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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

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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.

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A bacterial isolate was considered non-susceptible to an antimicrobial agent when it tested resistant, intermediate or non-susceptible when using clinical breakpoints as interpretive criteria, and not epidemiological cut-offs, provided by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the Clinical and Laboratory Standards Institute (CLSI) [26,27] and/or the US Food and Drug Administration (FDA). Only acquired antimicrobial resistance was taken into consideration in creating definitions for MDR, XDR and PDR; intrinsic resistance was not addressed. Lists were later created, however, with organisms within specific organism groups (e.g. the *Enterobacteriaceae* and *Enterococcus* spp.) that are intrinsically resistant to certain antimicrobial agents. This was done to ensure that these antimicrobial agents would not be taken into account when applying the definitions for these organisms.

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: (i) to post the proposed definitions on the internet for broad discussion, comments and further consultations by medical professional societies and other expert groups; (ii) to pilot-test the proposed definitions by analysing a database that contained an adequate number of antimicrobial resistant organisms; (iii) to convene a second ECDC Joint Expert Meeting for further review; and (iv) to present the final proposed definitions to the ECDC Advisory Forum.

In May 2009 and March 2010 the second and third ECDC Joint Expert Meetings 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 the analyses that were subsequently performed will be available as supporting information, but are not included in this document.

This draft version was put on the web for public comments from 22 July until 22 August 2010. The final proposed definitions were presented to the ECDC Advisory Forum on 30 September 2010.

Previous Definitions Applied to Bacteria Resistant to Multiple Antimicrobial Agents

MDR

In literal 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 being used in order to characterize patterns of multidrug resistance in Gram-positive and Gram-negative organisms [10,16,17,28,29]. The absence of specific definitions for MDR in clinical study protocols gives rise to data that are difficult to compare.

One of the methods used by various authors and authorities to characterize organisms as MDR is based on *in vitro* antimicrobial susceptibility test results, when they test 'resistant to multiple antimicrobial agents, classes or subclasses of antimicrobial agents' [10,16,17,30]. The definition most frequently used for Gram-positive [16,31–34] and Gram-negative [10,18,30,35–37] bacteria 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.* [10], where the authors note that a sizeable number of studies do not propose any specific definitions for MDR, but the majority define MDR as 'resistant to three or more antimicrobial classes'.

Another method used to characterize bacteria as MDR, is when they are 'resistant to one key antimicrobial agent' [17,38]. These bacterial isolates may have public health importance due to resistance to only one key antimicrobial agent, but they often demonstrate cross or co-resistance to multiple classes of antimicrobials, which makes them MDR. 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; 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 not only to their resistance to multiple antimicrobial agents, but also to their 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 that 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 antimi-

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crobials 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 antimicrobial agents'. Definitions in the literature for PDR vary even though this term is etymologically exact and means that, in order for a particular species and a bacterial isolate of this species to be characterized as PDR, it must be tested and found to be resistant to all approved and useful agents. Examples of current definitions are: 'resistant to almost all commercially available antimicrobials', 'resistant to all antimicrobials routinely tested'

TABLE 1. *Staphylococcus aureus*; antimicrobial categories and agents used to define MDR, XDR and PDR (worksheet for categorizing isolates)

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)
Aminoglycosides	Gentamicin	
Ansamycins	Rifampin/rifampicin	
Anti-MRSA cephalosporins	Ceftaroline	
Anti-staphylococcal β-lactams (or cephamycins)	Oxacillin (or cefoxitin)[a]	
Fluoroquinolones	Ciprofloxacin	
	Moxifloxacin	
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole	
Fucidanes	Fusidic acid	
Glycopeptides	Vancomycin	
	Teicoplanin	
	Telavancin	
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): (i) an MRSA is always considered MDR by virtue of being an MRSA, (ii) non-susceptible to ≥1 agent in ≥3 antimicrobial categories.
XDR: non-susceptible to ≥1 agent in all but ≤2 categories.
PDR: non-susceptible to all antimicrobial agents listed.
[a]Oxacillin or cefoxitin represents all other β-lactams (and cephamycins) and resistance to either of these predicts non-susceptibility to all categories of β-lactam antimicrobials listed in this document, with the exception of the anti-MRSA cephalosporins (i.e. all categories of penicillins, cephalosporins, β-lactamase inhibitors and carbapenems currently approved up until 25 January 2011).
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TABLE 2. *Enterococcus* spp.; antimicrobial categories and agents used to define MDR, XDR and PDR (worksheet for categorizing isolates)

