1   **Globalization and Antimicrobial Resistance: A Moving Target**

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ABBREVIATIONS:

AMR – Antimicrobial resistance, HAIs – Healthcare associated infections, HIV – Human

immunodeficiency virus, MRSA – Methicillin resistant *Staphylococcus aureus*, Mtb –

Mycobacterium tuberculosis

INDEX TERMS:

Antibiotic resistance, Antimicrobial resistance, Globalization, HAIs, Healthcare associated

infections, Population mobility, urbanization,

Learning Objectives:

1. Explain historical and current examples of how select pathogens can evade

antimicrobial treatments, and how this confers an evolutionary advantage to that

pathogen.

2. List and describe the effects of globalization in the spread of antimicrobial resistant

(AMR) pathogens, particularly international travel and urbanization.

3. Describe how proper public policy, medical intervention strategies, and development

of novel therapies can all be used to curtail the emergence of AMR pathogens.

Abstract

Antimicrobial resistance (AMR) is a complex issue that has currently reached a dangerous

tipping point. The nature of this critical public health and healthcare problem has two

primary components: 1) the emergence of diverse AMR pathogens, and 2) the alarming

rapid spread of these AMR pathogens in a wide array of geographic and densely populated

48 regions. The adaptation and survival of these dangerous pathogens is associated with

49 ongoing and increasing natural selective pressure as it relates to human, animal, and

50 environmental health settings. The primary drivers for this mounting trend of AMRs

51 include, but not limited to, changing patterns of pathogen epidemiology, emergence of

52 drug-resistance genes, animal husbandry, antimicrobial use / stewardship, population

53 mobility, increased rates of human urbanization, and the movement and ease of products

54 and goods across global settings. Simply stated, AMR pathogens are incredibly versatile

55 biological entities at adaptation to every natural (and unnatural) niche known and make

56 themselves at home regardless of where they land. Understanding AMRs is critical to

57 curbing their ongoing global drift. For this special article, we will address the emergence

58 and spread of AMR pathogens from a medical laboratory and public health lens, and how

59 this new threat affects the ever-evolving relationship between hosts and pathogens.

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61

62 **Introduction**

63 Antimicrobials have played a pivotal role in public health. The majority of their

64 mechanism of actions is to target a pathogen-specific process such as the synthesis of the

65 bacterial cell walls in bacteria (e.g., streptococci) or the reverse transcriptase used by

66 viruses (e.g., human immunodeficiency virus [HIV]). There are, of course exceptions to

67 this, but for this manuscript, we will focus on pathogen-specific processes. While these

68 antimicrobials initially showed remarkable effectiveness, many of their effects are waning.

69 Healthcare associated infections (HAIs) caused by pathogens such as methicillin-resistant

70 *Staphylococcus aureus* (MRSA) cost the healthcare industry billions each year due to their

71 difficulty to treat. As one can surmise by the name, the difficulty in treating these pathogens

72 is attributable to their antimicrobial resistance (AMR). The same drugs that were once used

73 to treat such infections have lost much of their utility, allowing for the spread of AMR

74 pathogens.

75   Although frequently associated with antibiotics, AMR is not a phenomenon

76 exclusive to bacteria. Other pathogens including viruses[1-7] and protozoa[8-10] also exhibit this

77 ability to respond to antimicrobials, further demonstrating the dangerous scope of AMR in

78 infectious diseases. Therefore, AMR represents a massive public health concern for

79 pathogens ranging from HIV to *Plasmodium falciparum* (the malaria parasite). This puts a

80 tremendous burden on healthcare providers and healthcare infrastructure, particularly in

81 developing countries where resources can already be scarce.[11]

82   A number of factors are involved in the spread of AMR pathogens, which we will

83 touch upon in this manuscript. It is not possible to address them all in their entirety nor in

84 the detail this topic deserves; but we will address the foundational drivers of this public

85 health crisis. From the acquisition of antimicrobial-resistance genes into the pathogen

