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Commentary

Antibiotic Resistance: The Need For a Global Strategy

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ABSTRACT

The development of antibiotic resistance is a major problem for mankind and results in fatal consequences on a daily basis across the globe. There are a number of reasons for this situation including increasing globalization with worldwide travel, health tourism, over use and ineffective use (both in man and animals), and counterfeiting of the antimicrobial drug products we have available currently. Although there are huge economical, demographic, legal and logistic differences among the global communities, there are also differences regarding the best approach to dealing with antibiotic resistance. However, as resistant bacteria do not respect international borders, there is clearly a need for a global strategy to minimize the spread of antibiotic resistance, to optimize the use of antibiotics, and to facilitate the development of new and effective medications. This commentary provides an insight into the issues and some of the ongoing programs to ensure an effective treatment for the future.

Introduction

History tells us that the globalization and the expansion of trading networks will inevitably lead to more rapid spread of disease and facilitate global pandemics. Infectious diseases have always followed the main arteries of global trade. Plague was distributed by European merchant traders throughout the 17th century. The slave trade triggered several large outbreaks of yellow fever in America in the 19th century. Global war and the rapid movement of tens of thousands of troops contributed to the last great pandemic of the 20th century, the "Spanish influenza."[1] Figure 1 shows the death rates per 100,000 persons according to age and indicates that compared to the interpandemic years (1911-1917), not only did the very young and elderly patients show high death rates (which may have been anticipated), but significant numbers of "healthy" adults also died. However, the prevailing wartime conditions were not the only explanations as to why so many people died in 1918, as multiple factors seemed to have played a role based on recent genetic analysis of autopsy material.[2] Currently, air travel has mostly been responsible for the rapid dissemination of several strains of avian flu, some of which reached pandemic status.[3] Woolhouse[4] reported that global patterns of disease have been evaluated between 1940 and 2004, and 335 emerging disease events have been identified. These could be novel species or strains, including drug resistant variants. Examples include hospital-acquired yeast infections, including different species of *Candida*, and worryingly, several bacterial infections acquired from animal reservoirs, for example, cat scratch disease, *Bartonella henselae*. Woolhouse[4] reported that there may be significant underreporting of these emerging global infectious diseases from other less developed regions in the world. Many emerging pathogenic organisms have a wide range of potential hosts, including mammals and birds. There are calls for international capability to detect, identify, and monitor these newly emerging pathogens, targeting those global regions that require this the most. This would benefit the global health care system. Because of globalization, these emerging diseases are the problem of all—not just the affected country.[4] In addition, infectious diseases are not standing still, the evolutionary pressures caused by poor antibiotic usage strategies (either inappropriate for the disease to be treated, the treatment stopped prematurely, or antibiotics dispensed or sold in daily packs) has led to an increase in global bacterial resistance.

Furthermore, there is an inequitable distribution of research and development (R&D) activities and funding favoring noncommunicable diseases (NCDs) at the expense of those health problems experienced by people living outside the developing world. This has been termed the 10/90 gap, as 10% of research activities and funding is used to address 90% of the world's disease burden.[5] More focus on NCD medicines could be at the detriment of those essential medicines identified by the World Health Organization (WHO) on the essential medicines list.

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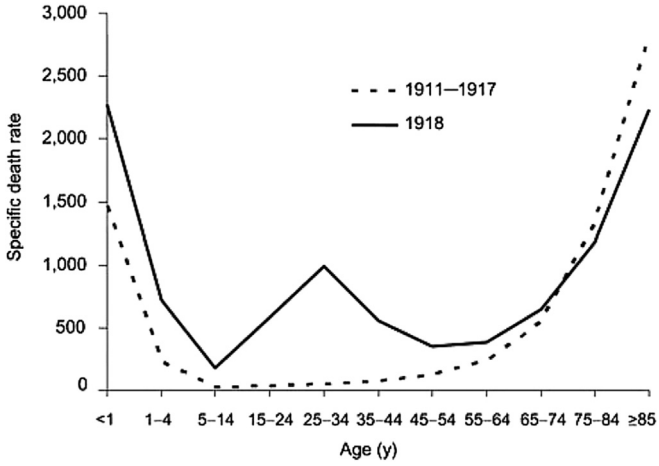

Figure 1. Combined influenza and pneumonia mortality versus age at death, per 100,000 persons in each age group (United States). The influenza and pneumonia death-specific death rates are plotted for the years 1911-1917 (dashed line) and for the pandemic year 1918 (solid line).[2]

