Multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria in healthcare settings. Expert proposal for a standardized international terminology

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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 increasingly fewer, or even 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 labeled as such because of their 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 like 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 how to define terms such as "multidrug-resistant" (MDR), "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 surveillance of 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 standard definitions for bacteria that are resistant to a significant number of therapeutically active drugs would be an important step to improve surveillance of these organisms and better assess their global, regional and local epidemiological importance and public health impact.

Purpose

This document proposes definitions for MDR, XDR and PDR for multidrug-resistant strains of pathogenic bacteria that are frequently found in healthcare settings, e.g. *Staphylococcus aureus*, *Enterococcus* spp., *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *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 on trends of increasing levels of antimicrobial resistance. Moreover, standard terminology will facilitate the exchange of information between the medical community, public health authorities, and policy makers in order to optimize epidemiological surveillance systems, 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. 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 should continue to fall within the remit of clinical specialists and local and national health authorities.

Approaches to Creating Definitions of MDR, XDR, 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. This group was later expanded by the addition of a few more experts, all of whom are co-authors of this article. The experts were chosen because of their experience with diagnosis, therapy and surveillance of antimicrobial-resistant bacteria. The scope of the initial meeting was to create definitions for highly-resistant, multidrug-resistant bacteria associated with healthcare-associated infections. 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).

A bacterial isolate was considered non-susceptible to an antimicrobial agent when it tested resistant, intermediate or non-susceptible when using interpretive criteria provided by European Committee on Antimicrobial Susceptibility Testing (EUCAST), the Clinical and Laboratory Standards Institute (CLSI) (26-27) and/or the FDA . Only acquired antimicrobial resistance was used in creating definitions for MDR, XDR and PDR.

After comments on the draft manuscript were circulated among the experts, the proposal for definitions of MDR, XDR and PDR bacteria was presented to the ECDC Advisory Forum, the official advisory body to the ECDC in October and December, 2008. Suggestions from the Advisory Forum were: (a) to post the proposed definitions on the internet for broad

discussion, comments and further consultations by medical professional societies and other expert groups, (b) to pilot-test the proposed definitions by analyzing a database that contained an adequate number of antimicrobial resistant organisms, (c) to convene a second ECDC Joint Expert Meeting for further review and (d) to re-submit the revised proposed definitions to the ECDC Advisory Forum.

In May, 2009 and March, 2010 the second and third ECDC Joint Expert Meeting were held in Helsinki, Finland and Stockholm, Sweden, respectively to further refine the definitions. Applying the definitions as a pilot-test on antimicrobial susceptibility databases was also discussed; results from these analyses that were subsequently performed will be available as supporting information, but are not included in this document.

This draft version has been put on the web for comments from 23 July until 21 August, 2010.

Previous definitions applied to bacteria resistant to multiple antimicrobial agents

MDR

In precise terms, MDR means “resistant to more than one antimicrobial agent”, but no standardized definitions for MDR have been agreed upon yet by the medical community. Many definitions are thus being used to characterize patterns of multidrug resistance in gram-positive and gram-negative organisms (5, 10, 16-17, 28). These definitions are primarily based on the two approaches used by various authors and authorities, including the Healthcare Infection Control Practices Advisory Committee (HICPAC) (16) and the National Healthcare Safety Network (NHSN) (17).

The first approach characterizes organisms as MDR based on *in vitro* antimicrobial susceptibility test results when they test “resistant to multiple antimicrobial agents, classes or subclasses of antimicrobial agents” (10, 16-17, 29). The variety of definitions used to describe MDR, XDR or PDR in specific clinical study protocols gives rise to data which are

difficult to compare. The definition most frequently used for gram-positive (30-34) and gram-negative bacteria (10, 18, 29, 35-37) is “resistant to three or more antimicrobial classes”. An overview of the variability of these definitions is provided in a comprehensive review of MDR in *P. aeruginosa* and *A. baumannii*, by Falagas *et al.* where the author notes that a sizable number of studies do not propose any specific definitions for MDR, but the majority define MDR as “resistant to three or more antimicrobial classes” (10).

The second method characterizes bacteria as MDR when they are “resistant to one key antimicrobial agent” (17, 38). Creating an acronym for a bacterium based on its resistance to a key antimicrobial agent, e.g. methicillin resistance in *S. aureus*, i.e. MRSA, immediately highlights its epidemiological significance. While these bacterial isolates may acquire public health importance via resistance to only one key antimicrobial agent, they often demonstrate cross or co-resistance to multiple classes of antimicrobials which makes them multidrug-resistant. The advantage of using this approach for surveillance purposes is that it can be easily applied.