86 population, to the increased population condensation into urban areas, AMR pathogens

87 have been able to establish themselves into our current society.[12,13]

88

89 *The Pendulum of Antimicrobial Resistance*

90   The use of antibiotics, an antimicrobial agent targeted towards bacteria, burst into

91 prominence during World War II. Wound sepsis was a leading cause of death and

92 disablement among military personnel and the need to develop rapid therapeutics against

93 infections was needed as the world entered into conflict. Hence, a large amount of attention

94 into the recent discovery of a novel antibacterial agent, penicillin, was paid. It's discovery

95 and initial publication in the late 1920's was perhaps the most consequential and fortuitous

96 observations in medicine of that century. The antibiotic was discovered by Dr. Alexander

97 Fleming when he noticed that his staphylococcus cultures were destroyed by a co-

98 contaminating mold, *Penicillium notatum*. Upon purification of the compound responsible

99 for the antimicrobial behavior, physicians and military personnel realized its potential use

100 to treat battlefield injuries and the U.S. and British governments invested heavily in the

101 bulk production of the antibiotic. Indeed, penicillin was broadly utilized by allied troops

102 throughout WWII, and saved many thousands of lives. In hindsight, the broad and

103 medically unsupervised use of penicillin in the war theatre was an early and then, unknown

104 push of the lever towards AMR. This problem has not yet been resolved and has actually

105 gotten much worse.

106   Penicillin acts by inhibiting cell wall synthesis of bacteria, thus explaining how the

107 mold was able to kill Dr. Fleming's *Staphylococcus* cultures. The molecule directly targets

108 the peptidoglycan synthesis, a saccharide-rich component of the cell wall of gram-positive,

109 and to a lesser extent, gram negative bacteria. Penicillin directly binds to and inhibits

110 bacterially-encoded enzymes involved in the peptidoglycan synthesis (termed

111 transpeptidases), thus destabilizing the integrity of the bacterial cell. Since its discovery by

112 Dr. Fleming, a number of penicillin derivative antimicrobials have been developed

113 including ampicillin, amoxicillin, methicillin, etc. Given their target, these drugs

114 collectively fall into a broader family of antimicrobials called the β-lactam

115 antibiotics.[11,14,15]

116

118   Given their propensity for elimination of pathogens, antimicrobials such as the β-

119   lactams have been widely prescribed for bacterial infections. Unfortunately, this selective

120   pressure has given rise to AMR pathogens. This can be visually articulated in terms of the

121   bottleneck effect (Figure 1). A selective pressure, in this case, an antimicrobial, is applied

122   to a population, in this case, a pathogen. This will result in the death of the majority of the

123   population, but a small fraction of the input population will escape this pressure and

124   multiply. This escaping population of the pathogen is more equipped to then survive

125   subsequent selection pressures by the same antimicrobial. This is a basic principle of

126   selection described by Charles Darwin: variations within a population that are desirable

127   will proliferate, while undesirable traits will be progressively eliminated.[16] We have been

128   imposing selective pressures on pathogens via antimicrobials for decades, and AMR

129   pathogens have become increasingly more prevalent as a result.

130   The rise of MRSA is an excellent example of how AMR pathogens can wreak

131   havoc on our medical infrastructure and public health. MRSA is a strain of *Staphylococcus*

132   *aureus* that has developed a strong resistance to the prescribed β-lactam antibiotic

133   methicillin. This AMR is conferred by the gene *mecA*, which encodes for the protein

134   pencillin-binding protein 2A (PBP2A)[14,15,17,18], a transpeptidase involved in peptidoglycan

135   synthesis. Unlike other transpeptidases, the β-lactam antibiotic does not directly bind to

136   PBP2A, allowing the enzyme to synthesize the cell wall and preserve the integrity of the

137   bacterial cell. Like other staphyloccoci, MRSA encodes for a number of virulence factors

138   that can cause local tissue damage and even lead to toxic shock syndrome.[11,19-22] Therefore

139 the presence of PBP2A is a potent driver of pathogenesis as it confers an advantage to the

140 bacteria.

