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Superbugs: Current Trends and Emerging Therapies

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1. Introduction

1.1 An era before antibiotic treatments

Modern pharmaceutical advancements have placed us in an era where fatalities due to common communicable diseases such as pneumonia or plague are rare. It is difficult to imagine a time when antibiotics were not used as the "fix all" for common illnesses, and even used in cases where antibiotic treatment is not indicated. Although we generally take current treatments for granted, it is important to point out that historically speaking, available treatments for bacterial illnesses were not developed until nearly one-third of the way through the 20th century. It is the accidental discovery of penicillin in 1928 by Alexander Fleming that is considered perhaps one of the largest medical advancements of modern medicine (Bellis, n.d). Prior to the discovery and subsequent development of penicillin, epidemics and pandemics were more frequent, more prominent, and carried larger death tolls.

Early records identify epidemics of plague in Egypt as early as 1650BC, although it is not clear whether it was plague or influenza (Austin, 2003; Daileader, 2007; Wade, 2010). The first major plague outbreak, which is now considered the beginning of the first plague pandemic, began in the Byzantine Empire around 541. The "Black Death" which affected Europe and Asia from 1338 to 1351 claiming 100,000,000 lives marks the beginning of the second plague pandemic and carries the largest death toll to date. The "Black Death" plague re-occurred in several smaller outbreaks including the 1665 "Great Plague of London" as well as outbreaks in France, Spain, and Vienna. The third plague pandemic began in 1873 in China and eventually spread to India, South Africa, North America, South America, and Australia. The death toll in Hong Kong and India from this pandemic breached 12,500,000 before 1957 (Williams, 1997).

Plague Pandemic	Death Toll	Location
1st Pandemic (Byzantine Plague) c541-c639	~25,000,000	Southern Europe
2nd Pandemic 1338-1665 (Black Death, 1338-1351)	>100,000,000*	N. Europe, Asia
3rd Pandemic 1873-1957	>12,500,000	Europe, N. Asia, India, China

Table 1. Comparison of death toll and location for historical plague pandemics (Austin, 2003; Daileader, 2007; Wade, 2010; Williams, 1997). *Death toll from black death period only.

As mortality trends are examined prior to the development of penicillin, it is easy to observe the effect that penicillin had on survival rates. Although we see a substantial number of fatalities, predominately in India, related to the third pandemic of plague, it is important to observe not only the difference in population at the time, but also length of time that continued outbreaks occurred. For example, it is roughly estimated that 75-200 million people were lost during the 14th century outbreaks, with a large geographical range including Northern European climates (England and France) in addition to Southern European regions such as Italy and Southern Spain. Recent studies suggest that this represented approximately 20% of the population in Northern European regions, and a striking 75-80% of the population in Europe's Southern countries (Daileader, 2007). The most recent plague pandemic started roughly in 1873 in China and spread throughout India, the Americas, South Africa and Australia claiming more than 12.5 million (in China and India alone) before the late 1950s. This particular pandemic encompassed a larger geographical region, albeit during a time of more expedited travel. Although the death toll associated with this plague pandemic is large, the plague of the 14th century claimed at least six times more individuals during a time when there were fewer people. Hong Kong experienced a prolonged and repeated outbreak for a few years which claimed approximately 90% of their population (an estimated 8600 total losses) (Pryor, 1975). Despite these isolated large death rates, the actual count of lives lost throughout the eight decades included in this most recent pandemic is extremely low when compared to those from the Black Death.

One might assume that the discovery and subsequent mass production of penicillin is related to this decrease in fatalities. Although the development of penicillin as well as other antibiotics or alternative treatments likely played a substantial role in ultimately stopping the pandemic, it is most definitely not that simple. Generally speaking, the following major differences existed this time around as compared to the first and second pandemics: 1) Penicillin was mass produced and readily available near the end of the third pandemic. 2) Increased travel opportunity and trade lines contributed to the increase in affected regions. 3) Scientific studies have suggested that this plague was not as contagious. 4) There were considerably larger populations during this pandemic. 5) Population density in the regions with highest fatality were high. 6) This pandemic (approximately 84 years \pm 2 years) was shorter than the first (approximately 98 years \pm 40 years) and second (approximately 327 years). 7) The population in general had a better understanding of the spread of disease. 8) Scientists and medical personnel had adopted better practices. 9) Drastic measures were taken to stop spreading. These differences are indeed relative, but do not necessarily suggest that "penicillin stopped the plague." In fact, these differences suggest that development of a drug that the organism thought to be responsible for each plague, *Yersinia pestis*, is susceptible to, was not the "cure all end all" for the disease. Nor will current antibiotics be the cure all for current and emerging diseases. Some of these differences suggest that without penicillin, the third pandemic could have been worse, or longer, or more deadly. For example, few people died despite the fact that more people were likely exposed and the pandemic ended sooner than the others. Figure 1 shows a graph of total reported infectious diseases of bacterial nature in the United States beginning in 1944 with the first available Morbidity and Mortality Weekly Report Summary (MMWR, 1994-2011).

In contrast however, some of these differences suggest that increased knowledge aided in the control of infection. Consider when comparing these pandemics, the trends within each pandemic. For example, during the second pandemic, there was little understanding about how to control infection; consequently we see a prolonged pandemic. During the third pandemic, we assume greater knowledge about infection control, we see shorter pandemics. After adding another variable, these seemingly related correlations lose strength. Consider also during the third pandemic, that the largest number of fatalities occurred during the first half of the pandemic, a time which perhaps surprisingly does not correlate to the availability of penicillin. The conclusion that should be drawn from these correlations is that the plague from the third pandemic likely differed enough that even without penicillin or increased knowledge of infection, the deterrents of the "Black Death" would not have been repeated. One then has to decide if the fact that our "miracle" drug may not have saved us should bring comfort as we face the emergence of other new "plagues" with no drugs to combat them, or whether the fact that the development of penicillin, if not solely responsible for stopping the plague, suggests that the development of new drugs may also not solve the "superbug" attack. As decision is considered, contemplate the following: It is most likely that genetic differences between the plague of the third pandemic and that of the second is responsible for the difference in outcomes, a difference in this case that likely spared much of the world's population; it is also these differences in genetics that are converting our bugs into "superbugs", perhaps this time not in our favor.