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)	Species with intrinsic resistance to antimicrobial categories (51)[a]
Aminoglycosides (except streptomycin)	Gentamicin (high level)		
Streptomycin	Streptomycin (high level)		
Carbapenems	Imipenem Meropenem Doripenem		*Enterococcus faecium*
Fluoroquinolones	Ciprofloxacin Levofloxacin Moxifloxacin		
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 all but ≤2 categories.
PDR: non-susceptible to all antimicrobial agents listed.
[a]When a species has intrinsic resistance to an antimicrobial category, that category must be removed from the list in this table 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.
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and 'resistant to all antibiotic classes available for empirical treatment' [10,43,44], 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: (i) how to create antimicrobial 'categories' that would be epidemiologically meaningful; (ii) how to select the antimicrobial categories and antimicrobial agents to be tested for each relevant bacterium; and (iii) 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) [45–47], antimicrobial subclasses, (e.g. third-generation cephalosporins) [48] or specific antimicrobial agents (e.g. ceftazidime) [49,50] 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 1–5 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,

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TABLE 3. ***Enterobacteriaceae*; antimicrobial categories and agents used to define MDR, XDR and PDR (worksheet for categorizing isolates)**

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)	Species with intrinsic resistance to antimicrobial agents or categories (51)[a]
Aminoglycosides	Gentamicin		*Providencia rettgeri* (*P. rettgeri*), *Providencia stuartii* (*P. stuartii*)
	Tobramycin		*P. rettgeri*, *P. stuartii*
	Amikacin		
	Netilmicin		*P. rettgeri*, *P. stuartii*
Anti-MRSA cephalosporins	Ceftaroline (approved only for *Escherichia.coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*)		
Antipseudomonal penicillins + β-lactamase inhibitors	Ticarcillin-clavulanic acid		*Escherichia hermannii* (*E. hermanii*)
	Piperacillin-tazobactam		*E. hermanii*
Carbapenems	Ertapenem		
	Imipenem		
	Meropenem		
	Doripenem		
Non-extended spectrum cephalosporins; 1st and 2nd generation 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; 3rd and 4th generation 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*
Fluoroquinolones	Ciprofloxacin		
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole		
Glycylcyclines	Tigecycline		*M. morganii*, *Proteus mirabilis* (*P. mirabilis*), *P. penneri*, *P. vulgaris*, *P. rettgeri*, *P. stuartii*
Monobactams	Aztreonam		
Penicillins	Ampicillin		*Citrobacter koseri* (*C. koseri*), *C. freundii*, *E. aerogenes*, *E. cloacae*, *E. hermanii*, *H. alvei*, *Klebsiellae* spp., *M. morganii*, *P. penneri*, *P. vulgaris*, *P. rettgeri*, *P. stuartii*, *S. marcescens*
Penicillins + β-lactamase 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*, *P. mirabilis*, *P. penneri*, *P. vulgaris*, *P. rettgeri*, *P. stuartii*, *S. marcescens*

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TABLE 3. Continued

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)	Species with intrinsic resistance to antimicrobial agents or categories (51)[a]
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 categories.
PDR: non-susceptible to all antimicrobial agents listed.
[a]When a species has intrinsic resistance to an antimicrobial agent or to the whole category, that agent or category must be removed from the list in this table 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.
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TABLE 4. *Pseudomonas aeruginosa*; antimicrobial categories and agents used to define MDR, XDR and PDR (worksheet for categorizing isolates)

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 + β-lactamase 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 all but ≤2 categories.
PDR: non-susceptible to all antimicrobial agents listed.
http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx.

XDR and PDR. These lists were designed to be as comprehensive as possible and reflect antimicrobial agents and testing practices currently 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

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TABLE 5. *Acinetobacter* spp.; antimicrobial categories and agents used to define MDR, XDR and PDR (worksheet for categorizing isolates)

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 + β-lactamase inhibitors	Piperacillin-tazobactam	
	Ticarcillin-clavulanic acid	
Extended-spectrum cephalosporins	Cefotaxime	
	Ceftriaxone	
	Ceftazidime	
	Cefepime	
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole	
Penicillins + β-lactamase 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 all but ≤2 categories.
PDR: non-susceptible to all antimicrobial agents listed.
http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx.