141 When it comes to harnessing beneficial genes, AMR pathogens are truly a model

142 organism for microbiologists to study. Bacteria can acquire and subsequently transfer

143 resistance genes through several methods. One mode of gene acquisition is through a

144 process termed conjugation. Conjugation is a rapid mechanism in which bacteria co-join

145 an outer appendage (pilus) to copy over different genes (traits) from extrachromosomal

146 plasmid DNA like toxin and resistance genes. This has been observed for genes such as

147 *mecA* in which the gene can be rapidly transferred horizontally to other genera and species

148 of bacteria.[23,24] If one envisions the healthcare environment rich with HAIs and AMR

149 pathogens, this scenario becomes even more problematic in the mingling of AMR

150 pathogens with "regular bacteria" because of this horizontal transfer issue. The transfer of

151 a resistance gene can also occur through the spread of bacterially-encoded phages. This

152 method of introduction of a gene, termed transduction, is when genetic material is

153 transferred by a virus from one cell to another. In this case, AMR genes such as *mecA* and

154 other genes conferring resistance to β-lactam antibiotics, have been shown to be present in

155 phage particles so that transfer of these genes can occur.[25,26]

156

157 *The Misuse of Antimicrobials*

158 The efficacy of antimicrobials, particularly antibiotics, has led to their overuse and

159 misuse. Whenever antibiotics are used, a selective pressure is applied, and the bacteria that

160 escape that pressure can then proliferate or transfer the resistance gene. This can occur

161 when antibiotics are taken during a virus infection. Antibiotics are meant to target bacteria,

162 and therefore have little-to-no effect when it comes to viral infections. Therefore, the virus

163 pathogen will be unaffected, but the bacteria existing in the patient's body are being put

164 through an antibacterial bottleneck.[27] The same scenario can be true when antibiotics are

165 incorrectly used during an allergy or for other non-bacterial agents. Examples of this could

166 include a fungal infection (like athlete's foot) or infection with a protozoan (like malaria).

167 So, not only will the consumption of antibiotics select for resistant bacterial populations,

168 the treatment will do nothing for the patient suffering from a non-bacterial infection. This

169 can then lead to the rise of AMR bacterial pathogens. Ultimately, whenever it is possible,

170 antibiotics should be prescribed only for a bacterial infection. It is critical that physicians

171 and others with the authority to prescribe antibiotics should do so based on a confirmatory

172 medical laboratory tests and antibiotic susceptibility panels.[28]

173

174 *Urbanization and International Travel as Drivers for AMR*

175   Accelerating the spread of AMR pathogens is a compaction of the human

176 population into large metropolitan areas, or urbanization. The rate of urbanization of the

177 human population in the United States is quite staggering. At the time of WWII, when

178 antimicrobials such as penicillin burst onto the scene, only about 50% of the U.S.

179 population lived in what is designated an urban population. This has jumped up to

180 approximately 80% in the most recent decade and is showing no signs of slowing down

181 (Figure 2A). Couple this urbanization with a robust population increase in the U.S. (Figure

182 2B), and you begin to see a picture of just how abrupt this shift has become. Not only has

183 the U.S. seen a tremendous population growth, the proportion of that growth localized to

184 urban areas has increased. This can be a breeding ground for pathogens.

