Multi drug resistance (MDR)
Extensively drug resistance (XDR)
Pan-resistance (PDR) :
definitions and limits

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Paris, France

MDR-TB definition (WHO)

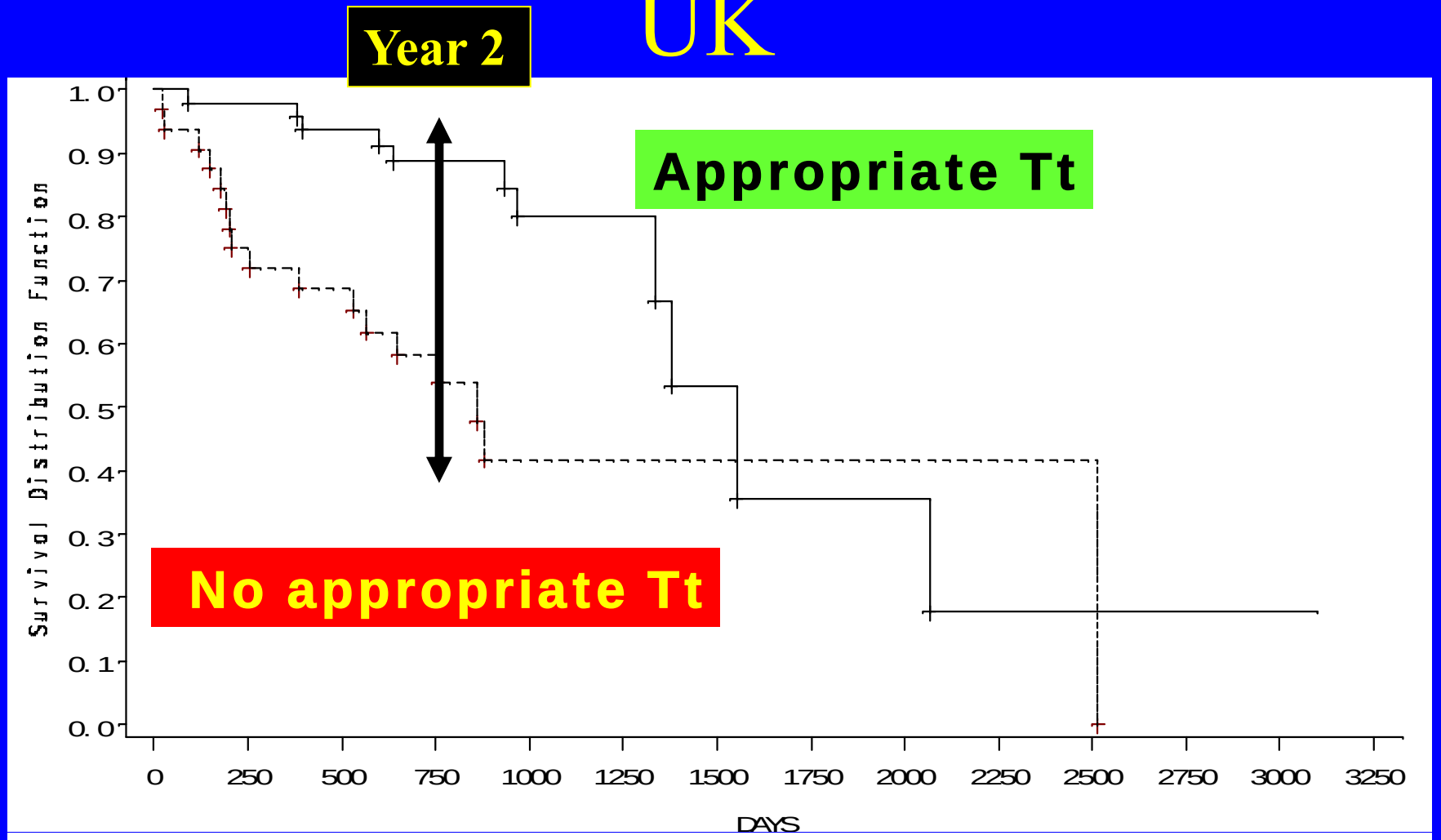
Resistance to INH and RIF

2 major antituberculous drugs :

Isoniazid (INH)