XDR

Bacteria that are classified as XDR are epidemiologically significant due to their high degree of antimicrobial resistance, but also because they carry the ominous likelihood of being resistant to all, or almost all approved antimicrobial agents. In the medical literature XDR has been used as an acronym for several different terms such as “extreme-drug resistance”, “extensive-drug resistance”, “extremely-drug resistant” and “extensively-drug resistant” (12, 15, 39-40).

Initially, the term XDR was created to describe extensively-drug resistant *Mycobacterium tuberculosis* (XDR MTB) and was defined as “resistance to the first-line agents isoniazid and rifampicin, to a fluoroquinolone and to at least one of the three second-line parenteral drugs

(i.e. amikacin, kanamycin or capreomycin)" (41-42). Subsequent to this, definitions for strains of non-mycobacterial bacteria that were XDR were constructed according to the principle underlying this definition for XDR MTB (i.e. describing a resistance profile which compromised most standard antimicrobial regimens). Two sets of criteria have mainly been used to characterize bacteria as XDR. The first is based on the number of antimicrobials or classes or subclasses to which a bacterium is resistant, and the second on whether they are "resistant to one or more key antimicrobial agents" (16-17, 38).

PDR

From the Greek prefix pan-, meaning "all", pandrug-resistant (PDR) means "resistant to all approved antimicrobial agents". Even though this term is etymologically precise and mandates testing all approved and useful agents for a particular species and determining that a bacterial isolate of this species is resistant to all the agents, definitions in the literature for PDR still vary. Examples of current definitions are: "resistant to almost all commercially available antimicrobials", "resistant to all antimicrobials routinely tested" and "resistant to all antibiotic classes available for empirical treatment" (10, 43-45), making the definition of PDR subject to inconsistent use and liable to potential misinterpretation of data.

Considerations in creating the definitions

Initially, the expert group agreed that three issues needed to be addressed to develop the definitions: **1)** how to create antimicrobial "categories" that would be epidemiologically meaningful, **2)** how to select the antimicrobial categories and antimicrobial agents to be tested for each relevant bacterium, **3)** how to define resistance within an antimicrobial category.

Creating antimicrobial categories

There has been no standard approach for determining the types, classes or groups of antimicrobial agents that should be used when defining MDR, XDR and PDR. Frequently, chemical structures for antimicrobial classes (e.g. cephalosporins) (46-48), antimicrobial subclasses, (e.g. third-generation cephalosporins) (49) or specific antimicrobial agents (e.g. ceftazidime) (50-51) have been used to define these terms. This approach is not always conclusive and makes it difficult to compare results between studies. The expert group, therefore, constructed "antimicrobial categories" for each of the organisms or organism groups with the intent of placing antimicrobial agents into more therapeutically relevant groups. These new categories are listed in Tables 1a-1e together with the proposed antimicrobial agents relevant for antimicrobial susceptibility testing for each organism or organism group.

Defining antimicrobial categories and antimicrobial agents to be tested for each organism or organism group.

Panels of lists of antimicrobial agents were developed for each organism or organism group, as proposed harmonized templates that could be used by clinical, reference, and public health microbiology laboratories that perform in vitro antimicrobial susceptibility testing, and wish to identify MDR, XDR and PDR. These lists were designed to be as comprehensive as possible and reflect antimicrobial agents and testing practices used in most countries around the world.

These lists were developed in a stepwise fashion. The first step was to include the antimicrobial agents listed for each organism or organism group in the CLSI table of "Suggested agents with FDA clinical indications that should be considered for routine testing and reporting by clinical microbiological laboratories" (26). An antimicrobial agent was

added or removed, based on recommendations included in EUCAST's Expert Rules (27) and also by applying specific inclusion and exclusion criteria. The inclusion criteria required that each antimicrobial agent: a) was currently approved as an antibacterial agent in humans by the European Medicines Agency (EMA) or the United States Food and Drug Administration (FDA) and b) had breakpoints for the organism or organism group established by either EUCAST (27), CLSI (26) or the FDA. An antimicrobial agent was excluded from an organism or an organism list if : a) the organism or the whole organism group was intrinsically resistant to the agent, b) the agent achieved therapeutic concentrations only in urine (i.e. nitrofurantoin) or c) the agent was infrequently tested due to widespread acquired resistance (i.e. penicillin for *S. aureus*).

Although this document does not address definitions for individual bacterial species that are intrinsically resistant to antimicrobial agents or categories, there are bacterial species within certain organism groups, i.e. the *Enterococcus* spp. and the *Enterobacteriaceae*, that are intrinsically resistant to one or more antimicrobial agents within a category or to all agents within a category. When applying the definitions for MDR, XDR and PDR to these organisms, those agents or categories will need to be removed and not included in the analysis. Therefore, a separate column was included in Tables 1b and 1c listing those organisms that have intrinsic resistance to the antimicrobial agent or category listed in that row (27).