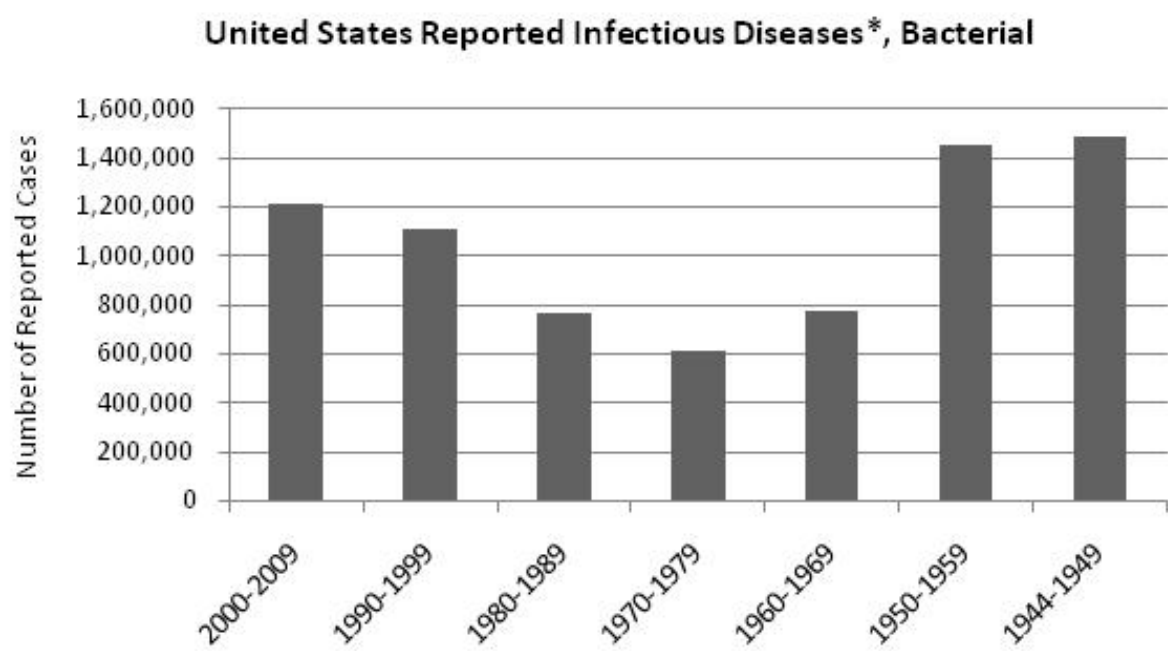


Fig. 1. Reported Bacterial Based Infectious Disease in the United States 1944-2009, population corrected. Data were compiled by the authors using The Center for Disease Control Morbidity and Mortality Weekly Reports 1944-2000. *Included diseases Cholera, *E. coli* O157:H7, *Meningococcal* disease, Pertussis, Plague, Salmonellosis, *Streptococcal* disease (invasive, Group A), *Streptococcus pneumoniae* (drug resistant, invasive disease), Syphilis, Tuberculosis, Typhoid fever.

1.2 Emergence of the "superbug"

The term "superbug" is readily used in the media and to some extent well understood by the public. The media has provided the public with a perceived understanding of the term, but unfortunately has not provided the same understanding of the implications of such "superbugs". Many of the references which are readily viewable on the internet are magazine articles that provide only bits of information with questionable accuracy. In general, the public thinks of a "superbug" as a uniquely contagious, potentially fatal infection that is not treatable with current medicines. Although the most important consideration is really the "superbug's" resistance to current antibiotics, the most prevalent issues to the public seem to be the endless number of dangerous nouns that can be preceded with the term "super." The concern over the development of the next pandemic of a "super-contagious" or "super-fatal" infection fuels the fear of the public. Although today's "superbugs" are certainly contagious, they are not necessarily any more contagious than today's "non-superbugs." Likewise, they are not necessarily more inherently fatal than "non-superbugs." Chances of fatality are higher because of the difficulty in treating and killing the bacteria.

Another public misconception comes from the perceived rarity of these "superbugs." Even with the media announcing that hospital bugs have moved out of the hospital and into the community, in general it seems that the public still views their presence as rare and is shocked and frightened by reports of infections near their community. People in general find it disheartening to know that *MRSA* (methicillin resistant *Staphylococcus aureus*) is commonly found in many gyms for example. Studies demonstrate that the presence of "superbugs" such as *MRSA* is growing, so are the numbers of cases of infections growing as well? If it is everywhere, why don't we all have it? The key here is the same thing that leads to a difference in plague outcomes between the second and third pandemics: genetic differences. In lay terms, some bugs (note the intentional absence of "super") are more infectious than others, some people are more likely to get an infection than others, some infections are easier to treat than others, and some bugs are more susceptible to antibiotics than others. Considering all these differences, the only reliable way to define a "superbug" is scientifically, based on evidence.

Ironically, the scientific definition of "superbug" doesn't have to differ much from the media definition, so long as the implications of the "superbugs" are understood clearly. Based on science, the term "superbug" refers to a bacterial organism which either is inherently or has developed resistance to at least one current antibiotic that would have typically been used to treat said bacteria. For example, the most well known type of hospital infection is staph, which when used to describe a post-operative infection is usually *Staphylococcus aureus*. Typical *Staphylococcus aureus* infections are treated with the penicillin class of antibiotics, such as nafcillin, oxacillin, dicloxacillin and methicillin. The more these infections were treated with these antibiotics, the better *Staphylococcus aureus* became at resisting the treatment. *MRSA*, stands for methicillin resistant *Staphylococcus aureus* and is perhaps the most well known "superbug."

It is important to differentiate that technically viruses cannot be considered "superbugs". The term "bug" is reserved for bacterial organisms, however, it is very common to find the

phrase "superbug" applied to both bacteria and viruses in the media, and occasionally even in the scientific arena. The fact that these terms have both been included stems from the fact that both have the ability to mutate and both are infectious. Many viral infections develop accompanying bacterial infections as well, further complicating the differentiation. Comparison of infection trends makes it difficult to strictly separate the two as well because many viral related illnesses result in death from the subsequent development of bacterial infections. Many bacteria develop virulent strains, a term which is used to describe the degree of infectious nature, not indicating that the bacteria are a virus.