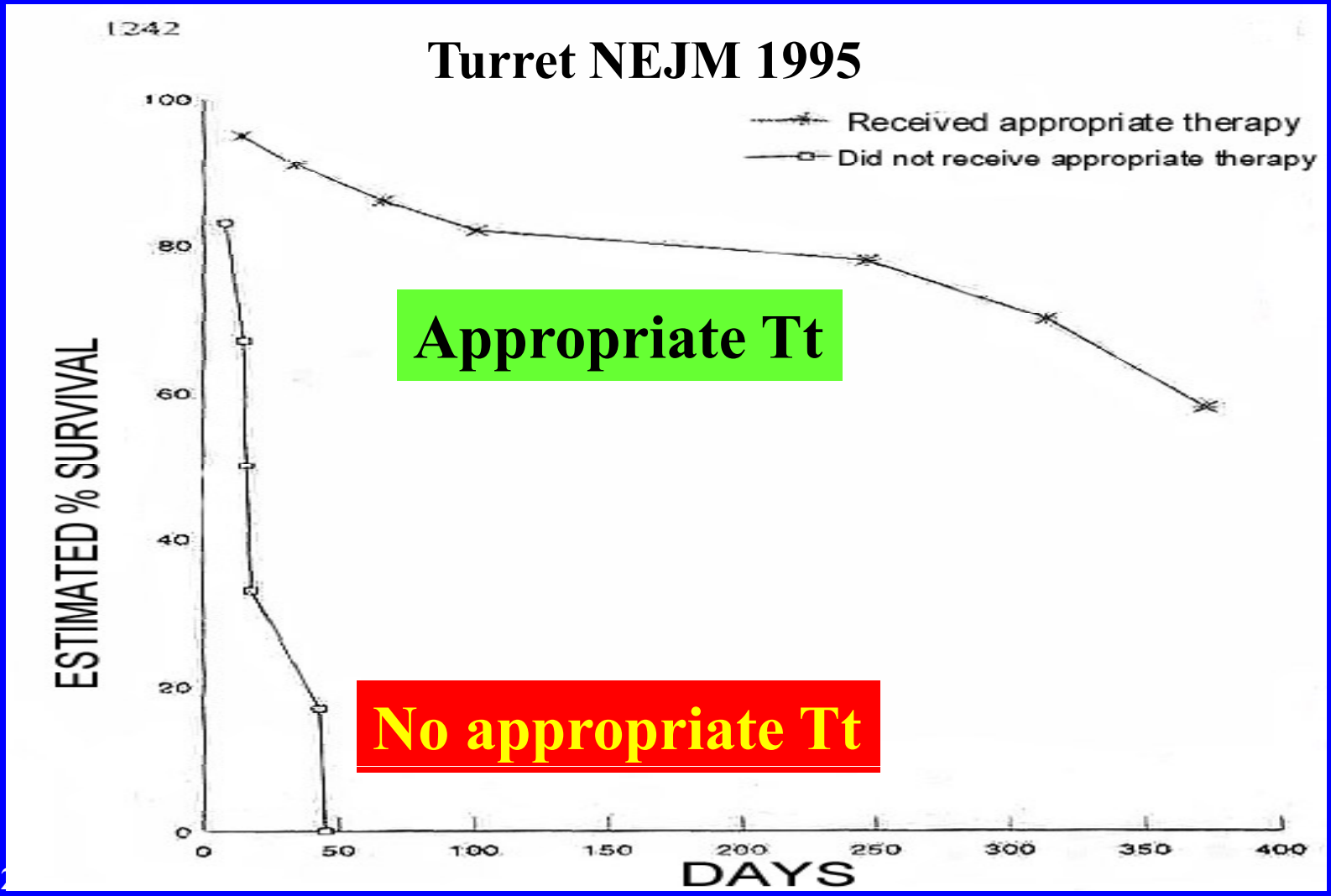
Rifampicine (RIF)