Finally, available rules of partial or complete cross-resistance from EUCAST (27) and CLSI (26) were applied to the lists of antimicrobial agents in order to minimize the number of agents proposed for testing. An example of a rule for full cross-resistance is when an *E. coli* isolate is considered non-susceptible to all fluoroquinolones when it is tested and found to be non-susceptible to ciprofloxacin (27, 52). Similarly, a *S. aureus* isolate is considered non-susceptible to all lincosamides when it tests non-susceptible to clindamycin (27, 53). When

rules of full cross-resistance could be applied to an antimicrobial category in Tables 1a-1e, one agent only from that category was recommended for antimicrobial susceptibility testing.

Defining antimicrobial resistance within an antimicrobial category

In the definitions proposed in this document a bacterial isolate is considered to be resistant to an antimicrobial category when it is "non-susceptible to at least one agent in a category". Antimicrobial resistance of a bacterial isolate to only one agent within that category could be used as a crude indicator of antimicrobial resistance to all agents.

In support of this, the definition used by the National Healthcare Safety Network (NHSN) considers a bacterial isolate resistant to a "class" when it is resistant to one or more antimicrobial agents within the class (17, 29). Thus, according to the previous definition carbapenem resistance in *Klebsiella* spp. is defined as "resistance to imipenem or meropenem, ertapenem or doripenem".

Proposed definitions for MDR, XDR and PDR

The definitions proposed for the characterization of bacterial isolates that are MDR, XDR or PDR are given in Table 2. MDR is defined as non-susceptibility to at least one agent in 3 or more antimicrobial categories. XDR is defined as non-susceptibility to at least 1 agent in all but 2 or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories). PDR is defined as non-susceptibility to all agents in all antimicrobial categories (i.e. no agents tested as susceptible for that organism). For all three definitions, non-susceptibility refers to either a resistant, intermediate or non-susceptible result obtained from in vitro antimicrobial susceptibility testing.

For a bacterial isolate to be characterized as XDR it needs to be first be defined as MDR. Similarly, a bacterial isolate would have to be an XDR in order for it to be further defined as PDR. Figure 2 illustrates that XDR is a subset of MDR, and PDR is a subset of XDR.

Bacteria that are PDR carry the most absolute type of antimicrobial resistance possible, implying that there are no approved and available antimicrobial agents that have activity against these strains. Figure 1 shows examples of possible antimicrobial susceptibility patterns that can fall under the definitions for MDR, XDR and PDR. Certain points and limitations are important and will be highlighted here.

A special rule has been applied in defining antimicrobial resistance in *S. aureus*. Once a *S. aureus* isolate is characterized as an MRSA it is instantly classified as an MDR, because resistance to oxacillin or cefoxitin infers non-susceptibility to all categories of β-lactam antimicrobials listed in this document (i.e. all categories of penicillins, cephalosporins, β-lactamase inhibitors and carbapenems currently approved up until July 22, 2010).

To conclusively define a bacterial isolate as PDR, it is necessary to test every antimicrobial agent listed for the respective organism or organism group in Tables 1a-e. A very broad spectrum of resistance is also implied when a bacterial isolate is characterized as XDR, because the proposed definition of XDR indicates that such strains are susceptible to only one or two categories of antimicrobial agents. Lastly, bacterial isolates that are MDR will have many different resistance profiles, since to fit this definition, antimicrobial agents from only 3 antimicrobial categories need to demonstrate a non-susceptibility result. For example, one MDR *E. coli* isolate can be resistant to trimethoprim-sulfamethoxazole, cefazolin and ciprofloxacin and another to ertapenem, gentamicin and tigecycline. Consequently, both these isolates will be grouped together under the term “MDR” and if one uses “MDR” as a measure of epidemiological or public health significance, it will be important to understand this limitation. Even though these differences will vary according to geographical area and endemicity, all countries, regardless of individual resistance patterns, will place high importance on monitoring bacteria that are XDR or PDR, because of their public health impact.

Applicability of MDR, PDR, and XDR Definitions

The proposed definitions can be applied to results obtained from antimicrobial susceptibility testing of bacterial isolates in any clinical, reference or public health microbiology laboratory. However, to apply the definitions correctly and to ensure their validity, certain conditions should be present.