1.3 Current and emerging threats

The list of current "superbugs" is undefined. New strains of bacteria showing drug resistance are rapidly being identified. In 2006, the Antimicrobial Availability Task Force (AATF) of the Infectious Disease Society of America generated a list of drug resistant pathogens that was published in *Clinical Infectious Disease* (Talbot et al., 2006). Six pathogens were identified as "high-priority" for concern including: *Acinetobacter baumannii*, *Aspergillus* species, extended spectrum β -lactamase (ESBL)-producing Enterobacteriaceae, vancomycin-resistant *Enterococcus faecium*, *Pseudomonas aeruginosa*, and methicillin-resistant *Staphylococcus aureus* (MRSA). The AATF selected this list of bacterial and fungal pathogens based on the following characteristics: current clinical and/or public health concern in the United States (based on high infection incidence and substantial morbidity), infection with high attributable mortality rates, unique virulence or resistance factors rendering current therapeutics ineffective, and a lack of substantial or novel drug candidates (primarily those that had few candidates in the phase 2 or 3 trials).

The gram negative bacterium *Acinetobacter baumannii* was included on the list because despite its historical lack of virulence, an increased number of severe infections have been identified. These infections have been identified as both hospital-acquired as well as community-acquired. A survey of infection in US intensive care units has indicated an increase of hospital acquired *Acinetobacter* pneumonia from 1.4% in 1975 to 6.9% in 2003. From 1975 to 2003 significant but smaller increases in bloodstream infection, surgical site infection, and urinary tract infection were also observed (Gaynes & Edwards, 2005). Increased incidence of *Acinetobacter* infections with drug-resistance have also been observed in military personnel with war-related injuries and survivors of the 2004 tsunami.

The inclusion of *Aspergillus* species on the list due to the increasing nature of invasive infections observed in immunocompromised individuals (Maschmeyer & Ruhnke, 2004). Infections from *Aspergillus* fungi have a 50-60% mortality rate (Boucher et al., 2004). Additionally, several current treatments for *Aspergillus* infections require improvement both in the realm of efficacy as well as patient tolerance and safety. The top three drugs of choice for treatment of aspergillosis only have an approximate success rate of 40% (Walsh et al., 1999, 2002, 2004 as cited in Talbot et al., 2006). These include amphotericin B deoxycholate, which is highly toxic unless administered in lipid formulation; caspofungin, which only has FDA approval for second-line defense which is based on a study with a relatively small number of individuals; and voriconazole, which has documented common drug-drug interactions (Johnson & Perfect, 2003; Boucher et al., 2004).

Escherichia coli and *Klebsiella* species strains producing the extended spectrum β -lactamase (ESBL) were selected for the list due to common infection in the urinary, biliary or gastrointestinal tracts. There is also a common occurrence in trauma injury and surgical sites as well as a high incidence of hospital acquired pneumonia and postoperative meningitis (Decré et al., 2004; Kang et al., 2004; Meyer et al., 1993; Paterson et al., 2004a, 2004b; Quale et al., 2002; Weiner et al., 1999 as cited in Talbot et al., 2006). A 2001 survey for US intensive care units identified 11.2% and 16.2% occurrence of ESBL production in *E. coli* and *Klebsiella* species, respectively (Biedenbach et al., 2004; Streit et al., 2004). The most alarming observation is the large increase in the percentage of resistant pathogens relative to total reported cases. During a 2 year period, 56 out of 57 samples collected of *Klebsiella oxytoca* exhibited multi-drug resistance (Decré et al., 2004 as cited in Talbot et al., 2006). A survey of 91 ESBL-producing *Klebsiella* species indicated resistance to gentamicin in 84% of the samples. Resistance to tri-methoprim-sulamethoxazole (70%), piperacillin-tazobactam (60%), and ciprofloxacin (51%) was also observed (Schwaoer et al., 2005).

Limited treatment options and increased infections have led to the high-risk classification of vancomycin-resistant *Enterococcus faecium*. Recently high rates of resistance to glycopeptides treatment have been observed in the United States compounded with an increased incidence of *Enterococcus faecium* blood infection in patients, particularly infections related to catheter use (Murray, 2000; Wisplinghoff et al., 2004). High-risk patients, such as those that have received a liver transplant or have cancer, face a disturbingly high rate of infection near 70% (National Nosocomial Infections Surveillance [NNIS] System Report, 2004; Streit et al., 2004; Wisplinghoff et al., 2004).

The severity of infections caused by *Pseudomonas aeruginosa* warrant the inclusion of this gram negative bacterium. Immunocompromised patients face potential fatal invasive infections (Maschmeyer & Braveny, 2000). *Pseudomonas aeruginosa* threatens a wide range of ages and includes lower respiratory and urinary tract infections. Infections occurring in patients with cystic fibrosis, often result in severe inflammation causing fatal damage to the lung tissue (Rajan & Saiman, 2002). Incidence of intensive care unit acquired pneumonia caused by *Pseudomonas aeruginosa* are increasing to approximately two times the rates observed in 1975. Similarly the infection rates of the urinary tract and surgical sites have doubled (NNIS System Report, 2004). Like other members of the "superbug" list, the rate at which *Pseudomonas aeruginosa* has developed drug resistance is distressing. From 1997 to 2001 resistance to fluoroquinolones increased 37%, resistance to imipenem increased 32%, resistance to ceftazidime increased 22%, resistance to multiple-drugs increased 4% (NNIS System Report, 2003; Obritsch et al., 2004).

The last pathogen included on the 2006 "superbug" list is perhaps the most well known, methicillin-resistant *Staphylococcus aureus* (MRSA). It is currently estimated that approximately 4 out of 1000 patients discharged from the hospital have a MRSA infection (Kuehnert et al., 2005). MRSA infections are more prominent in surgical or dialysis patients as well as premature infants. Hospital acquired MRSA infections were among the first identified and resulted in higher mortality rates. Recently, concern has risen over the number of cases occurring in the community, particularly in a crowded population. Currently vancomycin is the primary therapeutic used to combat MRSA infections, but strains showing vancomycin resistance are emerging (Fridkin et al., 2003). Hospitalizations due to MRSA infections, regardless of the cause of infection, have increased from 127,000 in 1999 to

280,000 in 2005 (Kallen et al., 2010; Klein et al., 2007; Klevens et al., 2007). Table 2 below summarizes the 2006 list of "superbug" threats as well as the reason for inclusion on the threat list.