Survival of MD-RTB in the 1990s UK



Drobniewski, Thorax 2002, 90 MDRTB patients

Survival of HIV-associated MDR-TB in the 1990s New York city, USA



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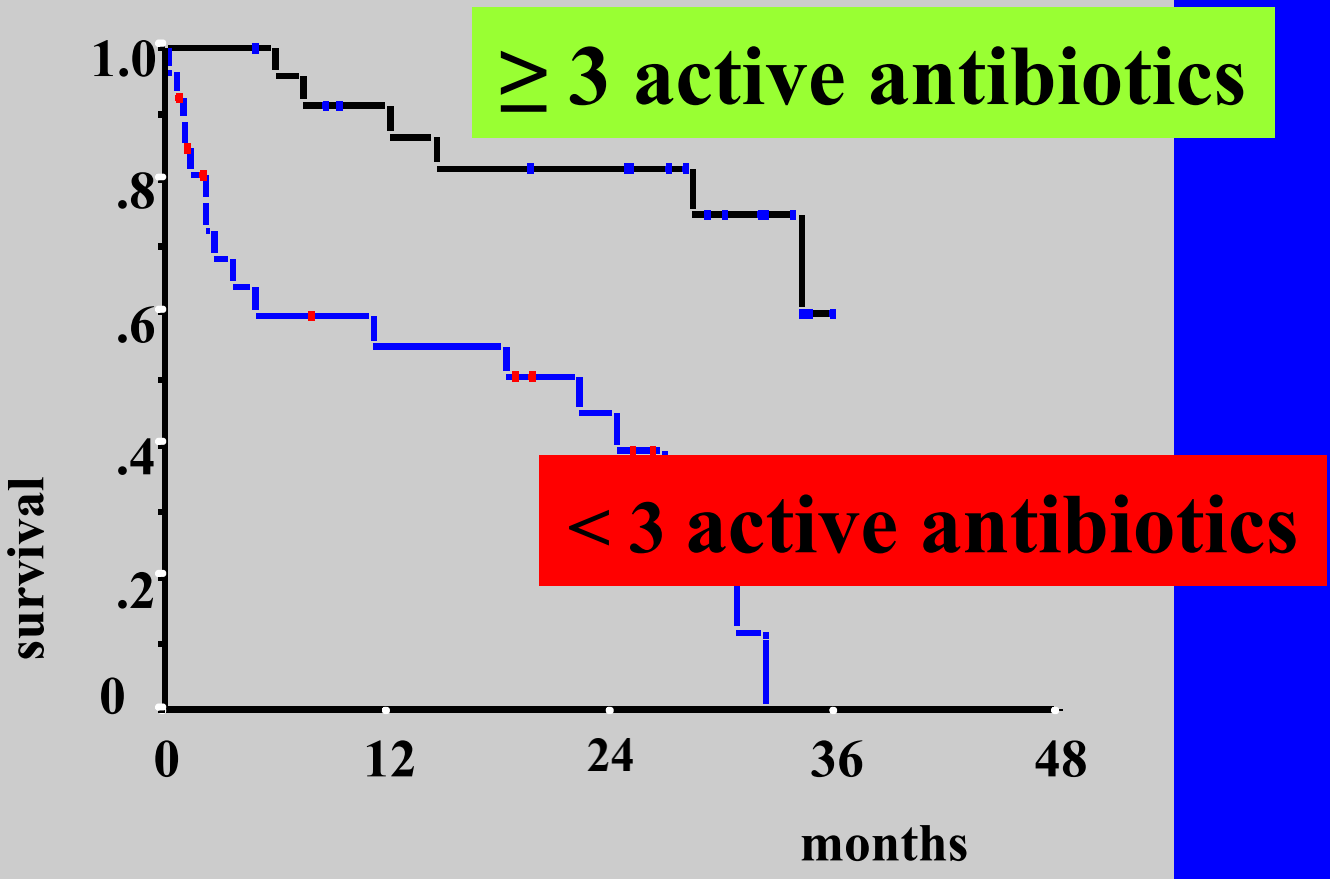
Outcome of MDR cases diagnosed in 1994 in France (n=51) depending on the number of active drugs used



Flament-Saillour AJRCCM 1999

Outcome of MDR-TB France

	1994 (n=51)*	1999 (n= 45)**	2006 (n= 53)***
No of tested drugs (including STR, EMB)	5	8	11
Treatment with > 3 active drugs	47%	84%	85%
Succes	41%	67%	> 70%

*** Saillour Am Resp Crit Care Med 1999 : non specialized teams**

**** Uffredi Inter J Antibiot 2006 : specialized team (lab/physicians)**

***** Veziris 2008 : specialized team (idem but systematic)**

MDR TB, WHO 4th report 2008

- Estimated MDR cases in the world in 2006 (based on DST of 91,577 patients) :

