ARCH
Annual Review of Changes in Healthcare

Antimicrobial Resistance: Updates to an Ongoing Global Crisis

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Abstract

Antimicrobial resistance is a threat that can no longer be ignored. Resistant bacteria pose a global threat that if not controlled, could be catastrophic. Antibiotics are used for many reasons other than treatment of infections in the 21st century, however their appropriateness in certain fields is being scrutinized by organizations like the CDC and FDA. In order to combat this, the CDC has invested in surveillance of resistant bacteria, antimicrobial stewardship programs, and many other areas of healthcare and public safety. Their 2013 report called great attention to the issue, and the 2019 update sheds light on just how much more work still needs to be done. Progress has been made to deter the resistant bacteria, but it will take a much larger scale, global effort in order to ensure the safety of the human population going forward.

Background

Antibiotic resistance is a rapidly developing issue in the field of healthcare, and in 2014, the White House announced the National Strategy for Combating Antibiotic-Resistant Bacteria (CARB).[1] The CDC reports that more than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die as a result of these infections.[2] Bacteria develop resistance to antibiotics almost since the advent of them. However, only in the past few years have we started to recognize the true dangers of highly resistant organisms. Dangers such as multi-drug resistant (MDR) and even pan-resistant (organisms resisting all current therapeutic options) bacteria cause infections that are very difficult to treat, often leading to hospitalizations which necessitate the use of antibiotics that are considered our last line of defense. There are many possible factors leading to the development of resistance, including the widespread use of antibiotics in animal agriculture, overprescribing and misuse of antibiotics for viral infections, and increasing toxicities and black box warnings being issued by the FDA during post-market surveillance leaving prescribers with fewer and fewer options. Desptie all signs pointing to potentially catastrophic effects, only in the past few years has an effort been conducted to combat the issue.

Sources of Antimicrobial Resistance

The first step to slowing resistance is to identify and control the source. Developing and approving new antimicrobial agents is a process that takes time and it alone is not enough to slow resistance due to organisms' ability to adapt and resist new medications. Especially at the very slow rate that new antimicrobials have been developed and subsequently approved by the FDA, it is unlikely that drug companies would be able to keep up with the rates of resistance as older antibiotics become obsolete and the new ones replace them as the standard of care. According to a report by the World Health Organization (WHO), there has been a void in discovery/development of new antimicrobial agents since the late 1980s.[3] However, the number of antibiotics being submitted has started to increase very recently. As more antibiotics get approved, this source of antimicrobial resistance will shrink.

Another source of resistance that has been identified is overuse of antibiotics. In 1950, a study performed by American Cyanamid found that adding antibiotics to live-stock feed accelerated animal growth rates and dramatically changed the way farmers saw animal nutrition.[4] Shortly after this article was published, the use of antibiotics became more widespread for growth promotion and routine disease prevention. Despite warnings later published by the *New England Journal of Medicine*,[4] antibiotics continued to be routinely used in animal agriculture for growth promotion, feed efficiency, and disease prevention. This effect snowballed until the vast majority of antibiotics consumed in the United States were being used for these purposes, with human use of antibiotics only making up a very small portion of the total.[4] Even more concerning is the fact that of the over 9 million kg of active drug material purchased in 2013 for agricultural purposes, most of the sales were without any veterinary oversight.[4] Since then, the FDA responded in 2017 by

releasing a Guidance for Industry (GFI) document regarding the use of antibiotics in food and food-producing animals. In this document the FDA proposed two main rules to combat antimicrobial resistance: "(1) limit medically important antimicrobial drugs to uses in animals that are considered necessary for assuring animal health, and (2) limit medically important antimicrobial drugs to uses in animals that include veterinary oversight or consultation."[5] This document attempted to solve theses two issues by preventing over the counter purchase of antibiotics, and removing the indication for "increased rate of weight gain" or "improved feed efficiency."[5] Looking at Table 1 in the Appendix, since the full implementation of GFI 213, the use of antibiotics for production purposes has dropped to 0 as it is no longer allowed by the FDA. However, it should be noted that a majority of the antibiotic use shifted to therapeutic use only. Since the FDA still considers the use of antibiotics for prevention of infection as "therapeutic use only," there is still much work to be done in defining the appropriate instances to use antibiotics in these animals so that the total amount of antibiotics being used annually drops significantly. Fortunately, the FDA and CDC are working closely together on this issue and more regulatory updates are coming in the future to ensure the safety of the human population.

Overuse of antibiotics isn't limited only to agriculture. Another source of resistance that has been suggested is unnecessary prescribing of antibiotics to patients without infections. The CDC is working to control this by funding antimicrobial stewardship programs in institutions across the United States.[6]

Effects on the Healthcare System

There are many uses for antibiotics aside from the treatment of bacterial infections. This is yet another factor contributing to antimicrobial resistance that must be considered when discussing the impact and the burden placed on the healthcare system and the population at large. There are some concerning situations that are likely to play out in a world where we no longer have effective antibioitcs. For example, antibiotics are routinely used in surgical procedures, cesarean sections in pregnant woman, and to paitents receiving chemotherapy. In any and all of these scenarios, patient outcomes would be much worse without antibiotics to protect against opportunistic infections. The British Medical Journal estimates that without antibiotic prophylaxis as a standard of care for hip replacement, the rates of infection will jump from 0.5-2% to 40-50%.[7] They also estimate that about 30% of those patients could die without proper antibiotics to fight the infection.[7] Of course, if this were the case, the rates of hip replacements would likely decrease, but that would also come along with reduced quality adjusted life years (QALYs) for patients and thus increased morbidity of hip pain.