Pathogen	Reason for list inclusion
<i>Acinetobacter baumannii</i>	Multi-drug resistant, hospital- and community-acquired, increasing incidence
<i>Aspergillus</i> species	Current drugs with low efficacy and/or side effects including drug-drug interactions, high mortality rate, increased invasive infections
ESBL-producing <i>Enterobacteriaceae</i>	Increasing incidence, rapidly increasing drug-resistance, multi-drug resistance
vancomycin-resistant <i>Enterococcus faecium</i>	Increasing incidence of blood infections, high infection rates, increasing infection rates across patient care areas
<i>Pseudomonas aeruginosa</i>	Severity of infections, high mortality rate in high risk patients, increasing incidence, increasing resistance, multi-drug resistance
methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Increasing resistance, hospital- and community-acquired, increasing incidence, rapid resistance development to current therapeutics

Table 2. Summary of AATF List of Drug Resistant Pathogens requiring concern, 2006.

Although not included on the 2006 AATF list, several additional organisms should be considered due to the emergence of similar characteristics. One such organism that should be added to a list of concern is *Clostridium difficile*. This organism has been identified as number one identifiable cause of diarrhea in HIV infected patients (Sanchez et al., 2005). Estimates suggest that drug-resistant and virulent form *Clostridium difficile* played a role in nearly 300,000 hospitalizations in 2005, a two-fold increase from 2000 before the virulent strain was prevalent. This study also suggested the fatality rate increased from 1.2% to 2.2% from 2000 to 2004 (Zilberberg et al., 2008). Infection with *Clostridium difficile* results in production of two toxins, A and B. New evidence suggests that toxin B provides the virulent nature of *Clostridium difficile* (Lyras et al., 2009). Another organism which has rising concern over the development of multi-drug resistance is *Neisseria gonorrhoeae*, the bacteria that causes gonorrhea. As early as the 1970s, the United States has seen strains of *Neisseria gonorrhoeae*, resistant to penicillin and tetracycline. Many of the more recent strains have developed resistance to fluoroquinolones. Just reported in 2011, a multi-drug resistant strain known as H041 was identified in Japan (Ohnishi et al., 2011). Food-borne diseases are also beginning to demonstrate resistance. Salmonella strains that are resistant to ciprofloxacin have recently emerged. An estimated 3.3 million cases of salmonella poisoning were reported in North American and Europe between 1999 and 2008, although these cases include both resistant and non-resistant strains (Le Hello et al., 2011; McConnell, 1999). Other diseases of particular concern that were included on the Notifiable Disease List in 2009 produced by the Center for Disease Control (CDC) include: *Streptococcal* species, *Streptococcus pneumoniae*, vancomycin-resistant *Staphylococcus aureus* (VRSA), *Mycobacterium tuberculosis*, *Neisseria meningitidis*, *Bordetella pertussis*, *Vibrio cholera*

(Christensen et al., 2009; Lynch et al., 2009; Morbidity and Mortality Weekly Report [MMWR], 2009; Phares et al., 2008; Robinson et al., 2001; Tanaka et al., 2003). Although in some of these cases antibiotic resistance is already observed, they are included primarily because of the availability of case reports with these diseases. Figure 2 represents a comparison of total reported cases of Streptococcal disease, invasive, group A to those that were drug resistant in the United States from 2002 to 2007. The percentage of cases that showed drug resistance are shown for each year. These data do not suggest a large increase in the number of reported cases but a trend of increasing resistance. Also, infections caused by these bacteria exhibit characteristics and trends similar to those bacterium that have been placed on the AATF list.

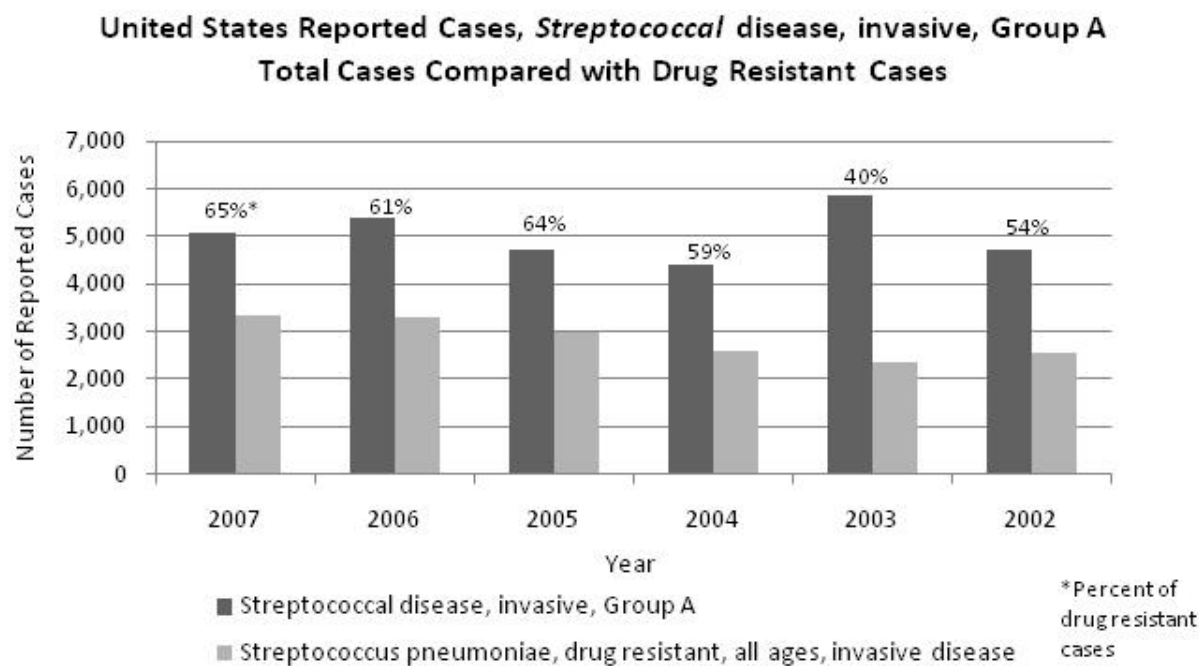


Fig. 2. The total number of *Streptococcal* disease (invasive, group A) cases reported in the United States between 2002 and 2007 compared to the number of cases that demonstrated drug-resistance (shown as a percentage each year.) Data were compiled by the authors from the Center for Disease Control Morbidity and Mortality Weekly Reports, 2002-2007.

