling work has centered on pneumococcal resistance to the whole beta-lactam class of antibiotics of which the penicillins and cephalosporins comprise the major portion. (The carbapenems are used much less frequently and almost exclusively for severe infections in hospital settings.) For modeling purposes, we assume that the PRP data presented above give an accurate indication of trends in resistance by pneumococci to beta-lactams generally.\(^\text{14}\) Although these data are specific to penicillin, it must be recognized that all beta-lactams, and not only penicillin, are capable of encouraging the spread of the sort of resistance genes that can inactivate penicillin.\(^\text{15}\) In other words, if one is trying to find a link between antibiotic use and PRP, it is important to track the use of beta-lactams generally and not only penicillin.

Unfortunately, we have so far found it difficult to locate nationwide data on beta-lactam use in the various countries for which we have time series data on PRP. At this time, we have managed only to construct a time series for the United States, as shown in Figure 8, and even this is incomplete and does not cover all categories of use. These data are drawn from the National Ambulatory Medical Care Survey (NAMCS), the only national survey in the U.S. to provide information on the prescribing of oral antibiotics by office-based physicians. The NAMCS has been conducted annually from 1973 through 1981, in 1985, and again annually since 1989 (McCaig and Hughes 1995). Figure 8 presents estimates of office-based beta-lactam prescriptions per thousand persons per year.\(^\text{16}\) From 1990 to 1995 (but excluding 1992, a year of

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\(^\text{15}\) These resistance genes alter the penicillin-binding proteins naturally present on streptococcal species, thereby reducing the affinity of these proteins for beta-lactams and effectively making it more difficult for beta-lactams to bind to the affected bacteria (Neu 1992).

\(^\text{16}\) Figure 8 reflects NAMCS data for 1980, 1985, 1989, and 1992 reported by McCaig and Hughes (1995), as well as data we have extracted directly from the annual NAMCS data sets for 1990 to 1997. In McCaig and Hughes, rates of use were reported for a variety of antibiotics, of which the beta-lactams include amoxicillin, ampicillin, the penicillins, and the cephalosporins. The beta-lactams for which we found mentions in the 1990-1997 NAMCS data sets, under both generic names (lower case) and brand names (upper case), are as follows: amoxicillin, Amoxil, Augmentin, ampicillin, penicillin, penicillin V,
unusually high use), these rates translate to about 60 million prescriptions per year, or 60% of the roughly 100 million office-based prescriptions reported for all antibiotics combined. Beta-lactam use increased significantly from 1985 to 1989, then gradually declined during the 1990s (with the exception of 1992); by 1996, it had declined to below where it was in 1980 and 1985. For Spain, we have found published data on the use of all antibiotics combined, but too little on beta-lactam use *per se* to allow us to draw any firm conclusions. Consumption of all antibiotics by outpatients peaked sometime during 1966-1976, and in 1976 amounted to 110 million units (boxes), equivalent to a European standard of 31 defined daily doses (DDD) per thousand persons per day. Consumption decreased to 29 DDD/1000/day in 1978, 26 in 1983, 21 in 1988, and 19 in 1993; thus, total outpatient use was reduced by about one-third from 1978 to 1993. As of 1993, about 50% of the consumed antibiotics were penicillins and another 13% were cephalosporins, but such a breakdown of use for prior years is not provided (Baquero *et al.* 1996).

A “bug-centric” model of antibiotic resistance

Our system dynamics model attempts to explain what we have learned about nationwide pneumococcal resistance to beta-lactams in a way that is straightforward and potentially generalizable, yet is able to fit the historical evidence. A somewhat simplified view of the 60-equation model is presented in Figure 9. The three levels of the model represent the three subsets

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Keflex, cephalexin, Ceclor, and Ceftin. The only year of overlap in these two sources is 1992. For 1992, McCaig and Hughes give a total rate of beta-lactam use of 303 prescriptions per thousand population, 19% higher than the rate of 254 that we calculated. We do not know what the source of this discrepancy might be (there are several one might consider) and have decided to resolve it for now simply by shifting all of our calculated rates for 1990-1997 up by 19%, in deference to McCaig and Hughes.

17 The total for office-based and hospital-based prescriptions combined is reported to be about 150 million per year (McCaig and Hughes 1995).