Cost of Developing New Drugs

A recent Tufts study has shown that the costs of developing new drugs have more than doubled over the last 10 years. DiMasi et al.[6] estimated that the total costs of a new marketed drug was U$2.6 billion, which represents a substantial cost increase relative to the costs derived 10 years earlier, that is, U$0.8 billion. This was based on a subset of 106 drugs being developed by 10 multinational drug companies. This included small molecules (87), monoclonal antibodies (10), and recombinant proteins (9). The increased costs were attributed to the very high attrition rates and increasing costs of clinical trials (increased complexity, size, and support costs). In particular, the increased requirements by international regulators for phase IV, postapproval clinical studies has introduced a heavy burden toward drug development costs (approximately U$300 million). These burgeoning developing costs may be supportable in the developed world for NCDs (but even this assertion is open to debate); however, they are not supportable when applied to the development of novel antibiotics for a global market.

During the "prime time" of blockbuster thinking, several major pharmaceutical companies refocussed their development efforts on other indications at the expense of infectious diseases. However, such alternative targets (in, e.g., the central nervous system or metabolism) proved to be equally intractable, and clinical trial costs sharply increased in line with the requirements of evidence-based medicine and evolving regulatory expectations. Moreover, several of the promising blockbuster indications have raised particular development risks, as for example, if there is a lack of adequate preclinical efficacy models. Pharmaceutical companies have therefore become more open to developing niche products,[7] which is one explanation for an increase in recent Food and Drug Administration (FDA) drug approvals. In the last 2 years (2014-2015), more than 40 new drugs were approved by the FDA, which was above the average number approved during the last decade, and the portion of antiinfective compounds was considerable (Table 1). Despite this promising outlook, there is still a clear gap relative to clinical needs, to adequately fight emerging bacterial resistance issues.[7] The urgent requirements for new antimicrobial therapies appear to have forced regulatory agencies to accept more focused and less costly clinical trials within this indication.[8,9] The recent FDA approval of Avycaz,[10] a combination of ceftazidime and avibactam, a novel β-lactamase inhibitor (BLI), was based on phase II data, which is at least partly a reflection of a changing regulatory mind set. It would appear that the reforms initiated with the agency's Generating Antibiotics Incentives Now (GAIN) in 2012 are beginning to bear fruit.[11]

Target Product Profiles for Novel Antibiotics

The attributes of the drug product to be used by the patient are covered by the target product profile (TPP),[12] which summarizes the objectives of any given drug development initiative across the different departments within a company. The indications for novel antibiotics offer some flexibility with several drug-related attributes. For example, the route of administration, dose frequency, or volume per dose are for many therapeutic indications of high marketing importance but have comparatively much lower relevance when potential life-threatening infections are targeted. This is true at least in the developed countries; however, for novel antibiotics to make a difference in less developed areas, a simple oral

Table 1
New Drugs Approved by the FDA[a] in 2015 and 2014 for Antiinfective Treatment (Retrochronological Dashed Line as Separation of the 2 Years)

Drug Name	Active Ingredient	Medical Use
Genvoya	A fixed-dose combination tablet containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide	For use as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older
Daklinza	Daclatasvir	Treatment of chronic hepatitis C virus (HCV) genotype 3 infections
Cresemba	Isavuconazonium sulfate	To treat adults with invasive aspergillosis and invasive mucormycosis, rare but serious infections
Avycaz	Ceftazidime-avibactam	Treatment of adults with complicated intraabdominal infections (cIAI), in combination with metronidazole, and complicated urinary tract infections (cUTI)
Rapivab	Peramivir	Influenza infection in adults
Zerbaxa	Ceftolozane/tazobactam	Treatment of adults with cIAI and cUTI
Viekira Pak	(Ombitasvir, paritaprevir, and ritonavir tablets copackaged with dasabuvir tablets)	To treat patients with HCV genotype 1 infection, including those with cirrhosis
Xtoro	Finafloxacin otic suspension	Treatment of acute otitis externa
Harvoni	Ledipasvir/sofosbuvir	Treatment of HCV genotype 1 infection
Orbactiv	Oritavancin	To treat adults with skin infections
Kerydin	Tavaborole	Topical treatment of onychomycosis of the toenails
Sivextro	Tedizolid phosphate	To treat adults with skin infections
Jublia	Efinaconazole	To treat mild to moderate onychomycosis
Dalvance	Dalbavancin	To treat adults with skin infections
Impavido	Miltefosine	To treat leishmaniasis

[a] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm430302.htm.