2. How did bugs become "super?"

2.1 Antibiotic misuse

Perhaps the most commonly known cause of the development of antibiotic resistance is the so-called misuse of antibiotics. This phrase refers not only to the patient's adherence to antibiotic prescription instructions, but also to the doctors that prescribe antibiotics unnecessarily. Many times problems with over prescription of antibiotics comes from the patients demand. Perhaps doctors are concerned with patient satisfaction or wish to decrease the likelihood of a follow up visit for a viral illness which could result in a bacterial infection. It is possible that the patients have developed an expectation to leave the doctor's office with prescription in hand. Regardless of the reason, antibiotics administered for

unnecessary purposes, including non-bacterial infections and prophylaxis, encourage the development and the spread of antibiotic resistance. Considering one study that estimated over 90% of all infections are viral, yet over half the US patients are taking antibiotics for these viral infections (*Science Daily*, 2005).

A study published in *Science* in 2010 utilized a genomic approach to examine single nucleotide polymorphisms using a high resolution second generation DNA sequencing platform. Researchers examined two samples: one was a global collection ranging from 1982 to 2003 and the second was a collection from Thailand over a seven month period. Sample one represents a random population while the second samples are limited to a single transmission. The data suggests specific European samples from the global collection relate to those collected from the Thailand hospital. The complete set of data allowed phylogenetic analysis and an estimation of time since the evolution of the resistance. The researchers observed that 28.9% of the homoplasies identified had direct links to current therapeutics, providing strong evidence that the misuse of antibiotics in today's medical practice is a major contributor to the development of resistance. Furthermore, this study has allowed an estimate of one single nucleotide polymorphism every six weeks, an essentially unimaginable rate in evolutionary time (Harris et al., 2010).

The second part of this concern is patient adherence. This usually stems from the fact that antibiotic treatment, assuming it is a non-resistant bug, usually improves clinical symptoms within 1 to 3 days. Patients have difficulty continuing to take the prescription when their symptoms have been alleviated. They also have a tendency to "save" the rest of the prescription in case they need it again in the future. The contribution of this action to antibiotic resistance is simple: initial treatment kills most of the bacteria, particularly those susceptible to the antibiotic; those with some minor susceptibility to the antibiotic survive and thrive as the dosing is waned. Essentially this is an acceleration of "survival of the fittest." Bacteria that have been able to survive, reproduce and pass along whatever genetic variance they carry which provides resistance.

Recent reports have warned the overuse of antibiotics as prophylaxis in the food industry, although there is some controversy over the actual contribution to food animal antibiotic administration to the growing problem of global "superbug" problems (Singer et al., 2003). It is proposed that unnecessary use of antibiotics in food animals will contribute to resistance in the same ways as over prescribing and lack of adherence in the human population.

2.2 Common household "superbug" advancement

Although antibiotic misuse is perhaps the most publicized cause of "superbug" development, several similar mechanisms advance the resistant strains as well. Antibacterial soap is one example in which a large sample of weaker bugs is being killed, allowing the tough survivors to expand their gene pool. Many antibacterial products contain the ingredient triclosan, which functions by inhibiting essential fatty acid synthesis. Surviving bacteria develop a resistance to triclosan and are therefore not affected by future triclosan based cleansing. Laboratory experiments demonstrate that *E. coli* variants which developed resistance to triclosan did so via a mutation in the *fab1* gene. *Fab1* encodes the enzyme enoyl reductase, an enzyme essential for fatty acid metabolism, a mechanism untouched by most of today's antibiotics (Levy, 2000). Further experiments suggest two hours (4-8 hours for

resistant strains) are required to kill 90% of susceptible *E. coli* when treated with soap containing 150 µg/ml triclosan (Levy, 2000).

The thought of "superbug" advancement in your home can be disturbing, but understanding where bacteria and fungi are found, where they live, and what strains they are can help educate the public about cleanliness in the home. It is important to point out here that my mentioning cleanliness in a review on "superbugs," one might imagine that evidence suggests we need to use more antibacterial cleaners and clean more, however, this is not necessarily the case. Most likely what is required is a solid education about the spread of the organisms, most importantly how to wash your hands. In reality, what is really required is not a better cleaner or more cleaning, but longer cleaning. A recent article in *Popular Mechanics* examined places in your home where microorganisms are likely thriving and identified the top five: refrigerator (particularly the vegetable drawer), dishwasher, air around the trash can and the trash can itself, washing machine, and the shower head. Presented results indicated that 23.4% of the bacteria found in the refrigerator was *Klebsiella pneumoniae*; the potentially infectious bacteria *Pseudomonas aeruginosa* were found in the washing machine; bacteria samples collected from the trash and the air around the trash contained *Staphylococcus aureus*, approximately 33% of which were methicillin resistant; *Exophiala* fungi capable of infecting humans was found in the dishwasher; and *Mycobacterium avium*, a bacteria that is usually benign but can infect immunocompromized individuals, was found in the shower head (Grunbaum, web, 2011). The important point to take from both of these "household" examples is that any cleansing treatment (hands, body, and refrigerator) must be approached with sufficient cleanser and sufficient time to ensure that maximal bacteria or fungus has been extinguished.

2.3 Resistant gene transfer

Misuse of antibiotics and antibacterial products have forced bacteria the opportunity to evolve resistance via one or more mechanisms of DNA alteration. Generally speaking, the result of these DNA alterations is either a modification that allows the bacteria to modify the drug chemically, rapidly remove the drug from the cell or prevent drug entry into the cell, or prevents binding of the drug by modifying the drug's target site. Likewise, certain bacteria are inherently resistant to some antibiotics. For example, gram negative bacteria are resistant to a number of antibiotics that are typically effective for gram positive bacteria, such as vancomycin. This resistance comes from the outer cell membrane layer that surrounds gram negative bacteria but not gram positive bacteria (Ibezim, 2005). The most pressing concern, however, is the rate of spread of so called acquired resistance. Acquired resistance refers to the presence of DNA encoding resistance, either through mutations or so called horizontal gene transfer (which is the exchange of resistance genes among different bacterial species). Mutations are thought to occur about one in every 10^8 to 10^9 bacteria (Todar, 2009). Once bacteria develop a mutation that allows it to survive in the presence of antibiotics, this trait is passed on via a process known as vertical gene transfer through the replication of DNA and growth of new cells. Of these two processes, it is horizontal gene transfer that contributes most considerably to the mass wave of resistant bacteria.