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 [51] and also by applying specific inclusion and exclusion criteria. The inclusion criteria required that each antimicrobial agent: (i) was currently approved as an antibacterial agent in humans by the European Medicines Agency (EMA) or the FDA; and (ii) had breakpoints for the organism or organism group established by either EUCAST [51], CLSI [26] or the FDA. An antimicrobial agent was excluded from an organism/organism group list if: (i) the organism or the whole organism group was intrinsically resistant to the agent; (ii) the agent achieved therapeutic concentrations only in urine (e.g. nitrofurantoin); or (iii) the organism exhibits widespread acquired resistance to the agent (e.g. penicillin for *S. aureus*). A noteworthy example of an antimicrobial agent that did not meet the criteria for inclusion is tigecycline, which does not have species-specific breakpoints for Acinetobacter *spp*. and was therefore, not included in Table 5.

Although this document does not address definitions for individual bacterial species that are intrinsically resistant to

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TABLE 6. 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 1[a]	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1.	Non-susceptibility to all agents in all antimicrobial categories for each bacterium in Tables 1–5
Enterococcus spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 2	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 2.	
Enterobacteriaceae	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 3	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 3.	
Pseudomonas aeruginosa	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 4	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 4.	
Acinetobacter spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 5	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 5.	

[a]All isolates are defined as MDR because resistance to oxacillin or cefoxitin predicts non-susceptibility to all categories of β-lactam antimicrobials listed in this document, with the exception of the anti-MRSA cephalosporins (i.e. all categories of penicillins, cephalosporins, β-lactamase inhibitors and carbapenems currently approved up until 25 January 2011).
http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx.

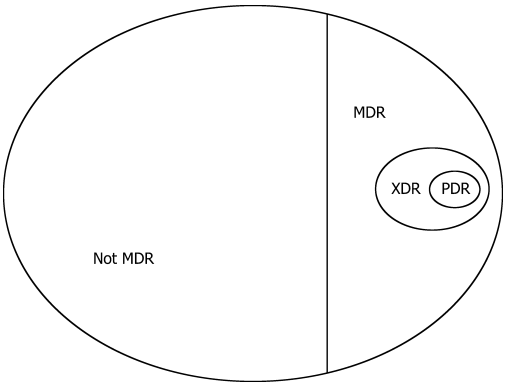


FIG. 1. Diagram showing the relationship of MDR, XDR and PDR to each other.

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 2 and 3 listing those organisms that have intrinsic resistance to the antimicrobial agent or category listed in that row [51].

Finally, available rules of partial or complete cross-resistance from EUCAST [51] 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 tested and found to be non-susceptible to ciprofloxacin, it is considered non-susceptible to all fluoroquinolones [51,52]. Similarly, a *S. aureus* isolate is considered non-susceptible to all lincosamides when it tests non-susceptible to clindamycin [51,53]. When rules of full cross-resistance could be applied to an antimicrobial category in Tables 1–5, one agent only from that category was proposed for antimicrobial susceptibility testing.

Defining antimicrobial resistance within an antimicrobial category

In the definitions proposed for MDR and XDR in this document, a bacterial isolate is considered resistant to an antimicrobial category when it is 'non-susceptible to at least one agent in a category'. Thus, resistance of a bacterial isolate to only one agent within a category is proposed as a crude indicator of antimicrobial resistance to the entire category.

In support of this approach used by the National Healthcare Safety Network (NHSN) a bacterial isolate is considered resistant to a 'class' when it is resistant to one or more antimicrobial agents within that 'class' [17,30]. Thus, according to this definition, carbapenem resistance in *Klebsiella* spp. would be defined as 'resistance to imipenem or meropenem or 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 6. For all three definitions, non-susceptibility refers to either a resistant, intermediate or non-susceptible result obtained from *in vitro* antimicrobial susceptibility testing.