It is important to point out that overall, a bacterial isolate will be considered resistant (or non-susceptible) to an antimicrobial agent or antimicrobial category, when it is found to be resistant (or non-susceptible) by using any of the available interpretative criteria established by EUCAST, CLSI or the FDA. Furthermore, for results to be compared between surveillance systems or facilities, it will be important to report details about the methods and interpretive criteria used for antimicrobial susceptibility testing along with the results from the application of the definitions of MDR, XDR and PDR.

It will also be essential for all clinical microbiology, reference and public health laboratories that will apply these definitions, to have the necessary software to perform the required analysis.

Lastly, for these definitions to be valid and comparable they should be applied to databases that contain sufficiently large numbers of bacterial isolates that have been tested to all or nearly all of the antimicrobial agents within the antimicrobial categories listed in Tables 1a-1e. Laboratories that utilize selective reporting protocols must make sure that results from all the antimicrobial agents tested are available for analysis, including those agents that might have been suppressed. When too few antimicrobial agents have been either tested or reported or both, there will be difficulties in applying the definitions and in particular, in reliably distinguishing XDR from PDR phenotypes (29). In cases of incomplete testing, bacterial isolates can only be characterized as “possible XDR” or “possible PDR” and these results cannot be compared to other “possible XDR”, “possible PDR” or to confirmed XDR and

PDR obtained from other studies. This problem cannot be circumvented by defining precise antimicrobial resistance profiles for the definitions of possible XDR and possible PDR, because their characterization depends on which antimicrobial agents are tested and reported. Possible XDR and possible PDR, however, should still be regarded as markers for extensive resistance and their use should be encouraged despite limitations in their interpretation.

When performing routine antimicrobial susceptibility testing on bacterial isolates in clinical microbiology laboratories, the limited number of agents generally tested will result in many MDR bacteria being categorized as “possible XDR” or “possible PDR”. This practical limitation underscores the necessity of testing an adequate number of antimicrobial agents, such as those suggested in Tables 1a-e in this document in order to effectively apply the definitions. It also emphasizes the need to test additional agents beyond those routinely tested in an individual clinical microbiology laboratory when a “possible XDR” or “possible PDR” is encountered. This additional testing might be done in the clinical microbiology laboratory by using a supplemental panel or by submitting the isolate to a reference laboratory to allow definitive classification of these bacteria.

Conclusions

Applying these definitions for MDR, XDR and PDR worldwide would allow comparability of data on and promote better comprehension of the problem of highly antimicrobial resistant bacteria. This has not been possible until now, not only due to the varied definitions that are being used, but also because of differences in the antimicrobial agents that are used for routine antimicrobial susceptibility testing in clinical, reference and public health microbiology laboratories.

The proposed definitions for MDR, XDR and PDR present an opportunity for clinical microbiology laboratories to review and if necessary, expand the antimicrobial agents

routinely tested against various organisms and organism groups and to consider testing additional agents when a bacterial isolate is encountered that could be XDR and PDR. The listing of antimicrobial agents found in Tables 1a-1e can be used as a guide and it is important to note again that these lists are based on current information available from the CLSI, the EUCAST and the FDA together with the opinion of the Expert Group. These lists will need to be regularly reviewed and updated as new recommendations are made and as new antimicrobial agents are approved and become available for therapeutic use.

Updates of this document will be posted, when performed, on the website of the European Centre for Disease Prevention and Control.

Table 1a. *Staphylococcus aureus*; antimicrobial categories and agents used to define MDR, XDR and PDR

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)
Aminoglycosides	Gentamicin	
Ansamycins	Rifampin/rifampicin	
Anti-staphylococcal β-lactams	Oxacillin (or cefoxitin)*	
Fluoroquinolones	Ciprofloxacin	
	Levofloxacin	
Folate pathway inhibitors	Trimethoprim-sulfamethoxazole	
Fucidanes	Fusidic acid	
Glycopeptides	Vancomycin	
	Teicoplanin	
Glycylcyclines	Tigecycline	
Lincosamides	Clindamycin	
Lipopeptides	Daptomycin	
Macrolides	Erythromycin	
Oxazolidinones	Linezolid	
Phenicols	Chloramphenicol	
Phosphonic acids	Fosfomycin	
Streptogramins	Quinupristin-dalfopristin	
Tetracyclines	Tetracycline	
	Doxycycline	
	Minocycline	

Criteria for defining MDR, XDR and PDR in *S. aureus*

MDR (one or more of these have to apply)

- an MRSA is always considered MDR by virtue of being an MRSA
- non-susceptible to ≥1 agent in ≥3 antimicrobial categories

XDR: non-susceptible to ≥1 agent in ≥ 14 of the 16 antimicrobial categories

PDR: non-susceptible to all antimicrobial agents

*Oxacillin or cefoxitin represents all other β-lactams and resistance to either of these infers non-susceptibility to all categories of β-lactam antimicrobials listed in this document (i.e. all categories of penicillins, cephalosporins, β-lactamase inhibitors and carbapenems currently approved up until July 22, 2010).