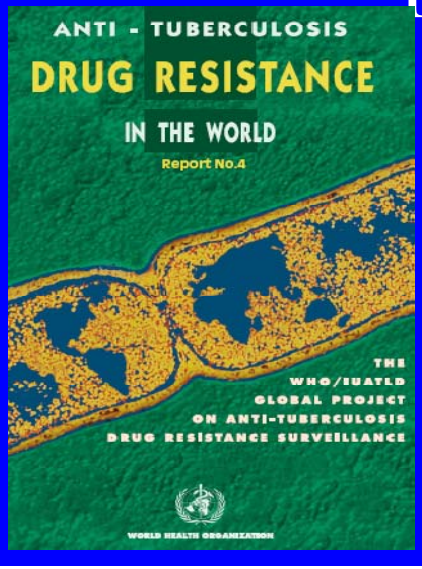
489,139

(95% CLs : 455 to 614,000)

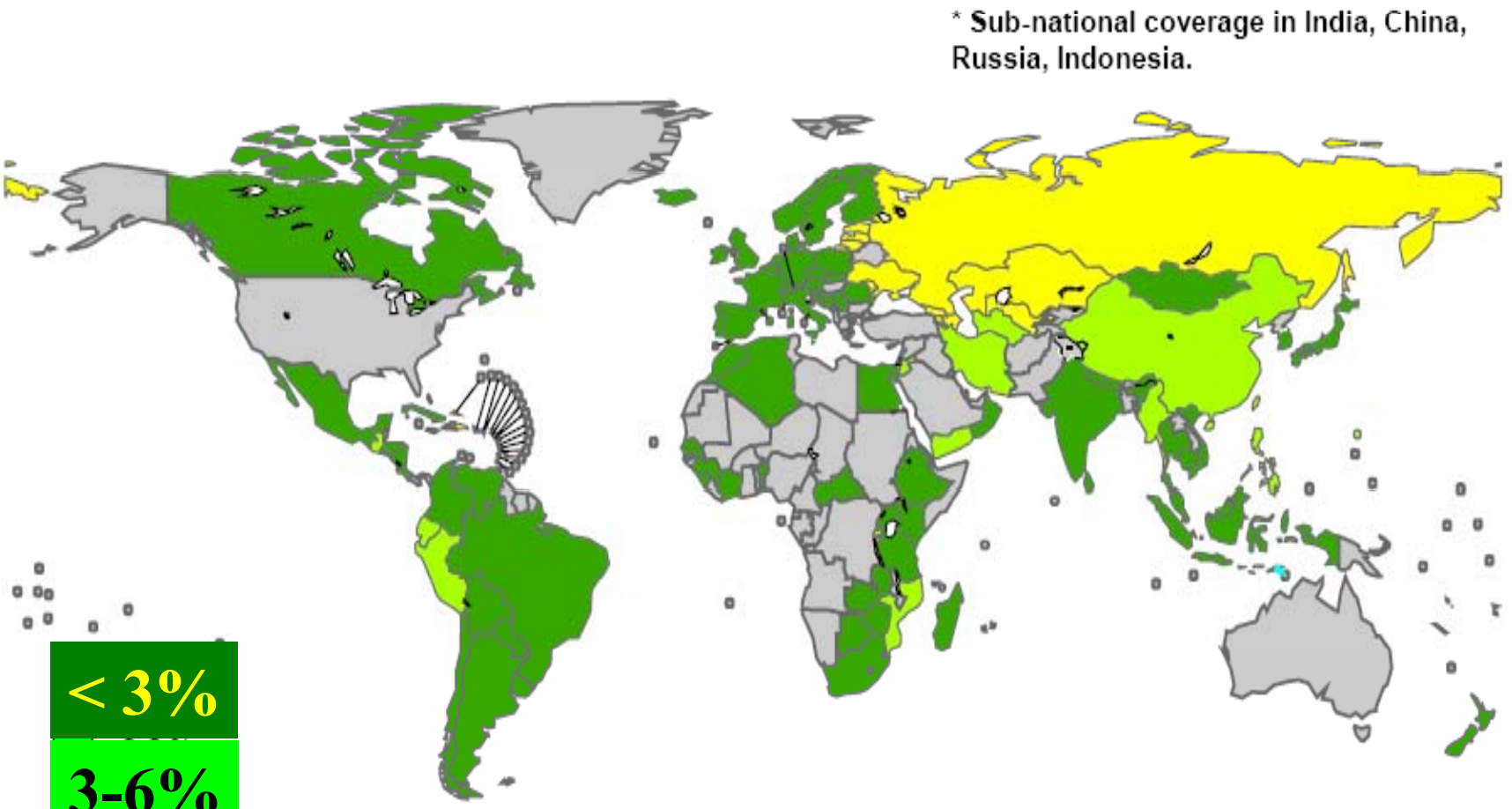
- Global proportion of MDR in all TB cases :