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TABLE 7. ***Pseudomonas aeruginosa*; examples of antimicrobial susceptibility profiles that fit MDR, XDR and PDR definitions; isolate no. 1 is PDR; isolate no. 2 is XDR and isolate no. 3 is MDR**

Antimicrobial category	Antimicrobial agent	Isolate no. 1 (PDR)	Isolate no. 2 (XDR)	Isolate no. 3 (MDR)
Aminoglycosides	Gentamicin	X[a]	X	
	Tobramycin	X	[b]	
	Amikacin	X		
	Netilmicin	X		
Antipseudomonal carbapenems	Imipenem	X	X	X
	Meropenem	X	X	
	Doripenem	X	X	
Antipseudomonal cephalosporins	Ceftazidime	X		X
	Cefepime	X	X	
Antipseudomonal fluoroquinolones	Ciprofloxacin	X	X	X
	Levofloxacin	X		
Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam	X		
	Ticarcillin-clavulanic acid	X	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 all but ≤2 categories.
PDR: non-susceptible to all antimicrobial agents listed.
[a]X = non-susceptible to the antimicrobial agent.
[b]Absence of an 'X' means the antimicrobial agent was either 'susceptible' or 'not tested'.
http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx.

MDR is defined as non-susceptibility to at least one agent in three or more antimicrobial categories. XDR is 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). PDR is defined as non-susceptibility to all agents in all antimicrobial categories (i.e. no agents tested as susceptible for that organism). Thus, a bacterial isolate that is characterized as XDR will also be characterized as MDR. Similarly, a bacterial isolate would have to be XDR in order for it to be further defined as PDR. Fig. 1 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 antimicrobial agents that have activity against these strains. One example is presented in Table 7 for *P. aeruginosa.* Fig. 2 shows additional examples of possible antimicrobial susceptibility patterns that can fall under the definitions for MDR, XDR and PDR.

Within the definition for MDR, a unique rule was applied when defining antimicrobial resistance for a *S. aureus* isolate that is an MRSA. Finding an isolate resistant to oxacillin or cefoxitin predicts non-susceptibility to all categories of β-lactam antimicrobials listed in this document, with the exception of the anti-MRSA cephalosporins (i.e. all categories of penicillins, cephalosporins, β-lactamase inhibitors and carbapenems, currently approved up until 25 January 2011). An MRSA isolate thus will always be characterized as MDR because it meets the definition for MDR, 'non-susceptible to at least one antimicrobial agent in three or more categories'. 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

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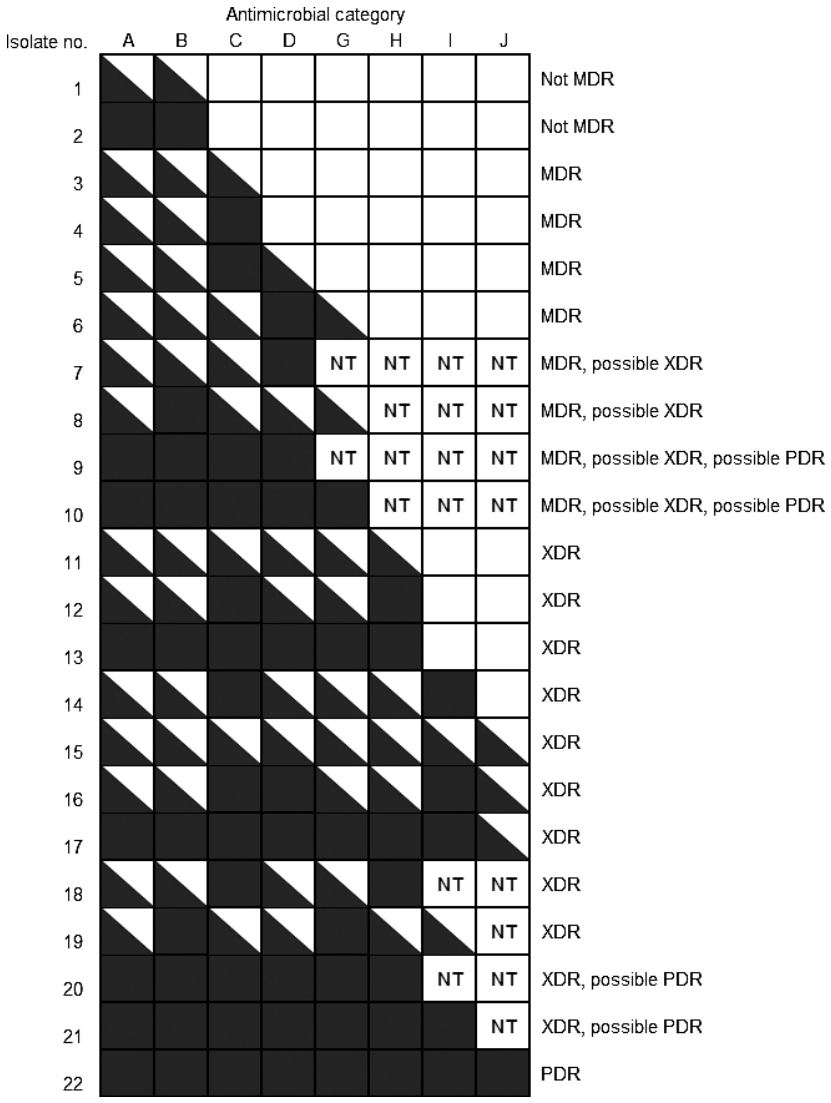