Table 1b. *Enterococcus* spp.; antimicrobial categories and agents used to define MDR, XDR and PDR

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)	Species with intrinsic resistance to antimicrobial categories (27)*
Aminoglycosides	Gentamicin (High level) Streptomycin (High level)		
Carbapenems	Imipenem Meropenem Doripenem		*Enterococcus faecium**
Fluoroquinolones	Ciprofloxacin Levofloxacin		
Glycopeptides	Vancomycin Teicoplanin		
Glycylcyclines	Tigecycline		
Lipopeptides	Daptomycin		
Oxazolidinones	Linezolid		
Penicillins	Ampicillin		
Streptogramins	Quinupristin-dalfopristin		*Enterococcus faecalis**
Tetracycline	Doxycycline Minocycline		

Criteria for defining MDR, XDR and PDR in *Enterococcus* spp.
MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories
XDR: non-susceptible to ≥1 agent in ≥ 8 of the 10 antimicrobial categories
PDR: non-susceptible to all antimicrobial agents listed

* When an organism has intrinsic resistance to an antimicrobial category, that category must be removed from the list in Table 1b prior to applying the criteria for the definitions and should not be counted when calculating the number of categories to which the bacterial isolate is non-susceptible.

Table 1c. ***Enterobacteriaceae***; antimicrobial categories and agents used to define MDR, XDR and PDR.

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)	Species with intrinsic resistance to antimicrobial agents or categories (27)*
Aminoglycosides	Gentamicin		*Providencia rettgeri (P. rettgeri)* *Providencia stuartii (P .stuartii)*
	Tobramycin		*P. rettgeri, P. stuartii*
	Amikacin		
	Netilmicin		*P. rettgeri, P. stuartii*
Antipseudomonal penicillins + inhibitors	Ticarcillin-clavulanic acid		*Citrobacter koseri (C. koseri),* *Escherichia hermannii (E. hermanii),* *Klebsiella* spp.
	Piperacillin-tazobactam		*C.koseri, E.hermanii, Klebsiella* spp.
Carbapenems	Ertapenem		
	Imipenem		
	Meropenem		
	Doripenem		
Non-extended cephalosporins	Cefazolin		*Citrobacter freundii (C. freundii)* *Enterobacter aerogenes(E. aerogenes)* *Enterobacter cloacae (E. cloacae)* *Hafnia alvei (H. alvei)* *Morganella morganii (M. morganii)* *Proteus penneri (P. penneri)* *Proteus vulgaris (P. vulgaris)* *P. rettgeri, P. stuartii* *Serratia marcescens(S. marcescens)*
	Cefuroxime		*M. morganii P. penneri,* *P. vulgaris, S. marcescens*
Extended-spectrum cephalosporins	Cefotaxime or ceftriaxone		
	Ceftazidime		
	Cefepime		
Cephamycins	Cefoxitin		*C. freundii ,E. aerogenes, E. cloacae,* *H. alvei,*
	Cefotetan		*C. freundii ,E. aerogenes, E. cloacae,* *H. alvei*

Criteria for defining MDR, XDR and PDR in *Enterobacteriaceae*
MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories
XDR: non-susceptible to ≥1 agent in ≥ all but 2 or fewer antimicrobial categories
PDR: non-susceptible to all antimicrobial agents listed

*When an organism has intrinsic resistance to an antimicrobial agent or to the whole category, that agent or category must be removed from the list in Table 1c prior to applying the criteria for the definitions and should not be counted when calculating the number of agents or categories to which the bacterial isolate is non-susceptible.

Table 1c. *Enterobacteriaceae*; antimicrobial categories and agents used to define MDR, XDR and PDR (continued).

