Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance

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Abstract

Many different definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria are being used in the medical literature to characterize the different patterns of resistance found in healthcare-associated, antimicrobial-resistant bacteria. A group of international experts came together through a joint initiative by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC), to create a standardized international terminology with which to describe acquired resistance profiles in *Staphylococcus aureus*, *Enterococcus* spp., *Enterobacteriaceae* (other than *Salmonella* and *Shigella*), *Pseudomonas aeruginosa* and *Acinetobacter* spp., all bacteria often responsible for healthcare-associated infections and prone to multidrug resistance. Epidemiologically significant antimicrobial categories were constructed for each bacterium. Lists of antimicrobial categories proposed for antimicrobial susceptibility testing were created using documents and breakpoints from the Clinical Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the United States Food and Drug Administration (FDA). MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) and PDR was defined as non-susceptibility to all agents in all antimicrobial categories. To ensure correct application of these definitions, bacterial isolates should be tested against all or nearly all of the antimicrobial agents within the antimicrobial categories and selective reporting and suppression of results should be avoided.

Keywords: Antimicrobial agents, definitions, extensively drug resistant, multidrug resistant, pandrug resistant
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Background

Emergence of resistance to multiple antimicrobial agents in pathogenic bacteria has become a significant public health

threat as there are fewer, or even sometimes no, effective antimicrobial agents available for infections caused by these bacteria. Gram-positive and Gram-negative bacteria are both affected by the emergence and rise of antimicrobial resistance. As this problem continues to grow, harmonized definitions with which to describe and classify bacteria that are resistant to multiple antimicrobial agents are needed, so that epidemiological surveillance data can be reliably collected and compared across healthcare settings and countries. In the strictest sense, multidrug-resistant organisms (MDROs) are labelled as such because of their *in vitro* resistance to more than one antimicrobial agent. Infections with MDROs can lead to inadequate or delayed antimicrobial therapy, and are associated with poorer patient outcomes [1–4]. Of the MDROs, highly-resistant Gram-negative bacteria (e.g. multidrug-resistant carbapenemase-producing *Klebsiella pneumoniae* and *Acinetobacter* spp.) require special mention; these organisms can be resistant to all currently available antimicrobial agents or remain susceptible only to older, potentially more toxic agents such as the polymyxins, leaving limited and suboptimal options for treatment [5–7]. The problem of increasing antimicrobial resistance is even more threatening when considering the very limited number of new antimicrobial agents that are in development [8,9].

No consensus has yet been reached on the definition and use of terms such as 'multidrug-resistant', 'extreme drug resistant', 'extensive, extensively or extremely drug resistant' (all XDR – in this document XDR refers to 'extensively drug-resistant') and 'pandrug-resistant' (PDR) [10–15], which characterize resistance in MDROs. This variability precludes reliable comparison of surveillance data for MDROs and consequently prevents the medical community from having a complete comprehension of the extent of the problem of antimicrobial resistance. Moreover, accurate information cannot be conveyed to the public and to policy makers about the rising threat of MDROs to public health [16–18]. Adopting standardized international terminology to define organisms that are resistant to a significant number of therapeutically active drugs would be an important step to improve the comparability of surveillance data for these organisms and to better assess their global, regional and local epidemiological importance and public health impact.

Purpose

This document proposes definitions for MDR, XDR and PDR strains of pathogenic bacteria that are frequently found in healthcare settings (e.g. *Staphylococcus aureus*, *Enterococcus* spp., *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter* spp.). By applying these definitions, clinical, reference and public health microbiology laboratories will use a common terminology for grading various antimicrobial resistance profiles. This will result in consistent reporting of comparable data that can reliably track trends of antimicrobial resistance locally, but also internationally. Moreover, the use of standard terminology will optimize epidemiological surveillance systems, facilitating the exchange of information between the medical community, public health authorities and policy makers in order to promote the prudent use of antimicrobials and other public health measures [19–21].

It is important to note that these definitions are meant for public health use and epidemiological purposes only. They are not intended to replace clinical judgment, to contribute to therapeutic decision-making or to offer guidance in infection control practices. These areas are beyond the scope of this document and remain the purview of clinical specialists and local and national health authorities. Similarly, these definitions do not represent and should not be construed to represent any agency determination of policy.

Approaches to Creating Definitions for MDR, XDR and PDR

In a joint initiative by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC), a first meeting of experts was held in Stockholm in January 2008. The scope of the initial meeting was to create definitions for highly-resistant, multidrug-resistant bacteria associated with healthcare-associated infections. This group was later expanded to include additional experts in the diagnosis, therapy and surveillance of antimicrobial-resistant bacteria, all of whom are co-authors of this article. The expert group decided to concentrate on applying the definitions to *S. aureus*, *Enterococcus* spp., *Enterobacteriaceae* (other than *Salmonella* and *Shigella*), *P. aeruginosa* and *Acinetobacter* spp., because of the epidemiological significance, the emerging antimicrobial resistance and the importance of these bacteria within the healthcare system. Mycobacteria and other bacteria most commonly associated with community-acquired infections such as *Streptococcus pneumoniae*, *Salmonella* spp., *Shigella* spp. and *Neisseria gonorrhoeae* were excluded, as their resistance patterns have been previously discussed in the literature by separate groups of experts [22–25]. These definitions, however, can also be applied to these organisms in the future, if the respective expert groups wish to do so.