FIG. 2. Examples of 22 possible antimicrobial susceptibility patterns that can fall under the proposed definitions for MDR, XDR and PDR. □, the isolate is susceptible to all agents listed in category; ◺, the isolate is non-susceptible to some, but not all agents listed in category; ■, the isolate is non-susceptible to all agents listed in category; NT, the isolate was not tested for susceptibility to any agent listed in this category.

are susceptible to only one or two categories of antimicrobial agents. In contrast to MDR and XDR, however, it is necessary to test every antimicrobial agent listed for the respective organism or organism group in Tables 1–5 in order to conclusively characterize a bacterial isolate as PDR.

Applicability and Limitations 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 note that overall a bacterial isolate will be considered non-susceptible to an antimicrobial agent or antimicrobial category, when it is found to be 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 applying the definitions for MDR, XDR and PDR.

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 against all or nearly all of the antimicrobial agents within the antimicrobial categories listed in Tables 1–5. Laboratories that utilize selective reporting protocols must make sure that results from all the antimicrobial

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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 [30]. In cases of incomplete testing, bacterial isolates can only be characterized as 'possible XDR' or 'possible PDR' and these results cannot be compared with other 'possible XDR','possible PDR' or 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 of 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 1–5 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' isolate is encountered. This additional testing might be carried out 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.

When using 'MDR' as a measure of epidemiological or public health significance, it will be important to understand one of the limitations in the construction of the definition of MDR proposed in this document, which also exists for those definitions currently found in the literature. Bacterial isolates that are MDR will have many different resistance profiles because by definition, non-susceptible results for even a single agent in only three antimicrobial categories defines an organism as MDR. For example, two *E. coli* isolates, one resistant to trimethoprim-sulphamethoxazole, cefazolin and ciprofloxacin and the other to ertapenem, gentamicin and tigecycline, will both be characterized as MDR even though the agents are different. Further characterizing of resistance in bacteria that are MDR, based on the agents to which they are resistant, is beyond the scope of these definitions.

Moreover, it must be emphasized that although MDR is an important characterization of multidrug resistance, in this era of extreme resistance and despite differences in the interpretation of MDR that can depend on geographical area and endemicity, countries should place high importance on monitoring resistant bacteria that are XDR and PDR because of their public health impact.

Conclusions

Applying these definitions for MDR, XDR and PDR worldwide would allow comparability of data 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 number of 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 list of antimicrobial agents found in Tables 1–5 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. As the title of the document indicates, these are interim definitions that, we hope, will provide some initial direction for clinicians, medical laboratory technicians and researchers alike. As the definitions are applied, we will learn more about their potential strengths, limitations and applications in various settings. These lessons learned will not only advance our understanding of drug-resistant bacteria, but will also help shape future iterations of these definitions.

Updates of this document will be posted, when performed, on the website of the European Centre for Disease Prevention and Control. For access to these updates and to download tables which can be used as worksheets, please go to: http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx.