18 Detailed analysis of the NAMCS data shows that most of the decline is accounted for by a reduction on the order of 50% in the use of beta-lactams for otitis media from 1990 to 1996. The majority of that reduction occurred in young children ages zero to two, who had in 1990 accounted for over 20% of all office-based beta-lactam use but by 1996 accounted for only 17%.

19 Human consumption of antibiotics has been tracked on a DDD basis in Scandinavian countries consistently since the late 1980s. As of 1994, the consumption rates in decreasing order were Iceland at 22 DDD/1000/day, Finland at 20, Sweden at 18, Norway at 15, and Denmark at 13 (Frimodt-Møller *et al.* 1997).
of a bacterial (“bug”) population as defined by accepted standards of resistance measurement – namely, antibiotic-susceptible, intermediately resistant, and highly resistant. These sub-populations are modeled not in absolute terms of number of bugs, but in terms of their relative density, where 100 represents the carrying capacity for the bacterial species or genus in question, within the entire human host population under study.

Thus, the model considers the dynamics of a widely dispersed bug population, and the impact of antibiotic use on that population, but without direct reference to human population dynamics. This sets it apart from previous epidemiological models of resistance that have attempted to model antibiotic resistance not by categorizing bacteria but by categorizing their human hosts as either noncolonized, colonized entirely by susceptible bugs, or colonized entirely by resistant bugs (Austin et al. 1997, Levin et al. 1997). We believe that the bug-centric perspective is a useful one, especially in light of the fact that pathogenic bacteria are highly mobile, and that individual humans may be found to harbor both susceptible and resistant strains of the same bacterial species.

Before moving on to the specifics of the model, we must consider whether, in the case of pneumococcal resistance, the model’s bug population represents only pneumococci or also includes the commensal viridans group streptococci with which pneumococci freely interact in the upper respiratory tract. On the one hand, pneumococci and the commensals share the same niche in the human body, both are inhibited by beta-lactam use, and the two share genes freely with each other. On the other hand, unlike the commensals, pneumococcal colonies are temporary guests rather than long-term residents in a human host, and consequently may tend to become less antibiotic resistant than the commensals. Because the two populations have aspects of overlap as well as aspects of non-overlap, they should perhaps be modeled separately. However, national time series data on resistance in commensals do not exist and probably never will. Pathogens are the typical concern of laboratories and our primary concern as well. Thus, for the sake of simplicity and verifiability, our current model walks a fine line. Our explicit modeling is of a population of pneumococci, but we assume that the commensal populations move in similar fashion, if not exactly in parallel with the pneumococci.

20 In a sample of 352 viridans group isolates from 43 medical centers in the U.S. during 1993-1994, total penicillin resistance was 56%, including 13% high resistance per se (Doern, Ferraro et al. 1996). This rate of resistance among oral streptococci is much higher than those found in any of the national surveys of PRP in the U.S. to date.
Each of the three bug population levels in Figure 9 is shown with a two-way flow that represents the net difference between additions to that level due to normal reproduction, gene exchange, and mutation, and reductions due to elimination. Mutation (or, perhaps, the absorption of DNA from another type of bacteria in the same niche) may create a new intermediately resistant bug from the subpopulation of susceptible bugs, or a new highly resistant bug from the subpopulation of intermediately resistant bugs. In this way, mutation may introduce resistance genes that were not previously present in the population. But growth in resistance occurs through the self-perpetuating processes of reproduction and gene exchange within the bug population, described in the model with the single term proliferation.

To formulate proliferation in the model, we define a basic proliferation ratio describing the rate of proliferation relative to the rate of elimination in the absence of antibiotic use or constraints such as niche size. By setting the basic proliferation ratio of susceptible bugs to exceed that of intermediately or highly resistant bugs, one may specify the fitness cost of resistance.

Much of the model is concerned with those factors that may inhibit or constrain proliferation. First, antibiotic use, expressed as prescriptions per thousand persons per year, significantly inhibits the proliferation of susceptible bacteria, but has less effect on the proliferation of intermediately resistant bacteria, and very little effect on the proliferation of highly resistant bacteria. Second, with or without antibiotic use, all three proliferation ratios are constrained equally (that is, by the same table function) when the total bug density starts to approach its limit of 100. This effect of niche saturation reflects the idea that as the bugs approach the limits of their natural niche in their human hosts, their ability to proliferate any further is constrained by problems of survival in the inhospitable surroundings.