Bacteria are equipped with a variety of mechanisms capable of gene exchange including conjugation, transduction, and transformation which are all methods of horizontal gene

transfer. Likewise, bacteria can undergo gene exchange by sequence specific mechanisms such as transposition. Conjugation refers the interaction between two bacterial cells through a sex pillus, which allows polymerase mediated duplication of plasmid DNA to be transferred or exchanged. Oftentimes, these plasmid molecules contain a gene which encodes resistance. The second method, transduction, also involves incorporation of new DNA. Transduction involves transfer of genetic material via a bacteriophage, which injects DNA with potential resistance genes included into a host cell. Infection stimulates the production of new phage molecules with both phage DNA and host cell DNA, which upon infection into another host cell will result in incorporation of the original host cell DNA (presumably containing a resistance gene) into the chromosome of the newly infected cell. Fragmented pieces of DNA from donor cells, which may confer resistance, are taken up by new cells via the process of transformation (Tortora, 2003).

Likewise, bacteria can undergo gene exchange by sequence specific mechanisms such as transposition. Transposition occurs when a resistance gene is flanked with genes encoding enzymes known as transpoase. These enzymes, together with sequences of DNA known as insertion sequences, when expressed, facilitate the transfer and insertion of the resistance gene into host DNA. This mechanism is referred to as horizontal gene transfer because the gene sequence along with DNA encoding machinery for further transposition activity are incorporated in a cross-over like process between two strands of DNA (Tortora, 2003).

Thus far, a variety of genes have been identified that confer resistance when expressed. One of the most widely publicized was the New Dehli Metallo- β -lactamase (NDM-1) (Kumarasamy et al., 2010). The NDM-1 gene encodes an enzyme known as carapenemase, which is a β -lactamase that acts specifically on carbanpenem antibiotics, a class which until recently reserved for infections demonstrating resistance to other antibiotics. Likewise the β -lactamase activity affords organisms carrying this gene resistance to all β -lactam antibiotics, including cephalosporins, many glycopeptides, monobactams, and penicillins (Walsh, 2008). The gene is capable of horizontal gene transfer and has been observed in select strains of *E. coli* and *Klebsiella pneumoniae* (Yong et al., 2009).

3. Current, emerging, and needed therapies

3.1 Current therapies

Many of the existing therapies for bacterial infections function via similar mechanisms of action. In general antibiotics inhibit one of three cellular mechanisms including: protein synthesis (aminoglycosides, macrolides, tetracyclines, and others including streptomycin, chloramphenicol, linezolid, quinupristin/dalfopristin); cell wall synthesis (carbapenems, cephalosporins, glycopeptides, and penicillins); or topoisomerase activity (quinolones) (Lexi Comp, Inc., 2011). There are a few select antibiotics that have a unique mechanism of action including: daptomycin, which binds to the cell membrane and causes rapid depolarization thus inhibiting synthesis of nucleic acids and proteins; trimethoprin-sulfamethoxazole, which interferes substantially with bacterial folic acid synthesis; and metronidazole, which results in breakdown of DNA helical structure (Lexi-Comp, Inc., 2011). Table 3 summarizes selected current antibiotics used for bacterial disease and infection, specifically those currently indicated for infections caused by organisms that have been added to the "superbug" list.

Generic	Common Uses
Aminoglycosides	
Gentamicin	Infections due to gram- organisms & gram+ <i>Staphylococcus</i>
Kanamycin	Infections caused by <i>E. coli</i> , <i>E. aerogenes</i> , <i>K. pneumoniae</i> , <i>Acinetobacter</i> spp
Carbapenems	
Imipenem/ Cilastatin	Infections of LRT, UT, bone, skin; infections due to gram+ bacteria (<i>S. aureus</i> , <i>Streptococcus</i> spp), resistant gram- bacilli (including EBSL-producing <i>E. coli</i> , <i>Klebsiella</i> spp, <i>Enterobacter</i> spp, <i>P. aeruginosa</i>)
Meropenem	Meningitis caused by <i>S. pneumoniae</i> , <i>N. meningitidis</i> ; skin infections
Cephalosporins	
Cefotaxime	Infections of RT, skin, bone, UT due to gram(- bacilli (not <i>Pseudomonas</i>), gram+ cocci (not enterococcus), many penicillin-resistant pneumococci.
Cefepime	UTIs due to <i>E. coli</i> , <i>K. pneumoniae</i> ; infections of skin due to methicillin-susceptible staphylococci; pneumonia due to <i>S. pneumoniae</i> , <i>K. pneumoniae</i> , <i>Enterobacter</i> spp; <i>Enterobacter</i> spp
Glycopeptides	
Vancomycin	Infections caused by staphylococcal spp, streptococcal spp, <i>C. difficile</i>
Lipopeptide	
Daptomycin	Infections due to gram+ organisms; endocarditis caused by MSSA or MRSA
Macrolides	
Azithromycin	Infections of U/LRT, skin; CAP, infections due to <i>S. aureus</i> , <i>S. pneumoniae</i>
Clarithromycin	Infections due to <i>S. pneumoniae</i> , <i>S. aureus</i> , <i>S. pyogenes</i> ,
Penicillins	
Ampicillin	Infections due to non-β-lactamase-producing organisms, streptococci, pneumococci, meningococci, some <i>Salmonella</i> , <i>Enterobacter</i> , <i>Klebsiella</i>
Penicillin G	Sepsis, pneumonia, endocarditis, meningitis; infections due to gram+ organisms (generally not <i>S. aureus</i>), some gram- organisms
Quinolones	
Ciprofloxacin	Infections of the UT, LRT, skin, bone infections; gonorrhea; HAP
Levofloxacin	CAP, MDRSP, HAP, UTI, skin infections
Moxifloxacin	CAP, MDRSP, bronchitis, skin infections, intra-abdominal infections
Sulfonamides	
Trimethoprim-Sulfamethoxazole	UTIs due to <i>E. coli</i> , <i>Klebsiella</i> & <i>Enterobacter</i> spp, bronchitis due to <i>S. pneumoniae</i>
Tetracyclines	
Doxycycline	Infections caused by <i>Chlamydia</i> , <i>Mycoplasma</i> , <i>N. gonorrhoeae</i> , <i>Clostridium</i> , <i>B. anthracis</i> , uncommon gram- & + organisms; syphilis; CAP
Others	
Chloramphenicol	Infections due to organisms resistant to other antibiotics caused by <i>N. meningitidis</i> , <i>Salmonella</i> ; vancomycin-resistant enterococci
Linezolid	HAP caused by <i>S. aureus</i> (including MRSA) or <i>S. pneumoniae</i> (including multidrug-resistant strains), skin infections, CAP caused by gram+ organisms, Vancomycin-resistant <i>E. faecium</i> (VRE) infections