Transparency Declaration

Y. Carmeli reports being a consultant for various pharmaceutical and diagnostic companies. M. E. Falagas reports sit-

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ting on the advisory boards of Pfizer, Astellas, Bayer/Nectar pharmaceutical companies: Merck, AstraZeneca, Novartis, Cipla and Grunenthal. C. G. Giske has received consulting fees and speaker honoraria from Wyeth Pharmaceuticals. S. Harbarth has received consulting fees and speaker honoraria from DaVolterra, BioMerieux and Destiny Pharma. J. F. Hindler reports being a consultant for the Association of Public Health Laboratories, and a member of Forest Laboratories Microbiology Advisory Board. She has also received honoraria from: bioMerieux, Inc., BD Diagnostics and Siemens Healthcare Diagnostics. D. L. Paterson reports receiving consultancy fees from Leo Pharmaceuticals, Merck, AstraZeneca, Novartis, Johnson & Johnson and that his institution has received funds from Novartis. Louis B. Rice reports consulting agreements with Theradoc and with Tetrapase Pharmaceuticals and that he has received speaker honoraria from Pfizer in the last year. M. J. Struelens reports consultancies and advisory board participation in the last 3 years with Wyeth, Novartis and Biomérieux, and research and epidemiological survey grants to his previous institution from Pfizer, Novartis and Biomérieux. None of the authors have received any financial support for this work or has any affiliations associated with any conflicts of interest with this manuscript.

References

1. Anderson DJ, Engemann JJ, Harrell LJ, Carmeli Y, Reller LB, Kaye KS. Predictors of mortality in patients with bloodstream infection due to ceftazidime-resistant *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2006; 50: 1715–1720.
2. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis* 2003; 36: 53–59.
3. Roberts RR, Hota B, Ahmad I *et al.* Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. *Clin Infect Dis* 2009; 49: 1175–1184.
4. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000; 118: 146–155.
5. McGowan JJE. Resistance in nonfermenting gram-negative bacteria: multidrug resistance to the maximum. *Am J Med* 2006; 119 (suppl 1): 29–36.
6. Bonomo RA, Szabo D. Mechanisms of multidrug resistance in *Acinetobacter* species and *Pseudomonas aeruginosa*. *Clin Infect Dis* 2006; 43 (suppl 2): 49–56.
7. Pitout JDD, Laupland KB. Extended-spectrum [beta]-lactamase-producing *Enterobacteriaceae*: an emerging public-health concern. *Lancet Infect Dis* 2008; 8: 159–166.
8. European Centre for Disease Prevention and Control/European Medicines Agency. ECDC/EMEA joint technical report: the bacterial challenge: time to react.: European centre for disease prevention and control & European medicines agency, Stockholm, Sweden & London, United Kingdom, 2009.
9. Boucher HW, Talbot GH, Bradley JS *et al.* Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 48: 1–12.
10. Falagas ME, Koletsi PK, Bliziotis IA. The diversity of definitions of multidrug-resistant (MDR) and pandrug-resistant (PDR) *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *J Med Microbiol* 2006; 55: 1619–1629.