Let us pause for a moment to consider the combined effects of antibiotic use and niche saturation. Start with a state of equilibrium in which antibiotic use is relatively low and the

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21 For each population level i, we define a baseline parameter b(i) describing the inhibitory effect when antibiotic usage U is at a level of 200 prescriptions (Rx) per thousand persons per year. For example, in calibrating the model to represent PRP in the United States, we ended up with the following values of b(i): 0.09 for susceptible bugs, 0.03 for intermediately resistant, and 0.004 for highly resistant. An exponential function is used to describe the multiplicative effect of antibiotic usage on proliferation, E(i), as follows: E(i) = (1-b(i))^{U/200}. With this formulation, a reduction in usage from 200 to 100 Rx/1000/year would increase E(susceptible) from .91 to .954, E(intermediate) from .97 to .985, and E(highly resistant) from .996 to .998.
susceptible bug density is high—high enough to reduce net population growth to zero. Now increase antibiotic use. The first thing that happens is that the net growth rate turns negative and the bug density therefore decreases. If there are no resistant bugs present, the susceptible bug population will simply decline to a new lower equilibrium, one where the antibiotic effect is exactly balanced out by a less restrictive effect of niche saturation. If there are some resistant bugs present, and antibiotics do relatively little to inhibit their proliferation, the easing of the niche saturation effect will allow them to proliferate quickly in a way they could not do before the increase in antibiotic use. As a result, resistance may now emerge rapidly until the niche limit is once again approached. Running through this simple scenario allows us to grasp an important concept, namely, that a high density of susceptible bugs (both pathogenic and commensal) can actually protect, by means of niche saturation, against the proliferation of resistant bugs.

The final type of constraint on proliferation to consider is that related to serotype variation, a subject which may be somewhat unique to pneumococci because of their remarkable diversity of serotypes. There are two of these effects in the model, one affecting both intermediately and highly resistant bugs, and the other affecting only highly resistant bugs. The first of these effects says that as total (intermediate plus high) resistance grows beyond some critical level (say, 40%) it becomes more and more difficult for resistance to spread to additional serotypes and therefore to additional bugs. This concept reflects the rather good evidence, discussed previously, that a significant proportion of common pneumococcal serotypes have a low propensity for becoming resistant.

The second of the serotype variation effects is specific to highly resistant bugs and says that as high resistance grows beyond some critical level (say, 10%) it becomes more and more difficult for high resistance *per se* to spread to additional serotypes and therefore to additional bugs. Unlike the first effect, we currently have no direct evidence to support this second effect. In fact, this second effect is something we added recently to the model only when we could find nothing else to explain the plateau of high PRP at 15% in Spain in the late 1980s. Not only is the effect a speculative one at present, but it may actually be contradicted by the data from Hungary
and Asia, cited previously, suggesting the possibility of percentages of high PRP well in excess of 15%.

22 To pursue this matter further, we would like to follow up with the authors of the Spanish study (Fenoll et al. 1998) to see whether they have data on high PRP for the 1990s. We would also like to follow up with the author of the Hungarian study (Marton 1992) to see whether nationwide time series data on high PRP in the 1980s or 1990s may exist for that country.

Basic model behaviors and historical replication

Our current model has proved capable of producing behaviors described in the literature on antibiotic resistance. These fundamental behaviors include the following:

♦ When antibiotic use is low enough, and provided there is a fitness cost of resistance, antibiotic resistance will not emerge. The threshold for emergence depends on values of the model’s other parameters, most importantly, the basic proliferation ratios and the antibiotic inhibition effect parameters for the three bug subpopulations.

♦ If resistance does emerge, it grows in S-shaped fashion, with the rate of emergence related to the level of antibiotic use, and with the emergence of highly resistant strains lagging behind that of intermediately resistant strains.

♦ If resistance does emerge and there is a constraining effect of serotype variation, then resistance will plateau at a value less than 100% but related to the level of antibiotic use. If there is no serotype variation effect, then resistance will grow to approach 100% provided antibiotic use exceeds the threshold amount.

♦ If antibiotic use is reduced, resistance will immediately start to decline toward a lower plateau level, though it may take several years finally to approach that lower level. (The next section describes the impact of antibiotic use reduction in greater detail.)