Table 3. Selected antibiotic therapeutics and selected common uses. Data were compiled with Lexi-Comp Online in August 2011. Spp=species; CAP=community acquired pneumonia; MDRSP = multidrug-resistant *S. pneumoniae*; U/LRT = upper/lower respiratory tract; UTI = urinary tract infection; HAP = hospital acquired pneumoniae (Lexi-Comp, Inc., 2011).

In regards to the specific organisms which have documented resistant strains, the following drugs demonstrate efficacy: The imipenem/cilastatin combination has been effective against resistant gram negative bacilli such as the ESBL-producing *E.coli* and *Klebsilla* species and the *Enterobacter* species and *Pseudomonas aeruginosa*. Ceftoaxime has demonstrated efficacy against some penicillin-resistant pneumococci. Treatment of MRSA and MSSA has been successful with daptomycin. The primary quinolones used for drug resistant *S. pneumoniae* are levofloxacin and moxifloxacin. Chloramphenicol, although quite toxic, has demonstrated activity against many vancomycin-resistant enterococci. Perhaps the most notable is linezolid, which is a newer antibiotic designed to inhibit bacterial protein synthesis, albeit by binding the bacterial 23S ribosomal RNA of the 50S subunit and preventing formation of the 70S subunit. This antibiotic has been effective against vancomycin-resistant *Enterococcus faecium* (VRE), nosocomial pneumonia caused by both methicillin susceptible and methicillin resistant forms of *Staphylococcus aureus* as well as *Streptococcus pneumoniae* including those that are multidrug resistant. Also of worthy attention is the relatively few side effects documented for patients treated with linezolid (Lexi-Comp, Inc., 2011). Table 4 summarizes selected infections as well as recommended and alternative treatment combinations.

Pathogen	Recommended Adult Drug Therapy	Alternative Drug Therapy
<i>Pseudomonas Aeruginosa</i>	Ceftazidime plus Aminoglycosides or Penicillins, Extended-Spectrum plus Aminoglycosides or Cefepime plus Aminoglycosides	Imipenem and Cilastatin or Meropenem plus Aminoglycosides or Ciprofloxacinplus Penicillins, extended Spectrum or Aztreonam
<i>Aspergillus</i> Species	Voriconazole	Amphotericin B (Lipid Complex), Echinocandins, Itraconazole, Posaconazole
<i>Salmonella</i> Species	Cephalosporins, 3rd Generation	Ampicillin, Sulfamethoxazole and Trimethoprim, Chloramphenicol, Ciprofloxacin
<i>Enterococcus</i> Species	Penicillin G plus (Gentamicin or Streptomycin) or Ampicillin plus (Gentamicin or Streptomycin); Vancomycin-resistant Enterococcus: Linezolid, Quinupristin and Dalfopristin, Doxycycline, Chloramphenicol	Vancomycin plus Gentamicin or Penicillin G Plus Streptomycin or Ampicillin plus Streptomycin
<i>Staphylococcus aureus</i> , Methicillin-Resistant	Vancomycin	Daptomycin, Doxycycline, linezolid, Quinupristin and Dalfopristin, Sulfamethoxazole and Trimethoprim
<i>Clostridium difficile</i>	Metronidazole	vancomycin
<i>Neisseria gonorrhoeae</i>	Cefixime, Ceftriaxone	Monotherapy: Cefotaxime, Spectinomycin
<i>Bordetella pertussis</i>	Erythromycin	Azithromycin, Clarithromycin, Tetracycline, Sulfamethoxazole and Trimethoprim, Chloramphenicol

Table 4. Summary of selected infectious organisms and the recommended and alternative treatments (Lexi-Comp, Inc., 2011).

3.2 Emerging therapies

In the recent years there have been a few significant developments of new antibiotics. Ceftaroline, often referred to as a 5th generation cephalosporin, has shown activity against multidrug resistant gram positive bacteria (Bazan et al., 2009; Steed & Ryback, 2010).

Ceftaroline fosamil is a prodrug form which is rapidly converted to the active form after administered (Bazan et al., 2009). Like other cephalosporins, it binds to penicillin binding proteins (PBP), but differs from other β -lactams in that it has a high affinity for PBP2a, which is unique to MRSA (Steed & Ryback, 2010). Ceftaroline has been successfully used for the treatment of skin and skin structure infections caused by methicillin resistant *S. aureus*, *S. pyogenes*, *S. agalactiae*, *E. coli*, *K. oxytoca*, and *K. pneumoniae* (Bazan et al., 2009; Product insert, 2010; Saravolatz et al., 2010a, 2011b; Snyderman et al., 2010; Steed & Ryback, 2010). The most common side effects reported were diarrhea, nausea, constipation, vomiting, increased transaminases, hyperkalemia, rash, and phlebitis (Hester et al., 2011).

Another recent addition to approved antibiotics is telavancin. Telavancin is a lipoglycopeptide derivative of vancomycin that inhibits bacterial cell wall synthesis (Saravolatz et al., 2009). When compared to vancomycin, telavancin has demonstrated effectiveness in treatment of skin and skin structure infections caused by methicillin resistant *S. aureus*, *S. pyogenes*, *S. agalactiae*, *S. pneumoniae*, and vancomycin resistant *E. faecalis* (Stryjewski et al., 2006a, 2006b, 2008c). The drug has also been explored for use in hospital acquired pneumonia (Rubinstein et al., 2011). The most common side effects reported included: nausea, vomiting, foamy urine, and disturbance in taste (Medical Letter, 2010).