Fluoroquinolones	Ciprofloxacin		
Folate pathway inhibitors	Trimethoprim-sulfamethoxazole		
Glycylcyclines	Tigecycline		
Monobactams	Aztreonam		
Penicillins	Ampicillin		*C. freundii, C. koseri, E. aerogenes, E. cloacae, E. hermanii, H .alvei, Klebsiellae* spp., *M. morganii, P. penneri, P. vulgaris, P. rettgeri, P. stuartii, S. marcescens*
Penicillins +inhibitors	Amoxicillin-clavulanic acid		*C. freundii, E. aerogenes, E. cloacae, H. alvei, M. morganii, P. rettgeri, ,P. stuartii, S. marcescens*
	Ampicillin-sulbactam		*C. freundii, C. koseri, E. aerogenes, E. cloacae, H. alvei, P. rettgeri, S. marcescens*
Phenicols	Chloramphenicol		
Phosphonic acids	Fosfomycin		
Polymyxins	Colistin		*M. morganii, Proteus mirabilis (P. mirabilis) P. penneri, P. vulgaris, P .rettgeri, P. stuartii, S. marcescens*
Tetracyclines	Tetracycline		*M. morganii, P. mirabilis, P. penneri, P. vulgaris, P. rettgeri, P. stuartii*
	Doxycycline		*M. morganii, P. penneri, P. vulgaris, P. rettgeri, P. stuartii*
	Minocycline		*M . morganii, P. penneri, P. vulgaris, P. rettgeri, P. stuartii*

Criteria for defining MDR, XDR and PDR in *Enterobacteriaceae*
MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories
XDR: non-susceptible to ≥1 agent in ≥ all but 2 or fewer antimicrobial categories
PDR: non-susceptible to all antimicrobial agents listed

*When an organism has intrinsic resistance to an antimicrobial agent or to the whole category, that agent or category must be removed from the list in Table 1c prior to applying the criteria for the definitions and should not be counted when calculating the number of agents or categories to which the bacterial isolate is non-susceptible.

Table 1d. ***Pseudomonas aeruginosa***; antimicrobial categories and agents used to define MDR, XDR and PDR

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)
Aminoglycosides	Gentamicin	
	Tobramycin	
	Amikacin	
	Netilmicin	
Antipseudomonal carbapenems	Imipenem	
	Meropenem	
	Doripenem	
Antipseudomonal cephalosporins	Ceftazidime	
	Cefepime	
Antipseudomonal fluoroquinolones	Ciprofloxacin	
	Levofloxacin	
Antipseudomonal penicillins+ inhibitors	Ticarcillin-clavulanic acid	
	Piperacillin-tazobactam	
Monobactams	Aztreonam	
Phosphonic acids	Fosfomycin	
Polymyxins	Colistin	
	Polymyxin B	

Criteria for defining MDR, XDR and PDR in *Pseudomonas aeruginosa*
MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories
XDR: non-susceptible to ≥1 agent in ≥ 6 of the 8 antimicrobial categories
PDR: non-susceptible to all antimicrobial agents listed

Table 1e. ***Acinetobacter*** spp.; antimicrobial categories and agents used to define MDR, XDR and PDR

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)
Aminoglycosides	Gentamicin	
	Tobramycin	
	Amikacin	
	Netilmicin	
Antipseudomonal carbapenems	Imipenem	
	Meropenem	
	Doripenem	
Antipseudomonal fluoroquinolones	Ciprofloxacin	
	Levofloxacin	
Antipseudomonal penicillins+ inhibitors	Piperacillin-tazobactam	
	Ticarcillin-clavulanic acid	
Extended-spectrum cephalosporins	Cefotaxime	
	Ceftriaxone	
	Ceftazidime	
	Cefepime	
Folate pathway inhibitors	Trimethoprim-sulfamethoxazole	
Monobactams	Aztreonam	
Penicillins+ inhibitors	Ampicillin-sulbactam	
Polymyxins	Colistin	
	Polymyxin B	
Tetracyclines	Tetracycline	
	Doxycycline	
	Minocycline	

Criteria for defining MDR, XDR and PDR in *Acinetobacter* spp.
MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories
XDR: non-susceptible to ≥1 agent in ≥ 8 of the 10 antimicrobial categories
PDR: non-susceptible to all antimicrobial agents listed

Table 2. Definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria

Bacterium	MDR	XDR	PDR
Staphylococcus aureus	The isolate is non-susceptible to at least 1 agent in ≥ 3 antimicrobial categories listed in Table 1a *	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1a.	Non-susceptibility to all agents in all antimicrobial categories for each bacterium in Tables 1a-e
***Enterococcus* spp.**	The isolate is non-susceptible to at least 1 agent in ≥ 3 antimicrobial categories listed in Table 1b	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1b.	
Enterobacteriaceae	The isolate is non-susceptible to at least 1 agent in ≥ 3 antimicrobial categories listed in Table 1c	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1c.	
Pseudomonas aeruginosa	The isolate is non-susceptible to at least 1 agent in ≥ 3 antimicrobial categories listed in Table 1d	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1d.	
***Acinetobacter* spp.**	The isolate is non-susceptible to at least 1 agent in ≥ 3 antimicrobial categories listed in Table 1e	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1e.	