In addition to producing these basic behaviors, the model is capable of replicating the time series from four countries previously presented in Figures 2, 3, 4, and 5. Recall that we have longitudinal data on beta-lactam consumption for the U.S., but not for the other three countries. For the three non-U.S. countries, we had no choice but to create hypothetical consumption curves, which we adjusted to some extent to improve the model fit to history. Consequently, the replication testing is currently a more persuasive test of the model in the case of the U.S. than it
is for the other three countries. We hope to acquire beta-lactam consumption data for the non-U.S. countries in the near future, if possible.

The results of historical replication testing for the United States, Spain, South Africa, and Hungary are presented in Figures 10, 11, 12, and 13, respectively. For each country, the graph allows a comparison of data and simulated results, and extends the simulated results for both total PRP and high PRP through 1999. The model is able to track the data trends rather well, with the exception of the very large drop in PRP recorded in Hungary for the period 1981 to 1984, followed by an even more dramatic rebound in 1985.23

The replication of historical trends builds confidence in a model only insofar as the underlying model assumptions are plausible. Toward this end, we attempted to take a careful approach to the setting of model parameters for the four countries. In regard to such constants as the basic proliferation ratios and the parameters for the inhibitory effect of antibiotics, we allowed for small differences among the countries, in recognition of the fact that there is some variation by country in the distribution of serotypes. Initial conditions for the bug levels could also vary by country, but we assumed that the table functions describing the constraints on proliferation of niche saturation and serotype variation would not vary by country. We also assumed that the small mutation rate constants would not vary by country.

We started by calibrating the model to represent the United States, since that was the one country for which we had at least a partial time series on beta-lactam use (Figure 8). Noting that PRP in the U.S. had still not risen above 5% by 1987, we filled in the missing U.S. beta-lactam data by assuming no change in use from 1979 through 1987, and then interpolated linearly from 1987 to 1989 to get a value for 1988. In addition, for testing purposes, we assumed that beta-lactam use would settle starting in 1998 at a value of 200 Rxs/1000/year, the average of what it had been during the period 1995-1997. The resulting beta-lactam use curve for the U.S. may be seen in Figure 14.

We next concentrated on Spain, where the plateaus in total PRP and high PRP allowed us to calibrate the table functions for the effects of serotype variation, something we had not done

23 It is hard to say how much credibility should be attached to the Hungarian data during this period. It is true that significant declines in resistance followed by large rebounds are seen in other time series, such as in Spain from 1980 to 1983 and South Africa from 1986 to 1989. But these changes are not as large as those seen in the Hungarian data. Also, the dips and rebounds in the Spanish and South African data may be viewed as relatively small fluctuations around the overall trend line, which cannot be said of the Hungarian data.
during the U.S. calibration process. As far as beta-lactam consumption is concerned, we adopted an approach that we took with South Africa and Hungary, as well. In particular, we assumed only relatively simple curves for beta-lactam use, flat with one possible period of deviation or fluctuation ending in a final value that may differ from the initial value. We also hypothesized that beta-lactam use in these other countries would, for the most part, lie within a range of use of 150-300 Rxs/1000/year as observed over 18 years in the U.S. data.

Given these constraints on the process, the antibiotic use curves for the three non-U.S. countries were adjusted to improve the model’s fit to the resistance data. The resulting curves may be seen in Figure 14. For Spain, a decline and partial rebound in use, starting in 1989 and ending in 1993, was introduced to explain a similar pattern seen in total PRP for 1990-1996.24 For South Africa, an increase in use 1984-1985, followed by a decline in use 1986-1988, was introduced to better fit the sudden but modest path of emergence seen in PRP during 1985-1990. For Hungary, a rather large decline in use 1981-1983, followed by an equally large rebound 1984-1986 back to the former level of use, was introduced to explain the dramatic drop and rebound seen in PRP for 1982-1985 on which we commented previously.

Testing the effect of reducing antibiotic use

Our modeling work was prompted by questions concerning the impact of antibiotic use reduction— in particular, the magnitude and timing of that reduction—on the emergence of antibiotic resistance. We have done a variety of tests of antibiotic use reduction for the four countries to which the model has been calibrated, and have come to the same general conclusions regardless of country. Because the effects of serotype diversity, which may be somewhat unique to pneumococci, contribute to these conclusions, we will restrict our remarks to the specific case of PRP. The key conclusions are as follows:

24 Another possible approach would have been to use the time series data on total oral antibiotic use in Spain described previously, which show an S-shaped decline in use of about 34% from 1978 to 1993. However, the experience in the U.S. and elsewhere suggests that various classes of antibiotics wax and wane in popularity, with newer classes generally supplanting older ones. Thus, it is likely that a 34% decline in total antibiotic use represents a much larger decline in older broad-spectrum drugs such as tetracycline and erythromycin, as well as penicillin, and perhaps no decline or even an increase in newer drugs such as the cephalosporins. With this as background, we feel that the 10% net decline in beta-lactam use from 1988 to 1993 we have assumed for Spain (see Figure 14) is plausible.
A reduction in beta-lactam use leads immediately to a downward trend in total PRP, but the reduction in PRP tends to be a gradual one with a decay half-life on the order of ten years.