185   One of the best examples of a high human density pathogen is *Mycobacterium*

186   *tuberculosis* (Mtb). Mtb is the causative agent for tuberculosis, in which Mtb colonizes the

187   lung and is spread from human to human by coughing. Although it is one of the most

188   prevalent bacterial human diseases in the world (thought to infect approximately one

189   quarter of the human population), Mtb is a surprisingly difficult pathogen to transmit.[29-32]

190   One of the factors that have facilitated its continuous spread in the human population is the

191   urbanization of humans, particularly in the Eastern hemisphere.[30,32,33] While it is not at all

192   surprising that those who encounter patients harboring Mtb are at a greater risk for

193   contracting it, it is this continuous exposure that allows the pathogen to maintain an almost

194   unparalleled level of success in human transmission. Also, given the disease burden (>1.5

195   billion currently infected), AMR of Mtb has become an increasingly burdensome health

196   issue. Approximately one third of all deaths attributed to Mtb infections are linked to

197   AMR.[30,34] A particularly worrisome development of Mtb is a class termed "extensively

198   drug resistant," in which the bacteria has developed AMR to a number of antibiotics.[31,34-

199   39] This typically arises through the misuse of prescribed antibiotics, in which the patient

200   skips a treatment or does not finish their antibiotic regiment, allowing the flourishing of

201   bacteria that were not immediately killed. This population has been previously exposed to

202   the antibiotics, indicating that it will be less likely to respond to further use of that particular

203   drug.

204   Along with the increase in urbanization, it is impossible to ignore the effect of

205   accessible and rapid interstate, intercountry, and intercontinental travel on AMR. An

206   excellent example of this is the spread of HIV. HIV likely emerged into the human

207   population in the early 20th century from the ancestral Simian Immunodeficiency Virus

208   (SIV).[40-43] While this emergence of HIV took place in Africa, it quickly spread throughout

209   Europe and into the Western Hemisphere by the 1970's. Much of this spread was likely

210   facilitated by the rapid rise in trade and intercontinental travel. The virus then quickly

211   established itself in the United States in populous-dense cities such as San Francisco and

212   New York City, among others.[12,40,43] Since then, HIV has become one of the foremost

213   human health crises, with current estimates of 1.8 million annual new infections and >1

214   million annual deaths from AIDS, even after the revolutionary highly active antiretroviral

215   therapy (HAART).[44] Complications with co-infecting agents such at Mtb, and its own

216   AMR potential, have been an exceptionally troublesome issue, particularly in developing

217   countries.[30,31,34,35]

218   Of course, HIV is just one example of a veritable laundry list of pathogens that

219   emerged into the population and rapidly escalated an epidemic with the help of human

220   travel and urbanization. An increase in world travel and tourism was predicted in the early

221   2000's by the World Tourism Organization (Figure 3) and it has borne out with striking

222   accuracy; this will continue to increase, as will the threat of intercontinental travel of AMR

223   pathogens.

224

225   *Animal Contributions to AMR*

226   Not every pathogen to humans is exclusively transmitted from human to human.

227   Many pathogens sustain enzootic cycles of transmission such rabies (rabies virus), lyme

228   disease (*Borrelia* bacteria), and the plague (*Yersenia pestis*). The ability for a pathogen to

229   maintain an enzootic cycle creates a number of barriers for health professionals in terms of

230   how to treat the disease. Should an outbreak occur in a community, patients can seek

231   medical intervention. However, when the disease is cleared from the population, it still can

232   maintain a cycle of transmission outside of humans and continuously spill over into the

233   human population at a later time. *Yersinia pestis* is a prime example of this type of pathogen

234   as it has seen fewer cases of human incidence in recent decades; however, the bacteria still

235   exists in fleas and animals. Because of this, the acquisition of AMR can be more difficult

236   to track. In the case of *Y. pestis*, resistant strains have been identified.[45,46]

237

238   *Environmental Contributions to AMR*

239   It may appear to the casual reader that AMR and global warming are distinct fields

240   of science. However, global warming has significantly contributed to the spread of

241   infectious diseases, particularly to the northern hemisphere.[47,48] A good example of this is

242   the increase in *Vibrio*-related infections in humans and marine life in the past few

243   decades.[49] *Vibro* is a genus of Gram-negative bacteria frequently found in unsterilized

244   water. Cholera is caused by *Vibrio cholera* which is acquired by the consumption of fecal-