Another negative impact of antimicrobial resistance is the economic burden it places on the healthcare system. Although it has been very difficult for researchers to quantify the economic burden of antimicrobial resistance, one study in 2002 estimated the total costs at roughly 55 billion USD.[8] However, it is estimated that the number would in fact be much higher.[7] A more recent review from 2013 would agree

with this thought, stating that the societal burden is closer to 150 billion USD.[9] The longer it takes for meaningful action to be taken, the more organisms will become resistant, and the more lives will be lost. There has yet to be an economic study with a better method for measuring the economic impact of antimicrobial resistance and it may take more time before we truly know how it compares to other diseases facing us today. However, it is not all bad news, as the CDC has recently updated their plan for combating antimicrobial resistance in 2019.

Action Plan

The CDC has been at the forefront of solving the antimicrobial resistance issue that we are currently facing. In the 2019 CDC update to *Antibiotic Resistance Threats in the United States*, CDC director Robert Redfield, MD, warned of some of the most important things to consider about the fight we are facing today. First, he suggested that we must realize that the post-antibiotic era is already here, and that we need to stop referring to it as if it is in the future.[6] In doing this, the threat seems further from us than it is in reality, possibly hindering progress toward solving the issue. He also advises that we must not rely solely on new antibiotics coming to market, for the reasons previously discussed in this article.[6] He ends his letter by outlining what will work to combat antimicrobial resistance, including prevention (whether it be hand washing or vaccinations), practicing antimicrobial stewardship, and detecting organisms that pose a threat before it is too late.[6]

The words of Dr. Redfield relate closely to the plan being implemented by the CDC. Their plan is not simple; it is as multifaceted as the issue itself, and it involves many organizations and individuals doing their part to combat the issue. They have invested over 300 milion USD in 59 state and local health departments to detect and prevent resistant threats.[6] They are taking advantage of new technologies such as whole genome sequencing in order to shed light on what may be the best way to attack the resistant organisms.[6] Another way they are combating resistance is investing in antimicrobial stewardship programs, which has helped decrease outpatient antibiotic prescribing by 5% in adults and by 16% in children.[6] The goal in this scenario is to prevent unnecessary prescribing of antibiotics to people complaining of cold and/or flu symptoms, as mentioned previously.

In the 2013 report on antimicrobial resistance, the CDC identified some of the major gaps in knowledge that needed to be more well understood and better funded. Since then, some of these knowledge gaps have closed, but there are still more that must be investigated further. The core actions that the CDC has proposed in 2019 seek to close the gaps in knowledge in the areas of infection prevention and control (immunization, sanitation, hand-washing, etc.), tracking and data, antibiotic use and access, vaccines, therapeutics, and diagnostics.[6] Many of these areas have been much improved since the 2013 report thanks to funding by the CDC through congressional approval.

However, antimicrobial resistance remains a global issue, and much more work must be done to contain and control the spread of infections as a whole in countries other than the United States.

Conclusions

In summary, there have been many advancements made thanks to the CDC and the FDA in combating antimicrobial resistance, but more work still needs to be done. In their 2019 report, the CDC calls upon everyone to do their part in combating antimicrobial resistance, stating that it will require a globally combined effort to get the situation under control. This means whether you are a regular citizen or someone in a healthcare profession, your efforts are needed in order to save the planet from the threat of deadly, resistant bacteria. From hand-washing to practicing antimicrobial stewardship, everyone can make a difference and doing so is crucial, now more than ever.

Appendix

Table 1	Indications		
	Production or Production/ Therapeutic Indications	**Therapeutic Indications Only**	**Total**
2009 Annual Totals (kg)[3]	5,563,029	2,123,536	**7,686,564**
2010 Annual Totals (kg)[3]	5,828,079	2,401,230	**8,229,309**
2011 Annual Totals (kg)[3]	5,770,871	2,484,827	**8,225,697**
2012 Annual Totals (kg)[3]	6,073,485	2,823,935	**8,897,420**
2013 Annual Totals (kg)[3]	6,664,835	2,528,458	**9,193,293**
2014 Annual Totals (kg)[3]	6,790,996,	2,688,343	**9,479,339**
2015 Annual Totals (kg)[3]	6,917,639	2,688,343	**9,702,943**
2016 Annual Totals (kg)[3]	5,770,655	2,585,685	**8,356,340**
2017 Annual Totals (kg)[3]	0*	5,559,212*	**5,559,212**
2018 Annual Totals (kg)[3]	0*	6,036,140	**6,036,140**
% Change 2009 – 2018	-100%	184%	**-21%**
% Change 2017 – 2018	**	9%	**9%**

Table 2					
Species	**2016 Estimated Annual Totals (kg)[3]**	**2017 Estimated Annual Totals (kg)[3]**	**2018 Estimated Annual Totals (kg)[3]**	**% Change 2016-2018**	**% Change 2017-2018**
Cattle	3,605,543	2,333,839	2,521,157	-30%	8%
Swine	3,133,262	2,022,932	2,374,348	-24%	17%
Chicken	508,800	268,047	221,774	-56%	-17%
Turkey	756,620	670,108	671,108	-11%	<1%
Other	352,114	263,564	247,753	-30%	-6%
Total	**8,356,340**	**5,559,212**	**6,036,140**	**-28%**	**9%**

Medically important antimicrobial drugs approved for use in food-producing animals
Actively marketed in 2016-2018
Domestic sales and distribution data
Reported by species-specific estimated sales

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