*All MRSA are defined as MDR because resistance to oxacillin or cefoxitin infers non-susceptibility to all categories of β-lactam antimicrobials listed in this document (i.e. all categories of penicillins, cephalosporins, β-lactamase inhibitors and carbapenems currently approved up until July 22, 2010).

Table 3. ***Pseudomonas aeruginosa***-examples of antimicrobial susceptibility profiles that fit MDR, XDR and PDR definitions; isolate #1 is PDR; isolate#2 is XDR and isolate #3 is MDR.

Antimicrobial category	Antimicrobial agent	Isolate #1(PDR)	Isolate #2 (XDR)	Isolate #3 (MDR)
Aminoglycosides	Gentamicin	X	X	
	Tobramycin	X	**	
	Amikacin	X		
	Netilmicin	X		
Antipseudomonal carbapenems	Imipenem	X	X	X
	Meropenem	X	X	
	Doripenem	X		
Antipseudomonal cephalosporins	Ceftazidime	X	X	X
	Cefepime	X		
Antipseudomonal fluoroquinolones	Ciprofloxacin	X	X	X
	Levofloxacin	X		
Antipseudomonal penicillins+ inhibitors	Piperacillin-tazobactam	X	X	
	Ticarcillin-clavulanic acid	X		
Monobactams	Aztreonam	X	X	
Phosphonic acids	Fosfomycin	X		
Polymyxins	Colistin	X		
	Polymyxin B	X		

Criteria for defining MDR, XDR and PDR in *Pseudomonas aeruginosa*
MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories
XDR: non-susceptible to ≥1 agent in ≥ 6 of the 8 antimicrobial categories
PDR: non-susceptible to all antimicrobial agents listed

*__X__= non-susceptible to the antimicrobial agent
Absence of an "X**" means the antimicrobial agent was either "susceptible" or "not tested"

Figure 1. Examples of 22 possible antimicrobial susceptibility patterns that can fall under the proposed definitions for MDR, XDR and PDR