245   contaminated water, and infections millions each year.[50] Other *Vibrio* species such as

246   *Vibrio vulnificus* can be acquired through the consumption of raw/undercooked oysters and

247   shellfish.[49,51,52] Unsurprisingly, the spread of *Vibrio* bacteria due to increases in ocean

248   water temperature has coincided with increasing rates of AMR.[49,51,53,54]

249   *Vibrio* is just one example of a pathogen that seems to be riding the wave of climate

250   change. Vector-borne diseases such as West Nile virus has been proposed to have shifted

251   more north in response to global warming. This is due to the migration of the disease vector

252   (in the case of West Nile virus, the *Culex* mosquito). Coupled with the urbanization in the

253   Americas, vector-borne diseases can establish new niches in highly populated regions.[55-59]

254   Through the introduction of novel pathogens into sustainable environments for their

255   continuous transmission, the development of AMR is inevitable.

256

257   *Where to go from here*

258   Certainly, population mobility is a driver in globalization of public health threats

259   and risks, specifically distribution of AMR organisms. Resistance to the majority of drug

260   classes is a major present and future risk in both healthcare and community settings. Too

261   often, our health policy paradigms in the past have focused on diseases of global public

262   health impact such as measles, influenza, tuberculosis, yellow fever, and cholera; however,

263   new and emerging diseases like Zika virus and resistant organisms, such as the growing

264   problem with multidrug resistant Gram-negative bacteria, challenge our traditional national

265   and global strategies. Public health and clinical policy challenges associated with

266   population mobility across global regions where pathogenic microbes, commercial and

267   agricultural goods, and toxins (e.g., geopolitical borders, patient care environments) are

268   increasingly difficult and politically challenging. How do we measure the benefit versus

269   risk of the travel in this context? Our existing travel systems, international law, and policies

270   must be rethought and designed to slow down and prevent adverse health outcomes.[60]

271   According to a recent report by the World Bank Group, drug-resistant infections

272   have the potential to cause a level of economic damage similar to, and likely worse than,

273   that caused by the 2008 financial crisis. Key findings of the report based on World Bank

274   Group projections of the world economy in 2017-2050 include impacts on the following:

275   global GDP, global trade, global poverty, livestock output, and healthcare. Overall, it

276   estimates a global economic impact of $100 trillion dollars and a human impact of 10

277 million deaths.[61] A recent study by the University of North Carolina concluded that

278 individuals who did not get vaccinated against the most common preventable diseases cost

279 the U.S. economy >$7 billion per year, with the flu contributing the largest portion of this.[62]

280 Given that this economic burden is placed on us by infections that can be prevented, one

281 can imagine the cost of epidemics of new diseases, particularly those with AMR.

282   The rise and spread of AMR pathogens is not going to cease. As long as there are

283 antimicrobial pressures, pathogens will continue to adapt. To that end, many resources are

284 being paid to the development of novel antimicrobials. Moreover, vaccine development

285 continues to be a priority for several of the infectious diseases we've outlined above and

286 many others. However, given the long timeframe from development to Federal Drug

287 Agency (FDA) approval for vaccines,[63] the need for new antimicrobials to combat existing

288 infections is pressing. Therefore, targeting these AMR pathogens is truly like attempting

289 to hit a moving target. Microbes do not read books or pay attention to public health policy

290 and they certainly do not follow the rules. Like the very AMR pathogens we are fighting,

291 we must all become better at evolving and adapting our approaches in a more timely and

292 urgent manner.

