Dangerous Antibiotics for the 21st Century

No one can dispute that multidrug-resistant "superbugs" are a key public health concern for the 21st century. Over 2 million people are infected with antibiotic-resistant bacteria each year, resulting in at least 23,000 deaths.

New antibiotics to overcome these superbugs have been slow in coming. No antibiotic with a truly novel mechanism of action has been discovered since the late 1980s. Yet this drought is not the fault of the Food and Drug Administration (FDA), which has long been under tremendous pressure to approve new antibiotics quickly. This pressure was increased even further by a 2012 law that accelerated review for qualifying antibiotics.

Thanks to the current review process for antibiotics, clinical development for these drugs is already quick by industry standards. A new antibiotic takes only seven years to get to market, compared with nine years for cancer drugs.

Quick approval is not without costs. Putting pressure on the FDA to approve new antibiotics makes the agency less likely to see or act upon evidence of important safety risks or problems with effectiveness. Many of the antibiotics approved over the past decade have suffered from safety and effectiveness problems. For example, tigecycline (Tygacil), an antibiotic that received special accelerated FDA approval in 2005, was slapped with a black-box warning in 2013 stating that the drug increases the risk of death.

Bedaquiline (Sirturo), granted accelerated approval in 2012, also increases the risk of death. This antibiotic was approved based on the fact that it effectively reduced the amount of tuberculosis in research subjects' sputum, a "surrogate endpoint" that does not actually benefit the patient but is thought to be a sign that patients could potentially benefit from treatment. Unfortunately in this case, improving the surrogate endpoint did not improve survival: Subjects who received the drug during clinical trials were five times as likely to die as those who did not. But since the clinical development program for this drug was small and short, the total number of deaths was also small (just 12 patients in all). The FDA announced that there was no clear pattern among these few deaths, and ultimately approved the drug.

Other recently approved antibiotics, including dalbavancin (Dalvance) and ceftazidime-avibactam (Avycaz), gained approval by showing that they were no less effective than an existing antibiotic, rather than showing they were more effective than an existing drug or placebo. Such "non-inferiority" trials are notorious for providing misleading results if there are flaws in trial design or conduct. Also, these trials become meaningless if bacteria have developed resistance to the drug being used for the comparison. If an old drug is ineffective, proving that the new drug is not worse by comparison is hardly evidence of anything.

This questionable string of antibiotics approvals should have triggered congressional oversight and possibly new legislation strengthening the FDA's review of these drugs. Yet the 21st Century Cures Act will do the opposite, creating yet another accelerated approval pathway to pressure the FDA to use even

smaller clinical trials, more surrogate endpoints and potentially even more questionable forms of evidence, casting further doubt on the safety and effectiveness of antibiotics approved during the coming century.

The only potential tip-off to physicians that a drug has been approved under this new, less rigorous pathway will be a small message in the label saying that the drug is "indicated for use in a limited and specific population of patients." This is not a clear warning that the evidence to establish safety and effectiveness is not up to the usual FDA standards. In fact, such a message is barely informative at all, since most drugs approved by the FDA are approved for uses in a specific and often limited population of patients.

Disturbingly, the bill requires the FDA to consider expanding this "limited population" pathway within four years to other drugs beyond antibiotics, without any further action required from Congress.

In addition to undermining approval standards, the 21st Century Cures Act includes a new Medicare payment system that will undermine recent federal efforts to prevent overuse of antibiotics by encouraging more careful stewardship of these drugs in hospitals and elsewhere. Overuse of antibiotics worsens the problem of multidrug resistance by accelerating the speed at which superbugs evolve to resist new drug treatments.

The new payment system will make the overuse problem worse, not better, by offering hospitals a financial bonus each time a patient receives certain new antibiotics during his or her hospital stay. Currently, antibiotics payments are included as part of a bundled hospital payment, so hospitals have little incentive to use antibiotics unless medically necessary, particularly expensive new antibiotics. The proposed payment system creates the opposite effect, offering strong financial incentives for hospitals to overuse new antibiotics.

Another troubling provision will allow the FDA to outsource important decisions involved in determining when the microorganism that has caused an infection is antibiotic-resistant and therefore requires newer antibiotics. This opens the door to industry influence in decisions that will affect how antibiotics are used, further contributing to the threat of overuse.

Cutting review periods and squandering new antibiotics to increase the profitability of these drugs is not the right way to create better antibiotics for the 21st century. Instead, Congress should invest public resources into early-stage research targeted at expanding the available options at the start of the antibiotics development pipeline. Truly innovative science will lead to better products at the end of the pipeline, ones that will not require lower FDA standards to gain approval.

The 21st Century Cures Act does aim to provide more research, but it ultimately comes up short. One of the most highly-publicized provisions of the bill provides more funding to the National Institutes of Health (NIH), which offers grants for basic, early-stage research. But this research funding is a temporary 4.5 percent increase to the annual NIH budget that will end abruptly after three years. An additional, smaller sum is dedicated to a new "Innovation Fund" that would be available for infectious disease research and other priorities, but this fund also would expire, after five years.

On balance, the antibiotics provisions in 21st Century Cures will be bad for patients and public health. In exchange for an ephemeral boost in research funding, the bill will pressure the FDA to approve dangerous new antibiotics and institutionalize a hospital payment system and other measures that promote antibiotics overuse and speed the development of drug resistance.

The American public does need a bill to create and preserve safer, more effective antibiotics in the 21st century, but the 21st Century Cures Act is not it.

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Background:

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