If the reduced level of use is still significantly above the critical value for emergence, then the ultimate decline in total PRP is likely to be a modest one.

If the reduced level of use is below the critical value for emergence, total PRP will decline substantially but need not tend to zero. While such a reduction in use does drive intermediate PRP toward zero, high PRP may remain significant.

If beta-lactam use is reduced below the critical level before the significant emergence of high PRP, then that emergence may be prevented. Otherwise, high PRP may emerge.

If high PRP has already emerged, the only way to make it decline substantially is to reduce beta-lactam use significantly below the critical level for emergence. In other words, there is what one might call a super-critical level of use, lower than the critical level, below which even high PRP can be driven toward zero.

A typical sequence of tests is illustrated in Figures 15 and 16, using the U.S. calibration of the model. Figure 15 presents results for total PRP while Figure 16 presents results for high PRP per se. The first of these tests is a baseline run, extended to the year 2020 based on an assumption that beta-lactam use remains at the level of 200 Rxs/1000/year for the entire period 1998-2020. In five other tests, beta-lactam use is reduced to a constant value of 150 as of some point in time: 1988, 1992, 1996, 2000, or 2004. In a final test, beta-lactam use is reduced to a constant value of 130 as of 2004. A usage level of 150 represents a 25% reduction below the 1995-1997 average of 200 and a 12% reduction below the low 1997 value of 170 (see Figure 8). This is a magnitude of reduction that seems feasible given the high percentages of unnecessary use of antibiotics for upper respiratory illnesses cited previously (see footnote 1). A usage level of 130 would represent a 35% reduction below 200, a magnitude of reduction that might be considerably more difficult to achieve in real life.

Given all of our model assumptions, the critical value of beta-lactam use for PRP emergence in the US-calibrated model is about 170 Rxs/1000/year. Below this critical value of beta-lactam use, susceptible bugs are able to proliferate more quickly than intermediately resistant ones (due to the fitness cost of resistance), leading to a decline in overall resistance. Figure 15 shows how total PRP can be reduced substantially and ultimately below 15%, even
after exceeding a value of 30%, if beta-lactam use is cut to 150 Rxs/1000/year. If beta-lactam use is cut even further, to 130 Rxs/1000/year, then total PRP can be sent on a trajectory toward zero.

Figure 16 shows that if the reduction in use does not occur early enough in the simulation (specifically, by about 1992), high PRP emerges and, at a usage level of 150, is driven down to a value no lower than 10% from its former plateau value of 13%. This behavior reflects the fact that, at levels of beta-lactam use of 200 or even 150, highly resistant bugs are naturally able to proliferate more quickly than both susceptible bugs and intermediately resistant bugs, because they are inhibited less by antibiotics. But if beta-lactam use is reduced to 130—below the super-critical level of about 140 Rxs/1000/year in our model—then the proliferation advantage of highly resistant bugs is reversed, and high PRP can be driven below 10% on a trajectory toward zero.

Conclusion

This paper reports on a modeling effort in progress. Focusing on the case of beta-lactam resistance in pneumococci, we have attempted to develop a model that reflects the full breadth of evidence and theory on the subject and that can replicate not just one but multiple national time series. This sort of demonstration makes an important statement about the general applicability of the model and is something that, to our knowledge, no other epidemiological model of antibiotic resistance has previously done.

Our model has also proved capable of generating new ideas about the dynamics of antibiotic resistance and the effect of reducing antibiotic use. In particular, the model has led us to understand the different dynamics of intermediately and highly resistant bugs and to introduce the concept of a super-critical level of use. Only when antibiotic use is reduced below this super-critical level—lower than the critical level required for the emergence of resistance in the first

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25 The natural proliferation advantage of highly resistant bugs is only neutralized when the effect of serotype variation on high PRP proliferation becomes constraining. Based on the high PRP data from Spain, we have assumed that this constraint only becomes binding when high PRP exceeds 10%.