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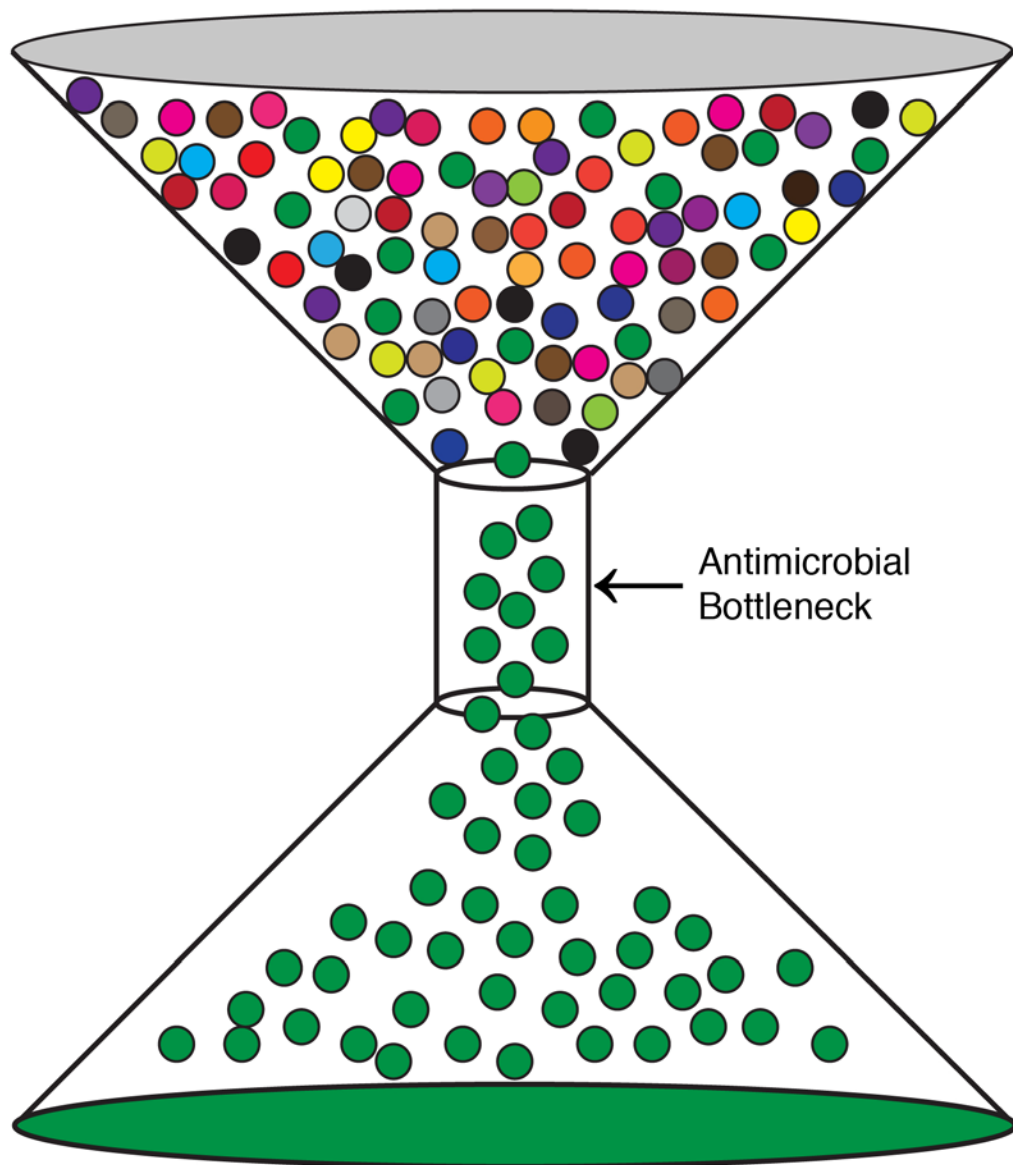464   63.   Offit SPWOP. Vaccines, 6th Edition: Saunders; 2012. 1570 p.

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482   **Figure Legends**

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484   **Figure 1. The Bottleneck Effect**. A population of a pathogen is exposed to an

485   antimicrobial. The majority of the pathogen population contains no resistance, but a

486   fraction does (green) and can flow through the bottleneck. This population can then

487   propagate, leading the rise of AMR in that particular pathogen.