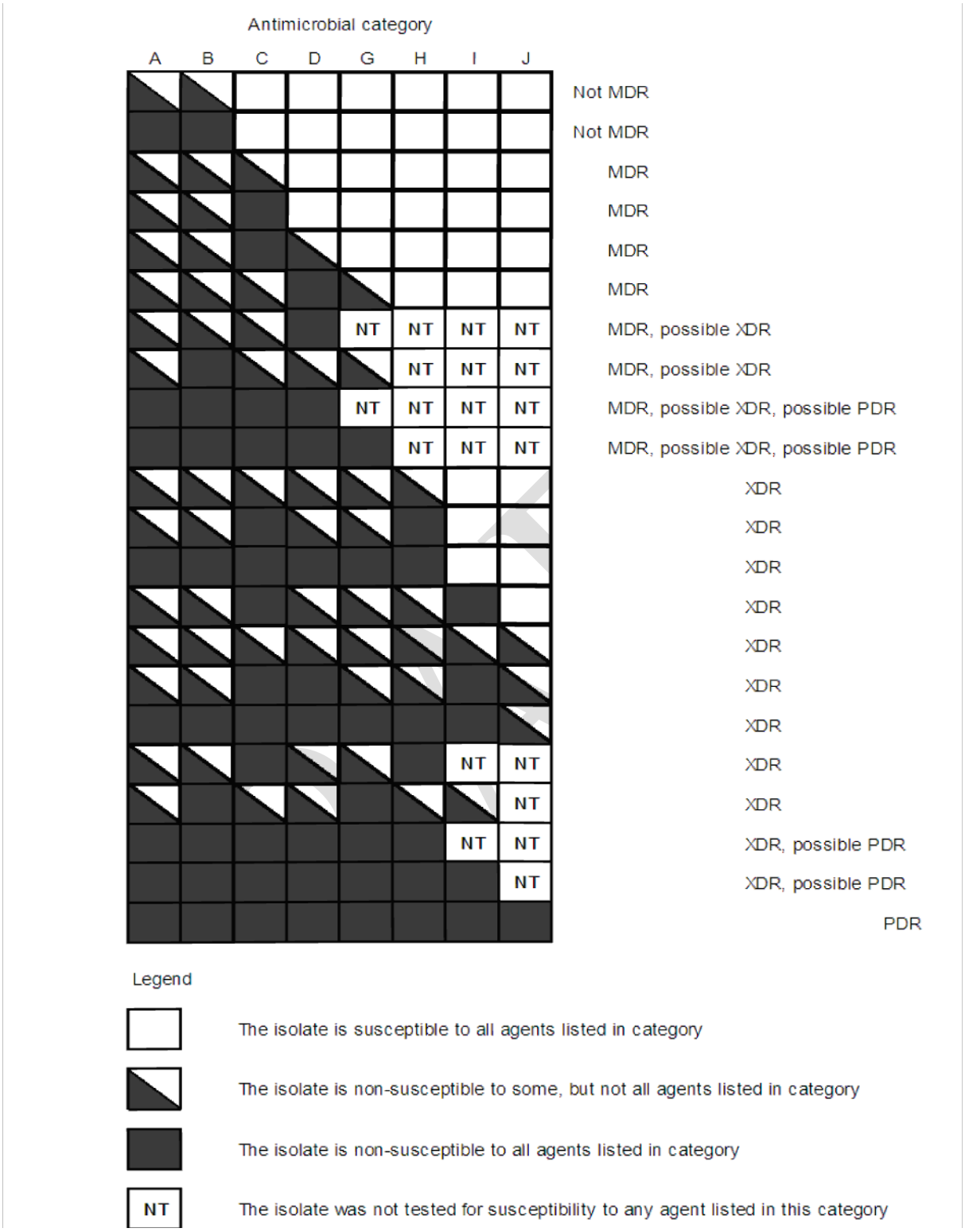
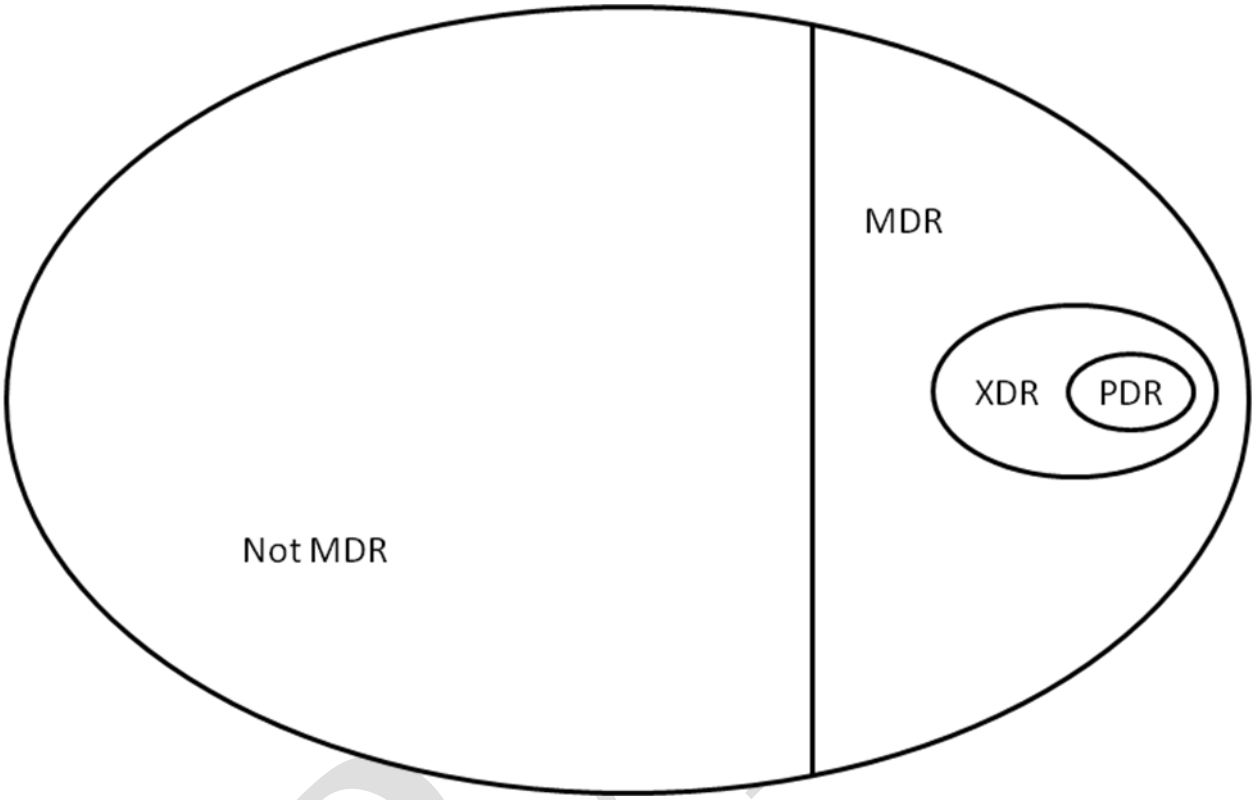


Figure 2. Diagram showing the relationship of MDR, XDR and PDR to each other



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