26 There is only one other case of model-based replication of resistance data of which we are aware. Austin et al. (1997) describe an upcoming (1998) paper that shows how their model, using available DDD antibiotic use data, can replicate the emergence of resistance in Moraxella catarrhalis in Finnish children.
place—can one definitively send both intermediately and highly resistant bugs on a trajectory toward zero.

There are several gaps in the data we have collected that should be filled in order to facilitate further progress on the model. These include more complete time series data on high PRP, data on the serotype distribution of high PRP, and data on beta-lactam use in countries other than the United States. From a modeling standpoint, the most pressing empirical question is whether high PRP can, in fact, grow well beyond the 15% value seen in the data from Spain, as the limited data from Hungary and Asia suggest. Our model currently does not allow for such high prevalence of high PRP, due to our inclusion of a constraining effect of serotype diversity on high PRP proliferation.

If the possibility of high national prevalence of high PRP is confirmed, then we will have to modify our model in some way to explain all available data. Various possibilities come to mind, though it is not obvious how they would solve the problem. One possibility is to explicitly model not only the pneumococcal bug population, but also the populations of commensal streptococci with which the pneumococci interact. Another possibility is to disaggregate the human host population in some way, as other epidemiological models have done (Austin et al. 1997, Levin et al. 1997).

It is important that we not only improve the model but also facilitate the use of model-based findings by the policymakers with which our team continues to work. A systematic approach to such facilitation (see, for example, Ritchie-Dunham and Rabbino 2001) involves returning to the larger policy context of the problem (as in Figure 1) and thinking further about the resources and actions available to policymakers, as well as the perceptions, incentives, and likely responses of the different stakeholders affected.

The development of a new dynamic theory of a phenomenon as complex as antibiotic resistance is never an easy thing, particularly when key data are missing or difficult to gather. Despite the difficulties, it is a process that can reward researchers and policymakers with new ideas as the work progresses.27 These ideas, in turn, serve to concentrate the process of

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27 We intentionally use the term “ideas” here rather than the popular term “insights” to describe new hypotheses and deductions that are made as the work progresses. The dictionary defines insight as “the act or result of apprehending the inner nature of things.” This strikes us as an overly strong and unscientific way to describe an idea that has not yet been adequately validated. Elsewhere, a distinction has been made between “apparent insights” and “validated insights” (Homer 1996).
information gathering and may evolve into firm policy findings when the model matures to the point that it can stand up to the preponderance of empirical evidence and reviewers’ critiques. For this reason, it is important to take stock periodically as a modeling project moves forward, and, in the case of nonproprietary work, to report one’s interim ideas and findings publicly as we have done here.

References


Figure 1. Antibiotic Resistance Policy Loops
Figure 2. Pneumococcal Resistance to Penicillin (PRP) in the United States, 1979-1998

Figure 3. PRP in Spain, 1979-1996
(Sources: Fenoll et al. 1991 [for 1979-89], Fenoll et al. 1998 [for 1990-96])
Figure 4. PRP in South Africa, 1979-1990
(Source: Koornhof et al. 1992)

Figure 5. PRP in Hungary, 1975-1990
(Source: Marton 1992)
Figure 6. Serotype Distribution of PRP in the United States, 1979-1987
(Source: Spika et al. 1991)

Figure 7. Serotype Distribution of PRP in Spain, 1979-1989
(Source: Fenoll et al. 1991)
Figure 8. Office-Based Beta-Lactam Antibiotic Use in the United States, 1980-1997
Figure 9. Basic model structure
Figure 10. PRP in the United States, Simulated vs. Data

Figure 11. PRP in Spain, Simulated vs. Data
Figure 12. PRP in South Africa, Simulated vs. Data

Figure 13. PRP in Hungary, Simulated vs. Data
Figure 14. Assumed Beta-Lactam Antibiotic Use in Four Countries
(USA 1980-1997 based on data in Figure 8. For other countries, we assumed simple curves calibrated to improve model fit to resistance data in Figures 11, 12, and 13.)
Figure 15. Total PRP in the United States Simulated to 2020:
Sensitivity to Antibiotic Use Reduction and its Timing

Figure 16. High PRP in the United States Simulated to 2020:
Sensitivity to Antibiotic Use Reduction and its Timing