11. Goossens H. Susceptibility of multi-drug-resistant *Pseudomonas aeruginosa* in intensive care units: results from the European MYSTIC study group. *Clin Microbiol Infect* 2003; 9: 980–983.
12. Falagas ME, Karageorgopoulos DE. Pandrug resistance (PDR), extensive drug resistance (XDR), and multidrug resistance (MDR) among gram-negative bacilli: need for international harmonization in terminology. *Clin Infect Dis* 2008; 46: 1121–1122.
13. Apisarnthanarak A, Pinitchai U, Thongphubeth K, Yuekyen C, Warren DK, Fraser VJ. A multifaceted intervention to reduce pandrug-resistant *Acinetobacter baumannii* colonization and infection in 3 intensive care units in a Thai tertiary care center: a 3-year study. *Clin Infect Dis* 2008; 47: 760–767.
14. Doi Y, Husain S, Potoski BA, McCurry KR, Paterson DL. Extensively drug-resistant *Acinetobacter baumannii*. *Emerg Infect Dis* 2009; 15: 980–982.
15. Park YK, Peck KR, Cheong HS, Chung DR, Song JH, Ko KS. Extreme drug resistance in *Acinetobacter baumannii* infections in intensive care units, South Korea. *Emerg Infect Dis* 2009; 15: 1325–1327.
16. Cohen AL, Calfee D, Fridkin SK *et al.* Recommendations for metrics for multidrug-resistant organisms in healthcare settings: SHEA/HICPAC Position paper. *Infect Control Hosp Epidemiol* 2008; 29: 901–913.
17. Hidron AI, Edwards JR, Patel J *et al.* NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infect Control Hosp Epidemiol* 2008; 29: 996–1011.
18. Paterson David L, Doi Y. A step closer to extreme drug resistance (XDR) in gram-negative bacilli. *Clin Infect Dis* 2007; 45: 1179–1181.
19. Carmeli Y, Akova M, Cornaglia G *et al.* Controlling the spread of carbapenemase-producing Gram-negatives: therapeutic approach and infection control. *Clin Microbiol Infect* 2010; 16: 102–111.
20. The Alliance for the Student use of Antibiotics. Executive summary: select findings, conclusions, and policy recommendations. *Clin Infect Dis* 2005; 41 (suppl 4): 224–227.
21. Jones RN, Masterton R. Determining the value of antimicrobial surveillance programs. *Diagn Microbiol Infect Dis* 2001; 41: 171–175.
22. Tapsall JW, Ndowa F, Lewis DA, Unemo M. Meeting the public health challenge of multidrug- and extensively drug-resistant *Neisseria gonorrhoeae*. *Expert Rev Anti Infect Ther* 2009; 7: 821–834.
23. Richter SS, Heilmann KP, Dohrn CL, Riahi F, Beekmann SE, Doern GV. Changing epidemiology of antimicrobial-resistant *Streptococcus pneumoniae* in the United States, 2004-2005. *Clin Infect Dis* 2009; 48: e23–e33.
24. Parry CM, Threlfall EJ. Antimicrobial resistance in typhoidal and nontyphoidal salmonellae. *Curr Opin Infect Dis* 2008; 21: 531–538, doi: 10.1097/QCO.0b013e32830f453a.
25. Hendriksen RS, Mikoleit M, Carlson VP *et al.* WHO Global Salm-Surv external quality assurance system for serotyping of *Salmonella* isolates from 2000 to 2007. *J Clin Microbiol* 2009; 47: 2729–2736.
26. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing; nineteenth informational supplement*. CLSI document M100-S19, Wayne, Pa: Clinical and Laboratory Standards Institute, 2009; 29(3).
27. European Committee on Antimicrobial Susceptibility Testing (EUCAST). *Breakpoint tables for interpretation of MICs and zone diameters*.