488

489   **Figure 2. The Rise in the Population in the U.S. and Urbanization**. (A) The U.S. has

490   seen >3X population growth in the past 100 years. (B) The percentage of the U.S.

491   population living in urban areas has increased dramatically in the past 100 years. All data

492   was obtained from the publicly accessible www.census.gov.

493

494   **Figure 3**. Increase in global travel and tourism, as predicted in the early 2000's by the
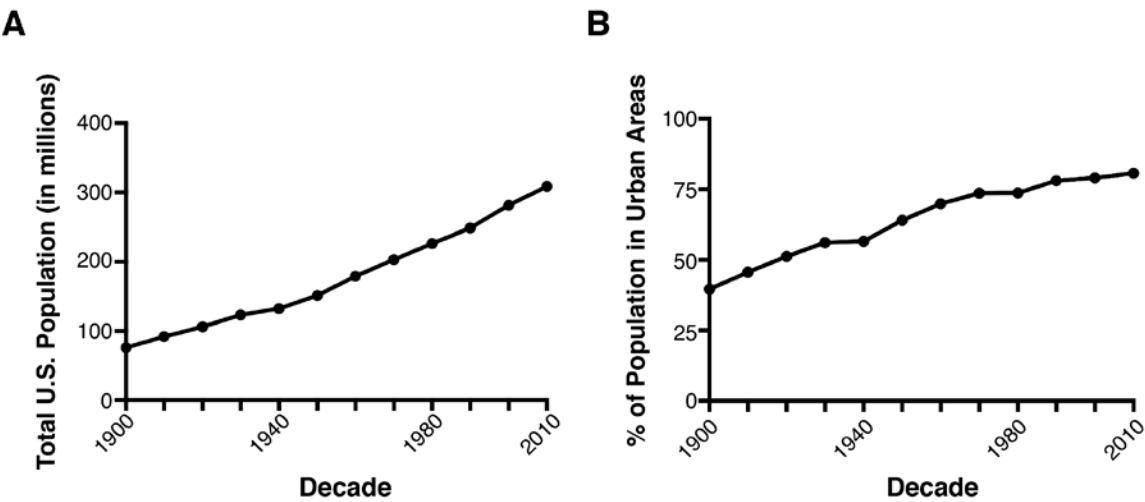
