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October 4, 2016

Dr. Margaret Chan
Director-General
World Health Organization
Avenue Appia 20
1211 Genève 27, Switzerland

Dear Dr. Chan:

The Infectious Diseases Society of America (IDSA) applauds the World Health Organization (WHO) for undertaking a project to develop a list of global research and development (R&D) priorities with respect to antibacterial resistant pathogens. IDSA has been sounding the alarm on the urgent threat of antibiotic resistance for over a decade, with our 2004 [Bad Bugs, No Drugs](#) report, our 2011 [Combating Antimicrobial Resistance: Policy Recommendations to Save Lives](#) report, and ongoing advocacy in support of policies to incentivize the development of urgently needed new antibiotics and increased stewardship, surveillance, data collection, research and other activities to combat resistance. The burden of antibiotic resistance is significant and growing. The antibiotic pipeline is fragile, as R&D fails to keep pace with evolving patient needs. Developments such as the recent United Nations high-level meeting on antimicrobial resistance (AMR), the U.S. National Action Plans on Combating Antibiotic Resistant Bacteria (CARB) and Combating Multidrug Resistant Tuberculosis, and the Declaration on Combating Antimicrobial Resistance signed by 85 pharmaceutical, diagnostics, and biotechnology companies from 18 countries are encouraging and indicate a broad based will to strengthen antibiotic R&D. The development of a "Global R&D Priority Pathogens List," (PPL) will contribute to this effort by helping to build consensus among expert stakeholders about the most urgent threats and guide the work of policymakers and industry. Such a list can help target limited resources to the areas of greatest need. We are pleased to offer our expert perspective to the WHO as you begin this important project, and we hope to assist you throughout this process.

Process for developing the Global R&D Priority Pathogens List (PPL)

As WHO determines the process that will be used to develop the PPL, we urge you to consider the following factors we believe to be critical to this effort's ability to produce a list that accurately reflects global needs and threats:

- The process should be inclusive of appropriate experts, including infectious diseases (ID) physicians;
- The process should embody a One Health approach, recognizing that the health of humans is connected to the health of animals and the environment;

- The process should balance the needs and capabilities of low, middle and high income countries;
- The process should consider how to build upon or incorporate existing priority pathogen lists and similar efforts already underway;
- The process should utilize diagnostics and identify gaps in diagnostic capabilities; and
- The PPL should be dynamic to account for evolving threats.

ID physicians are on the frontlines of the battle against antibiotic resistance—treating patients with or at risk of infections caused by multidrug resistant pathogens, leading antimicrobial stewardship as well as infection prevention and control programs, conducting research, and informing ongoing public health efforts such as surveillance and data collection. IDSA would be happy to make our members available to assist with this project through surveys, panels, focus groups, participation in meetings, or any other mechanism that would be useful to WHO. In addition, IDSA convenes the [U.S. Stakeholder Forum on Antimicrobial Resistance \(S-FAR\)](#), which includes over 110 partner organizations representing human and veterinary health care providers, scientists, patients, public health, industry, and private advocates. We would be happy to utilize S-FAR to share information about the WHO's activities in this area and seek feedback and support.

We strongly encourage the WHO to adopt a One Health approach for this effort and related efforts on antimicrobial resistance. Such an approach would take into account threats in the human, animal and environmental domains. Given the transmission of microbes across these three settings and the impact that antibiotic use and resistance in one setting can have on the others, One Health is an important organizing principle for this effort. The recent discovery of *mcr-1*, a gene that conveys resistance to an antibiotic of last resort called colistin, highlights the importance of a One Health approach. The *mcr-1* gene is thought to have emerged in part due to high levels of colistin use in agricultural settings in China, where it was first detected in November 2015.¹ It quickly spread throughout Asia, Europe, and North America, and was detected in the U.S. in May 2016.² As *mcr-1* spreads to bacteria that are already resistant to carbapenems, this resistance mechanism will become an increasingly grave threat to patients and public health.

A truly global threat assessment will need to consider and appropriately balance the unique needs of countries that may differ due to resource levels, geography, climate and other factors. Pathogens that are currently a serious threat in one country may not be a current threat in another country. However, the global nature of our society, with frequent human travel and transportation of food, can and does allow for the quick and easy spread of pathogens from one country to another. The WHO will also have to consider the vastly different capabilities of countries with enhanced surveillance systems for resistant pathogens versus those with much more limited capabilities. It will be critical to accurately capture the burden of antibiotic resistance in countries across the spectrum of capabilities. Some experts have proposed creating an international road map to strengthen surveillance of antibiotic resistance

¹Yi-Yun Liu, BS, et al. [Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study](#). *The Lancet Infectious Diseases*. Vol. 16, No. 2, p. 161-168, February 2016.

