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The path of least resistance: Paying for antibiotics in non-human uses

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ABSTRACT

Antibiotic resistance is a critical threat to human and animal health. Despite the importance of antibiotics, regulators continue to allow antibiotics to be used in low-value applications – subtherapeutic dosing in animals, and spraying tobacco plants for blue mold, for example – where the benefits are unlikely to outweigh the costs in terms of increased resistance. We explore the application of a user fee in non-human uses of antibiotics. Such a fee would efficiently deter low value uses while also providing funding to support the development of the urgently needed new antibiotics.

1. Introduction

Alexander Fleming's discovery of penicillin in 1928 is regarded as one of the greatest achievements in therapeutic medicine. Antibiotics have improved control of infectious disease, and made surgeries and other treatments much safer and more effective. 258 million courses of antibiotics were prescribed in the US in 2010 [1]. Antibiotics are also central to modern high-density agricultural operations. And yet all the benefits could be easily lost in what critics are calling an antibiotic "apocalypse."

Just as Fleming warned, injudicious use of antibiotics has led to an antimicrobial resistance crisis in which standard treatments are ineffective and infections persist, prolonging illness and increasing risk of death. WHO Director General Dr. Margaret Chan warns that resistance could end modern medicine as we know it [2]. Antibiotic resistance is also creating a substantial economic burden currently estimated as a $35 billion increase in the US hospital bill [3]. The Centers for Disease Control and Prevention estimates that more than two million Americans are sickened annually with drug resistant infections, and at least 23,000 die as a result [4]. The World Health Organization reports that there were roughly 450,000 new cases of multi-drug resistant tuberculosis in 2012, with mortality of approximately 170,000 [5].

The resistance crisis is leading to calls for a ban on certain non-human uses of antibiotics, including as animal growth promoters (AGPs), following European countries. The US FDA has gradually imposed stiffer controls on AGPs but there remains considerable flexibility for subtherapeutic dosing with antibiotics for prophylaxis and metaphylaxis under veterinary oversight. Indeed, after Denmark banned the unprescribed used of antibiotics as AGPs in 1999, the use of prescribed antimicrobials more than doubled, which compensated for most of the reduction in AGPs [6]. In this paper, we explore user fees as an alternative or complementary policy designed to slow the development of resistance, support funding for new antibiotics, and minimize costs for farmers.

Antimicrobial resistance can be framed as an ecological challenge; selection pressure favors antibiotic-resistant bacteria. Though resistance is a natural phenomenon, it is hastened by a number of controllable factors.

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Over-prescription, aggressive promotion by pharmaceutical companies, underinvestment in infection control, non-compliance by patients, and weak hospital management practices all contribute to diminishing efficacy of our existing antibiotic resource.

Aggravating the resistance problem is a decline in new drug development. New antibiotics are typically reserved for patients with resistance, limiting the sales volume and hence profits. As a result, only five large multinational companies remain in this field [7] and no new classes of antibiotics have been developed since 1987 [7]. Thus, we urgently need both new mechanisms to support R&D in antibiotics and policies to preserve existing antibiotics.

Non-human use of antibiotics (NHUA) is a troubling contributor to antimicrobial resistance. Almost 14 million kg of antibiotics were fed to animals in the US in 2011, comprising 80% of the total [9]. In fact, many of the antibiotics used to treat humans are also used for growth promotion and infection control in raising livestock, aquaculture and for companion animals. These include macrolides, streptogramins, aminoglycosides and tetracyclines, all classified as being of high importance for treating life-threatening human health conditions [10].

According to a growing body of scientific evidence a direct link can be demonstrated between antimicrobial resistance in livestock and in humans [11,12]. A recent study found that 36.6% of industrial livestock workers carried biomarkers associated with methicillin-resistant *Staphylococcus aureus* (MRSA), compared with 19% of workers at antibiotic-free farms [13]. Furthermore, almost 50% of industrial livestock workers had bacteria resistant to tetracycline compared with 2.4% of workers working with antibiotic-free livestock [13]. Collignon et al. estimate that cephalosporin use in poultry contributed to over 1500 deaths of people in Europe in 2007 [14]. The frequency of resistance isolates across European countries tended to be at approximately the same levels in animals and food as in people in each country, suggesting that resistant organisms are being transmitted from people to animals, or from animals to food and people [15]. A particularly interesting study in Quebec, Canada explored the effect of a temporary halt in chicken hatcheries' extra-label use of ceftiofur in ovo. Resistance to this important antibiotic fell rapidly not only in chickens, but also in human isolates [16].

Aside from the effect on human health, resistance is also a problem in agriculture, as farmers are increasingly facing resistant strains of bacteria in their farming operations, and are forced to use more costly or less effective antibiotics. Development of policies to limit the development of resistance is therefore of great economic and human significance.

2. Methods

We first conduct a literature review, surveying the current data and reports on non-human uses of antibiotics. Second, we compare potential policies for limiting non-human uses of antibiotics, focusing on regulatory solutions (bans of various types of applications) and a market-based solution (a user fee). We employ an economics lens to compare aspects of the different policies, such as cost, efficiency, equity and enforceability. Third, we illustrate how to determine the level of user fees required to generate a given total annual revenue. Our methodology for this exercise is to calculate the required fee given a range of demand elasticities, using data on 2012 NHUA in the United States. Further description is given below.

3. Non-human uses of antibiotics

3.1. Agriculture

The use of antibiotics in agriculture dates back to the 1940s when farming practices transitioned to factory farms with thousands of animals in confinement. The new practices and technology increased productivity and profits, enabling the US to become the world's largest beef producer. This success would not have been possible without antibiotics to combat disease arising from cramped living quarters, poor ventilation and sanitation [17].

Antibiotic use in agriculture can be categorized under four main purposes: therapeutic use, prophylactic use for disease prevention, metaphylactic use for infection control, and as animal growth promoters (AGPs). The latter three purposes constitute subtherapeutic use: low level doses primarily used for infection prevention or changing digestive processes but insufficient to kill bacterial infections [17]. It is estimated that 80–90% of agricultural antibiotics are used sub-therapeutically for greater weight gain and lower mortality [18]. Subtherapeutic antibiotics are most commonly administered in feed. This mass medication not only prevents disease, facilitating intensive farm operations, but also has an effect on digestive efficiency, increasing weight gain [17]. The Centers for Disease Control has recommended that the use of antibiotics as AGPs should be phased out [4], but other subtherapeutic uses continue to be permissible.

3.2. Aquaculture

Antibiotics in aquaculture are primarily used for infection control and increased productivity and are administered through medicated feeds. FDA-approved drugs include sulfadimethoxine, ormetoprim, and oxytetracycline to control for disease in salmonids and catfish and even lobsters. Total US aquaculture industry use is roughly between 100,000 and 200,000 kg [19].

As much as 80% of these antibiotics are released into the aquatic environment as fecal and urinary excretion [20]. This leads to a buildup of antibiotics in aquatic systems, a high presence of drug residues in fish products, and ultimately, increased antimicrobial resistance. 74–100% of wild fish in close proximity to treated ponds contain quinolone residues.

Cabello et al. conclude that available evidence "strongly suggests" that aquaculture is an important source for the passage of a large amount of antimicrobials into the environment, where they select for resistant bacteria [21]. Furthermore, there is evidence of substantial transfer of bacteria from marine to terrestrial environments.