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Infectious Diseases Society of America

HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2020-N-1736 on the Concept Paper: Potential Approach for Ranking of Antimicrobial Drugs According to Their Importance in Human Medicine: A Risk Management Tool for Antimicrobial New Animal Drugs

March 16, 2021

On behalf of the Infectious Diseases Society of America (IDSA), thank you for the opportunity to comment on FDA's potential approach for ranking antimicrobial drugs according to their importance in human medicine. IDSA represents over 12,000 infectious diseases physicians, scientists and other public health and health care professionals. Our members care for patients with serious infections, including those caused by multidrug-resistant pathogens; lead antimicrobial stewardship and infection prevention programs; conduct research on antimicrobial resistance and drive innovation in vaccines, diagnostics and therapeutics; and collaborate with public health departments to better prevent, detect and contain resistance threats.

There is broad agreement among the scientific community that the overuse and misuse of antibiotics — particularly those important to human medicine — is contributing to the development of antimicrobial resistance and threatening human health. IDSA greatly appreciates FDA's work to reduce inappropriate use of antimicrobial drugs in all animals. The proposed approach for ranking antimicrobial drugs according to their importance in human medicine is an important component of these efforts, and IDSA appreciates this opportunity to provide feedback on FDA's concept paper.

Overall, IDSA supports the criteria and tiers proposed by FDA and is pleased to offer recommendations regarding the proposed rankings of some antimicrobials and a few additional issues for FDA to consider.

Criteria and Tiers

The tiers are appropriately conservative, with drugs properly skewed toward more protective rankings. It is essential to protect all of these antimicrobial drugs, as our treatment arsenal is already too meager.

In addition, FDA may wish to consider whether the toxicity of an antimicrobial agent and the availability of better alternative therapies should be included among the criteria for ranking antimicrobials. For example, a highly toxic agent could be ranked lower when better alternatives exist, though an agent with high toxicity may still be ranked highly if few or no alternative therapies are available. FDA should also consider adding a criterion based on the potential for development of resistance to a drug or class of drugs.

Application of Criteria to Antimicrobial Classes

IDSA recommends the following changes to the proposed rankings of certain antimicrobials.

First-generation cephalosporins

First, cefazolin is the only first-generation cephalosporin classified as highly important in the proposed rankings. IDSA recommends that the entire group be classified as highly important, as they meet the second criterion: "Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat non-serious bacterial infections in humans."

For example, cephalexin and cefadroxil are key antibiotics for treatment of cellulitis and streptococcal pharyngitis in children with penicillin allergy. They have been more frequently used recently for treatment of urinary tract infections given the increase in fluoroquinolone and sulfa resistance rates.[1,2] They are also commonly used now for treatment of osteomyelitis and septic arthritis, since recent data have demonstrated efficacy of oral antibiotics for treatment of bone and joint infections.[3]

Sulfonamides

IDSA also recommends that sulfonamides be ranked as critically important. As FDA considers the importance of a drug in treating infections across the lifespan and in treating infections in immunocompromised patients, we assert that sulfadiazine (a sulfonamide) is the drug of choice in some patients, including infants with congenital toxoplasmosis, children with toxoplasma chorioretinitis and recurrence of toxoplasmosis.[4]

We also urge FDA to consider the potential for the development of resistance to a drug or class of drugs as a further basis for classifying sulfonamides as critically important.

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[1] Stapleton A et al. *Escherichia coli* Resistance to Fluoroquinolones in Community-Acquired Uncomplicated Urinary Tract Infection in Women: a Systematic Review. Antimicrobial Agents and Chemotherapy Sep 2020. https://aac.asm.org/content/64/10/e00862-20.abstract

[2] Wagenlehner, FM, Naber, KG. Understanding clinical variables to improve empirical antibiotic therapy for UTI. Nat Rev Urol 2019. https://www.nature.com/articles/s41585-019-0240-0

[3] Ramchandar N et al. Frequency of Dosing of Cephalexin for Oral Step-Down Therapy of Pediatric Osteoarticular Infections Caused by Methicillin-Sensitive *Staphylococcus Aureus.* The Pediatric Infectious Diseases Journal. June 2020. https://journals.lww.com/pidj/Abstract/2020/06000/Frequency_of_Dosing_of_Cephalexin_for_Oral.13.aspx

[4] Zhang Y et al. Current treatment of ocular toxoplasmosis in immunocompetent patients: a network meta-analysis Acta Tropica. September 2018. https://www.sciencedirect.com/science/article/abs/pii/S0001706X17315267

Trimethoprim/sulfamethoxazole (TMP/SMX) exposure has been found in some studies as a potential risk factor for CTX-M extended-spectrum β-lactamases (ESBL) *E. coli,* and the genes causing resistance to TMP/SMX in the CTX-M *E. coli* are primarily sulfonamide resistance genes. CTX-M Enterobacteriaceae colonize both humans and animals, and animals are a potential source of human acquisition.

Additional Category and Class

IDSA recommends that antifungals, specifically azoles, be added to the FDA ranking of antimicrobial drugs according to their therapeutic use in human medicine. CDC ranks drug resistant *Candida auris* as an urgent threat that can cause severe infections and spread easily among patients in hospitals and nursing homes. *C. auris* is often multidrug-resistant, with some strains resistant to all three available classes of antifungals. *C. auris* began spreading in the United States in 2015. Reported cases increased 318% in 2018 when compared to the average number of cases reported in 2015 to 2017.[5]

As another example, triazole resistance is an increasing problem in invasive aspergillosis (IA). Small case series show mortality rates of 50–100% in patients infected with a triazole-resistant *Aspergillus fumigatus*, though a direct comparison with triazole-susceptible IA is lacking. A multicenter retrospective cohort study found that voriconazole resistance was associated with an excess overall mortality of 21% at day 42 and 25% at day 90 in patients with IA.[6]

Updating the Rankings of Medically Important Antimicrobials

IDSA recommends that the FDA process for updating these rankings engage external experts and key stakeholders, including medical societies, through formal comment opportunities.

In order to keep pace with the development of resistance, IDSA recommends that FDA review relevant data every two years to determine the need for an update. Every five years, FDA should undertake a more formal update process. A five-year interval should be sufficient to account for new antimicrobial drug development, based upon the current pipeline.

In addition to these routine reviews and updates, FDA should establish a process through which external experts, including medical societies, may formally call for a review at any time based upon a timely need.

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[5] CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019. www.cdc.gov/DrugResistance/Biggest-Threats.html

[6] Lestrade PP, Bentvelsen RG, Schauwvlieghe AFAD, Schalekamp S, van der Velden WJFM, Kuiper EJ, van Paassen J, van der Hoven B, van der Lee HA, Melchers WJG, de Haan AF, van der Hoeven HL, Rijnders BJA, van der Beek MT, Verweij PE. Voriconazole Resistance and Mortality in Invasive Aspergillosis: A Multicenter Retrospective Cohort Study. Clin Infect Dis. 2019 Apr 24;68(9):1463-1471. doi: 10.1093/cid/ciy859. PMID: 30307492.

Once again, IDSA thanks FDA for its leadership on this important effort and for the opportunity to provide comment. If you have any questions or if there is anything further we can do to assist you, please feel free to contact Amanda Jezek, IDSA Senior Vice President for Public Policy & Government Relations, at ajezek@idsociety.org.

Sincerely,

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