²McGann P, Snesrud E, Maybank R, et al. [Escherichia coli Harboring mcr-1 and bla_{CTX-M} on a Novel IncF Plasmid: First Report of mcr-1 in the United States](#). *Antimicrobial Agents and Chemotherapy*. 2016; 60(7): 4420-4421.

in low resource countries. Such an effort could include a research agenda and a map of existing networks and recommendations on how to unite them.³

As you likely are aware, the U.S. Centers for Disease Control and Prevention (CDC) undertook a similar prioritization process and produced a threats report in 2013.⁴ The European Centers for Disease Control (ECDC) is undertaking its own antibiotic resistance threat assessment. The Asian Network for Surveillance of Resistant Pathogens implemented an extensive survey of antimicrobial drug resistance in isolates causing pneumococcal infections in 11 Southeast Asian countries.⁵ While these efforts are specific to individual countries or regions, and the WHO effort will need to encompass a much more global view, we encourage you to consider ways to build upon existing and ongoing efforts.

Diagnostic tests—especially tests that can be easily deployed in an array of settings, including low resource settings—will be crucial in efforts to accurately assess the burden of antibiotic resistant pathogens globally. In addition to optimally utilizing existing diagnostics, this project can also help identify and call attention to gaps where new diagnostic tests are urgently needed.

While IDSA believes the generation of a PPL is a very important undertaking, we must underscore that such a list cannot be static. While some predictability is important to allow pharmaceutical companies to pursue targets for new antibiotics, it is also important that the WHO establish and implement a process for the PPL to be regularly reassessed and updated as necessary to keep pace with emerging threats. We recommend that the PPL be considered a living document and that the WHO establish an ongoing process to handle the necessary but challenging reassessment and revisions. We believe this can be feasible within the context of broader efforts to expand surveillance and data collection in accordance with the WHO Global Action Plan on AMR. It should also be noted that improved surveillance and data collection will reap additional long term benefits, allowing experts to rapidly identify and respond to outbreaks, thereby preventing the spread of infection. Infection prevention is the optimal way to prevent antibiotic use and limit the development of resistance. IDSA strongly supports greater global investment in antimicrobial resistance surveillance infrastructure and activities.

Criteria for Prioritization

IDSA greatly appreciates the potential criteria that WHO listed in its request for proposals for this project and largely agrees with those that are included. We want to underscore the need for criteria to be considered and applied in such a way as to capture both current and future threats. Given the significant amount of time required to develop new therapies, it is

³Vernet, Guy et al. [Surveillance for Antimicrobial Drug Resistance in Under-Resourced Countries](#). *Emerging Infectious Diseases*, Vol. 20, No. 3. March 2014.

⁴Centers for Disease Control and Prevention. [Antibiotic Resistance Threats in the United States, 2013](#).

⁵Kim SH, Song JH, Chung DR, Thamlikitkul V, Yang Y, Wang H, ANSORP Study Group. [Changing trends in antimicrobial resistance and serotypes of *Streptococcus pneumoniae* isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens \(ANSORP\) study](#). *Antimicrobial Agents and Chemotherapy*. 2012; 56: 1418–26.

important to give researchers, industry, policymakers, and other stakeholders as much advance notice as possible regarding R&D targets to help ensure that new antibiotics are available when we need them.

We greatly appreciate that WHO's list of possible prioritization criteria includes "absence of treatment," and encourage that this be heavily weighted. Infections caused by antibiotic resistant bacteria for which there are few or no existing treatments are an immediate threat to patients and global health security. In the United States, unmet medical need is considered a key factor in allocating resources for antibiotic R&D.

Lastly, we encourage the WHO to add an additional criterion: pathogens that are understudied. A review of recent and ongoing research on resistant pathogens will be an important component of this effort to help determine pathogens for which greater research dollars are needed.

Priority Pathogens

IDSA has long maintained that the "ESKAPE" pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species), cause significant morbidity and mortality. These and other drug-resistant gram negative bacteria are an extremely serious threat, given their high level of resistance to existing antibiotics, ability to cause serious or life-threatening infections, and the lack of new antibiotics in the pipeline with activity against them.⁶ Among these pathogens, *A. baumannii* has arisen as a particularly worrisome threat for which there are no new antibiotics in development. *A. baumannii* is a major cause of healthcare associated infections and is highly resistant, even to carbapenems and polymyxin/colistin in some instances. *A. baumannii* is becoming increasingly common in intensive care units, causing infections that include bacteremia, ventilator associated pneumonia, meningitis, urinary tract infections, central venous catheter-related infection, and wound infections.⁷

Other ESKAPE pathogens continue to pose serious threats globally as well. In 2005, infections in hospital-born babies were estimated to account for up to 56% of all neonatal deaths in some under-resourced countries. *K. pneumoniae*, *E. coli*, *Pseudomonas* spp., *Acinetobacter* spp., and *S. aureus* were the most frequent causative pathogens of neonatal sepsis; 70% of these isolates would not be eliminated by an empiric regimen of ampicillin and gentamicin. Many infections could be untreatable in resource-constrained environments, as a recent report demonstrated that 51% of *Klebsiella* spp. were extended-spectrum β -lactamase (ESBL) producers, 38% of *S. aureus* strains were methicillin-resistant, and 64% were resistant to co-trimoxazole.⁸

⁶Boucher, Helen W. et al. [10 x '20 Progress—Development of New Drugs Active Against Gram-Negative Bacilli: An Update from the Infectious Diseases Society of America](#). *Clinical Infectious Diseases*. 2013.