495   World Tourism Organization.
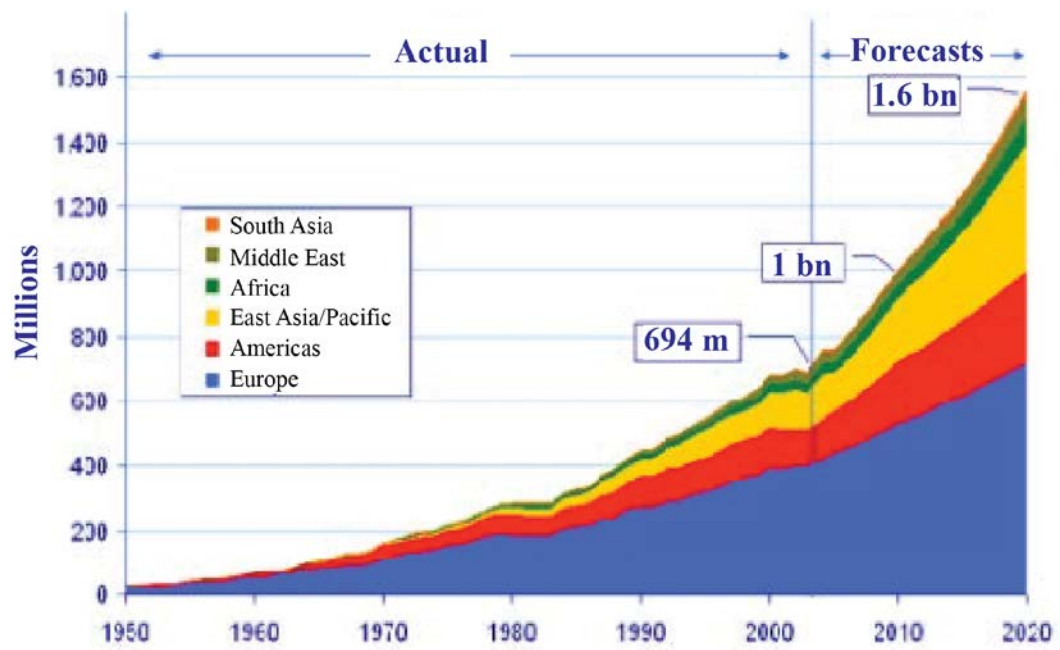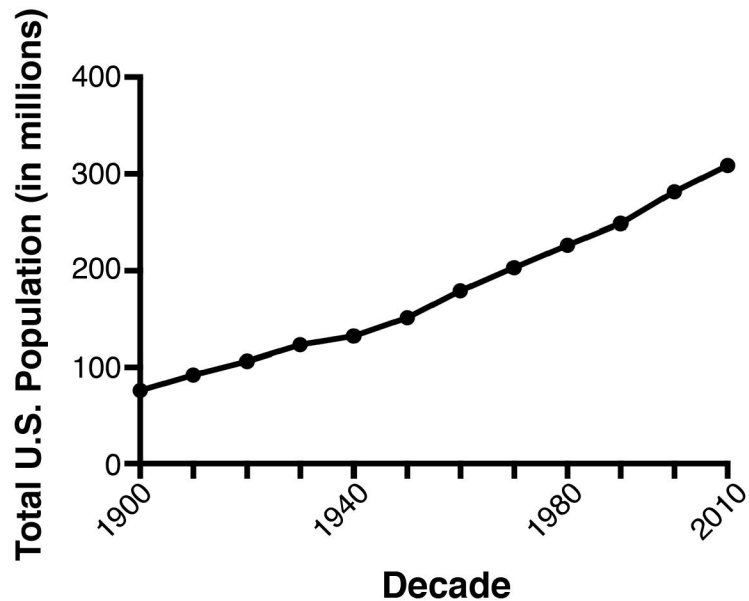
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Figure 1
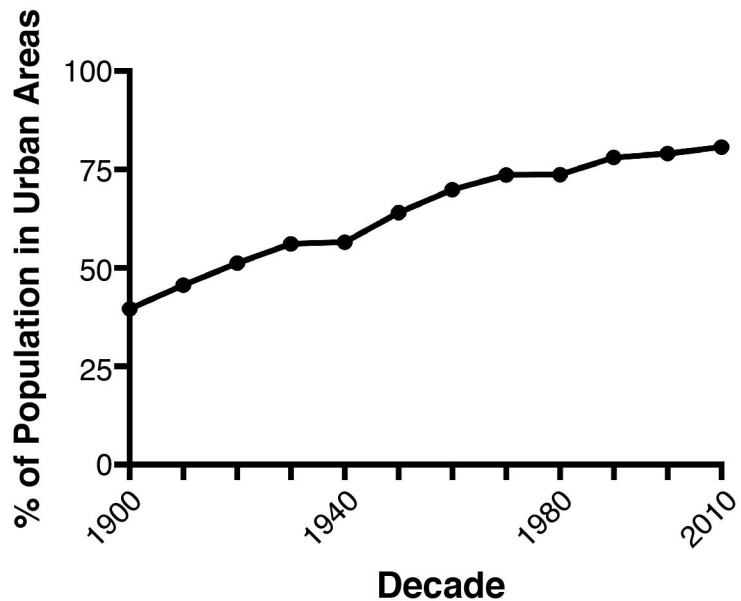

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Figure 2

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Figure 3

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Figure 2

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Figure 3

Figure 1

Antimicrobial
Bottleneck