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2008; Available at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Disk_test_documents/EUCAST_breakpoints_v1.1 (updated 27 April, 2010; last accessed 29 October, 2010).
28. MacGowan AP, on behalf of the BWPoRS. Clinical implications of antimicrobial resistance for therapy. *J Antimicrob Chemother* 2008; 62 (suppl 2): 105–114.
29. Paterson DL. The epidemiological profile of infections with multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species. *Clin Infect Dis* 2006; 43 (suppl 2): 43–48.
30. Kallen AJ, Hidron AI, Patel J, Srinivasan A. Multidrug resistance among gram-negative pathogens that caused healthcare-associated infections reported to the National Healthcare Safety Network, 2006-2008. *Infect Control Hosp Epidemiol* 2010; 31: 528–531.
31. Pillar CM, Draghi DC, Sheehan DJ, Sahm DF. Prevalence of multidrug-resistant, methicillin-resistant *Staphylococcus aureus* in the United States: findings of the stratified analysis of the 2004 to 2005 LEADER Surveillance Programs. *Diagn Microbiol Infect Dis* 2008; 60: 221–224.
32. Seas C, Hernandez K, Ramos R *et al.* Oxacillin-resistant and multidrug-resistant *Staphylococcus aureus* in Lima, Peru. *Infect Control Hosp Epidemiol* 2006; 27: 198–200.
33. Jeong HY, Lee JE, Choi BK *et al.* Molecular epidemiology of community-associated antimicrobial-resistant *Staphylococcus aureus* in Seoul, Korea (2003): pervasiveness of multidrug-resistant SCCmec type II methicillin-resistant *S. aureus*. *Microb Drug Resist* 2007; 13: 178–185.
34. Critchley IA, Draghi DC, Sahm DF, Thornsberry C, Jones ME, Karlowsky JA. Activity of daptomycin against susceptible and multidrug-resistant Gram-positive pathogens collected in the SECURE study (Europe) during 2000–2001. *J Antimicrob Chemother* 2003; 51: 639–649.
35. O'Fallon E, Gautam S, D'Agata EMC. Colonization with multidrug-resistant gram-negative bacteria: prolonged duration and frequent cocolonization. *Clin Infect Dis* 2009; 48: 1375–1381.
36. Andrade SS, Jones RN, Gales AC, Sader HS. Increasing prevalence of antimicrobial resistance among *Pseudomonas aeruginosa* isolates in Latin American medical centres: 5 year report of the SENTRY Antimicrobial Surveillance Program (1997–2001). *J Antimicrob Chemother* 2003; 52: 140–141.
37. Gould IM. The epidemiology of antibiotic resistance. *Int J Antimicrob Agents* 2008; 32 (suppl 1): 2–9.
38. Siegel JD, Rhinehart E, Jackson M, Chiarello L. Management of multidrug-resistant organisms in health care settings, 2006. *Am J Infect Control* 2007; 35 (suppl 2): 165–193.
39. Brink A, Feldman C, Richards G, Moolman J, Senekal M. Emergence of extensive drug resistance (XDR) among Gram-negative bacilli in South Africa looms nearer. *S Afr Med J* 2008; 98: 586, 8, 90 passim.
40. Tseng YC, Wang JT, Wu FL, Chen YC, Chie WC, Chang SC. Prognosis of adult patients with bacteremia caused by extensively resistant *Acinetobacter baumannii*. *Diagn Microbiol Infect Dis* 2007; 59: 181–190.
41. CDC. Emergence of *Mycobacterium tuberculosis* with extensive resistsance to second-line drugs – Worldwide, 2000–2004. *MMWR Morb Mortal Wkly Rep* 2006; 55: 301–305.
42. CDC. Notice to readers: revised definition of extensively drug-resistant tuberculosis. *MMWR Morb Mortal Wkly Rep* 2006; 55: 1176.
43. Kuo LC, Teng LJ, Yu CJ, Ho SW, Hsueh PR. Dissemination of a clone of unusual phenotype of pandrug-resistant *Acinetobacter baumannii* at a university hospital in Taiwan. *J Clin Microbiol* 2004; 42: 1759–1763.
44. Kuo LC, Yu CJ, Lee LN *et al.* Clinical features of pandrug-resistant *Acinetobacter baumannii* bacteremia at a university hospital in Taiwan. *J Formos Med Assoc* 2003; 102: 601–606.
45. Ortega B, Groeneveld AB, Schultsz C. Endemic multidrug-resistant *Pseudomonas aeruginosa* in critically ill patients. *Infect Control Hosp Epidemiol* 2004; 25: 825–831.
46. Lang BJ, Aaron SD, Ferris W, Hebert PC, MacDonald NE. Multiple combination bactericidal antibiotic testing for patients with cystic fibrosis infected with multiresistant strains of *Pseudomonas aeruginosa*. *Am J Respir Crit Care Med* 2000; 162: 2241–2245.
47. Davies G, McShane D, Davies JC, Bush A. Multiresistant *Pseudomonas aeruginosa* in a pediatric cystic fibrosis center: natural history and implications for segregation. *Pediatr Pulmonol* 2003; 35: 253–256.
48. Dubois V, Arpin C, Melon M *et al.* Nosocomial outbreak Due to a multiresistant strain of *Pseudomonas aeruginosa* P12: efficacy of cefepime-amikacin therapy and analysis of {beta}-lactam resistance. *J Clin Microbiol* 2001; 39: 2072–2078.
49. Pagani L, Colinon C, Migliavacca R *et al.* Nosocomial outbreak caused by multidrug-resistant *Pseudomonas aeruginosa* producing IMP-13 metallo-{beta}-Lactamase. *J Clin Microbiol* 2005; 43: 3824–3828.
50. Jung R, Fish DN, Obritsch MD, MacLaren R. Surveillance of multidrug resistant *Pseudomonas aeruginosa* in an urban tertiary-care teaching hospital. *J Hosp Infect* 2004; 57: 105–111.
51. European Committee on Antimicrobial Susceptibility Testing (EUCAST). *Expert rules in antimicrobial susceptibility testing*, 2008, Available from: http://www.eucast.org/fileadmin/src/media/PDFs/4ESCMID_Library/3Publications/EUCAST_Documents/Other_Documents/EUCAST_Expert_rules_final_April_20080407.pdf (updated April, 2008; last accessed 28 October 2010)
52. Komp Lindgren P, Karlsson A, Hughes D. Mutation rate and evolution of fluoroquinolone resistance in *Escherichia coli* isolates from patients with urinary tract infections. *Antimicrob Agents Chemother* 2003; 47: 3222–3232.
53. Leclercq R. Mechanisms of resistance to macrolides and lincosamides: nature of the resistance elements and their clinical implications. *Clin Infect Dis* 2002; 34: 482–492.

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