⁷Michalopoulos, A, Falagas ME. [Treatment of Acinetobacter Infections](#). *Expert Opinion on Pharmacotherapy*. 2010 April, 11(5): 779-88.

⁸Lubell Y, Ashley EA, Turner C, Turner P, White NJ. [Susceptibility of community-acquired pathogens to antibiotics in Africa and Asia in neonates—an alarmingly short review](#). *Tropical Medicine & International Health*. 2011; 16: 145–51.

Bacteria that carry *mcr-1* or *mcr-2*, genes that convey colistin resistance, should also be considered a high priority. Colistin has been a drug of last resort for many infections that are resistant to all other antibiotic classes. Traveling via plasmid, *mcr-1* and *mcr-2* can easily be taken up by other bacteria. In fact, a U.S. patient was recently found to have a complicated urinary tract infection caused by a colistin and carbapenem resistant *E. coli* harboring *mcr-1*.⁹ New antibiotics with activity against highly resistant bacteria that now contain one of these new genes are needed.

Neisseria gonorrhoeae should also be considered for inclusion in the PPL. In August 2016, the WHO recommended that physicians no longer should use quinolones to treat gonorrhea due to increasing rates of resistance, leaving us with cephalosporins as the only remaining recommended treatment option for gonorrhea. In some countries, strains of gonorrhea are already resistant to this class of drugs. Left untreated, gonorrhea can be spread to additional individuals and can increase the risk of acquiring additional sexually transmitted infections, including HIV.

Lastly, it must be noted that multidrug resistant tuberculosis (MDR TB) is a significant global threat. About 480,000 people developed MDR-TB in the world in 2014. More than half of those cases were in India, China and Russia. The WHO has already established its End TB Strategy, which includes research and innovation among its key pillars. Global efforts to combat MDR TB and stimulate the development of new therapies must be robust and should be well coordinated with other global efforts on antimicrobial resistance.

Related Priorities for Global Antibiotic R&D

While a PLL will be very useful in guiding global antibiotic R&D efforts, there are other important factors that will impact the utility of new antibiotics in responding to antibiotic resistance. First, we do not only need new antibiotics. We need new classes of antibiotics and antibiotics with novel mechanisms of action. Such antibiotics are expected to retain clinical efficacy longer than “me-too” antibiotics possessing mechanisms of action identical to existing antibiotics to which organisms have already developed resistance. There have only been six first-in-class antibiotics approved since the 1960s. All of these were developed to combat gram-positive pathogens and they all have very little or no activity against gram-negative bacteria.¹⁰ We also need more narrow spectrum antibiotics that can target an infecting pathogen with little or no impact on other bacteria. Such agents will help minimize the development of resistance and put patients at significantly less risk of complications including *Clostridium difficile* infection and disruption to their microbiome. Lastly, it can be useful for researchers and companies to discover and develop ways to repurpose older antibiotics to which resistance has developed, and to study combinations of older antibiotics. One recent example of such an effort is ceftazidime-avibactam, which combined an existing cephalosporin with a beta-lactamase inhibitor.

⁹Mediavilla, Jose R. et al. [Colistin- and Carbapenem-Resistant Escherichia coli Harboring mcr-1 and bla_{NDM-5}. Causing a Complicated Urinary Tract Infection in a Patient from the United States.](#) *mBio*. Vol. 7. No. 4. August 30, 2016.

¹⁰Fair, Richard J and Yitzhak Tor. [Antibiotics and Bacterial Resistance in the 21st Century.](#) *Perspectives in Medicinal Chemistry*. 2014; 6: 25-64.

Additional considerations

As the WHO undertakes the important work of developing a PLL, we encourage you to be mindful of broader efforts—globally and within specific countries and regions—to address antimicrobial resistance and incentivize the development of urgently needed new therapies, including traditional antibiotic drugs and alternative therapies [antibodies, phage therapy, etc.], diagnostics, and vaccines. It is critical that our efforts balance the need for innovation and new antibiotics with the need to ensure appropriate stewardship or conservation of both new and existing antibiotics as well as access for all patients who need these drugs. This is particularly true in lower resource countries in which many individuals struggle to access health care providers and afford necessary medications.

As discussed above, robust surveillance and data collection activities across a wide variety of countries and settings will be necessary to appropriately inform the PLL.

Once again, IDSA thanks the WHO for its continued attention to the public health crisis of antibiotic resistance and particularly for undertaking this project to develop a priority pathogen list. We hope our perspective is helpful, and we look forward to working closely with you and other stakeholders to advance this important work.

Sincerely,

A handwritten signature in black ink that reads "Johan S. Bakken MD, PhD". The signature is written in a cursive, slightly slanted style.

Johan S. Bakken, MD, PhD, FIDSA
President, IDSA