A recent carbapenem, doripenem, has demonstrated a broad spectrum of antimicrobial activity against gram positive and negative bacteria including *P. aeruginosa* (included some carbapenems resistant strains) (Jones et al., 2004; Lister, 2007; Mushtaq et al., 2004). Doripenem is indicated for complicated intra-abdominal and urinary tract infections due to enterococci, anaerobes, and *P. aeruginosa* as well as hospital acquired pneumonia resulting from *Klebsiella*, *Enterobacter*, *Acinetobacter*, and *Serratia* species or in some cases *S. aureus* (Medical Letter, 2007; Solomkin et al., 2003). Aside from allergic reactions, the most commonly reported side effects included: headache, nausea, diarrhea, rash, and phlebitis (Horiuchi et al., 2006).

Retapamulin is a recently approved topical antibiotic effective for treatment of impetigo due to *S. pyogenes* and methicillin-susceptible *S. aureus* (Rittenhouse et al., 2006). Activity against MRSA has been observed *in vitro* (Rittenhouse et al., 2006). This antibiotic is derived from fermentation of fungi and represents the first in a class of antibiotics known as pleuromutilins. Drugs from this class interfere with bacterial protein synthesis by acting on the 50S subunit of the ribosome (Yan et al., 2006). Reported side effects are minimal and included only site irritation (Parish et al., 2008; Parish et al., 2006).

Lastly, consideration of some not yet approved but promising antibiotics is warranted. In early 2011, results of a phase 3 clinical trial for a new antibiotic called fidaxomicin were published (Louie et al., 2011). Fidaxomicin starts a new class of antibiotics referred to as macrocycles. The drug offers a narrow range of activity as it is designed specifically for *C. difficile* (Louie et al., 2011). The clinical studies reported that fidaxomicin treated patients had

fewer recurrent episodes of *C. difficile* infection than patients taking vancomycin (Louie et al., 2011). Another potential antibiotic worth considering is referred to as kibdelomycin, which was selected based on screening against multiple engineered strains of *S. aureus*. Although the structure identified was unique, it was found to function as a type II topoisomerase inhibitor and has demonstrated activity primarily against gram positive bacteria. Although it functions as a topoisomerase inhibitor, it is unique in the fact that it specifically inhibits the ATPase activity of bacterial type II topoisomerases (Phillips et al., 2011). Another promising publication in *Nature* suggests that a new inhibitor (GSK299423) has demonstrated broad spectrum activity by inhibiting DNA gyrase. The promising detail about this inhibitor is that crystal structures have indicated that the inhibitor binds to a non-catalytic site on the DNA gyrase, as compared to the binding site for most fluoroquinolones, thus representing a new class of antibiotics and making this a prime target for further development (Bax et al., 2010).

3.3 Therapeutic concerns and the need for continued antibiotic development

The concern over the current antibiotics available is that the majority function via one or two general mechanisms. Currently the carbapenems are "last line" therapy for many resistant bacteria; the emergence of the NDM-1 gene demonstrates not only an organism's ability to withstand treatment from the majority of available antibiotics, but also demonstrates the threat of effective transposition based spreading from the gene. Many "newer" antibiotics function via some slight variation of previous mechanisms, for example inhibiting protein synthesis by binding one of the ribosomal subunits at a different location or with a different affinity. Bacteria are likely to rapidly develop resistance mechanisms for antibiotics that function so similarly. Currently there are very few approved antibiotics with novel mechanisms and the "drug development pipeline" does not include a substantial number of new designs.

The emergence of the multidrug resistance element NDM-1 suggests the urgency for the development of drastically novel function antibiotics. The over publicized, and perhaps mis-publicized, evolution of "superbugs" has forced both public and government attention to the uncertain nature of our microbial defense. The necessity of government support through funding is essential in order to develop drugs that are positioned to enter the "pipeline." Considering the time required for drug development, the risk of global spread of resistance is alarming.

4. Conclusion

4.1 Prevention of antibiotic resistance

Data clearly demonstrate a rise in the number of resistant organisms as well as an increase in the number of multidrug resistant bacteria. Based on the relative mutation rate and gene transfer rates, there is indeed a global concern over a future inability to treat bacterial infection effectively and without toxic side effects. Today's medical treatments and surgical capabilities have advanced modern medicine just as the discovery and development of penicillin marked a turning point in therapeutics. Emerging resistant mechanisms and organisms place the world on a path not only similar to an era before penicillin, but also to an era where medical surgical procedures become impossible to the risk of infection. New

multidrug resistance elements, in particular, NDM-1, is concerning because of its potential to travel between species and produce "superbugs" at rates well beyond the limit of natural selection. History has demonstrated that organisms have been able to develop resistant mechanisms rapidly once introduced to new antibiotics, and in particular once introduced to a new class of antibiotics. Continued responsible use of antibiotics is currently the best way to attempt to slow down the development of resistant strains. Careful attention should be paid to when antibiotics are prescribed, but even more importantly which antibiotics are prescribed. It is extremely important to reserve new antibiotics for strains that have demonstrated resistance to other drugs. Infatuation with "hot" new drugs has the potential to accelerate the selection of resistant organisms and render the new drugs ineffective as well. Consideration for patient compliance is also important; ensuring that the full course of antibiotic is taken will produce maximal eradication of the bacteria, leaving no remaining cells to pass on their "secret" of survival.

4.2 Spread the research and spread the word

Financial cutbacks by large drug companies and governmental funding cuts have slowed the potential for development of novel antibiotics. Although the high risk - high payoff drug development programs are waning, smaller research groups and companies are in a position to collaborate and share promising results thereby forming a network of antibiotic development team members. In recent years, the pressure to "develop and sell" outweighed the pressure to "develop and share". Perhaps with the economic setbacks, the "develop and share" model will accelerate design of new drugs. The importance of sharing knowledge with colleagues is evident, but the necessity of correctly explaining our current state to the general public should be equally considered. A clear understanding of the investment, both time and financial, required to bring a drug to market needs to be highlighted so that everyone has the motivation to slow the spread of resistance and give the drug development industry an opportunity to excel.

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