4.8 %

(95% CLs : 4.6 to 6.0)



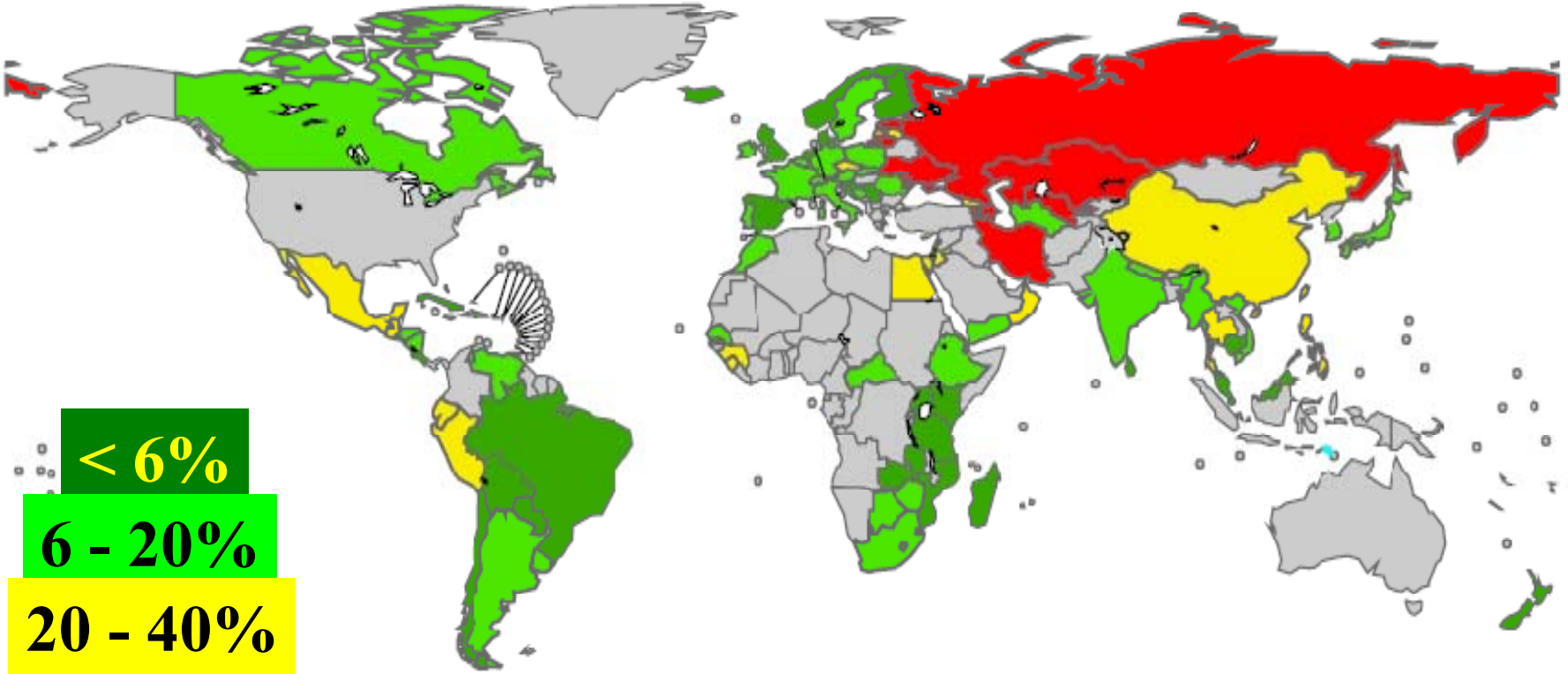
MDR-TB **in new cases** 1994-2007 (in %)



WHO 4th Report 2008

MDR-TB in previously treated cases 1994-2007 (in %)

* Sub-national coverage in India, China, Russia, Indonesia.



WHO 4th Report

TB Extensive Resistance to 2nd line Drugs (CDC, MMWR March 2006)

XDR = resistance to :

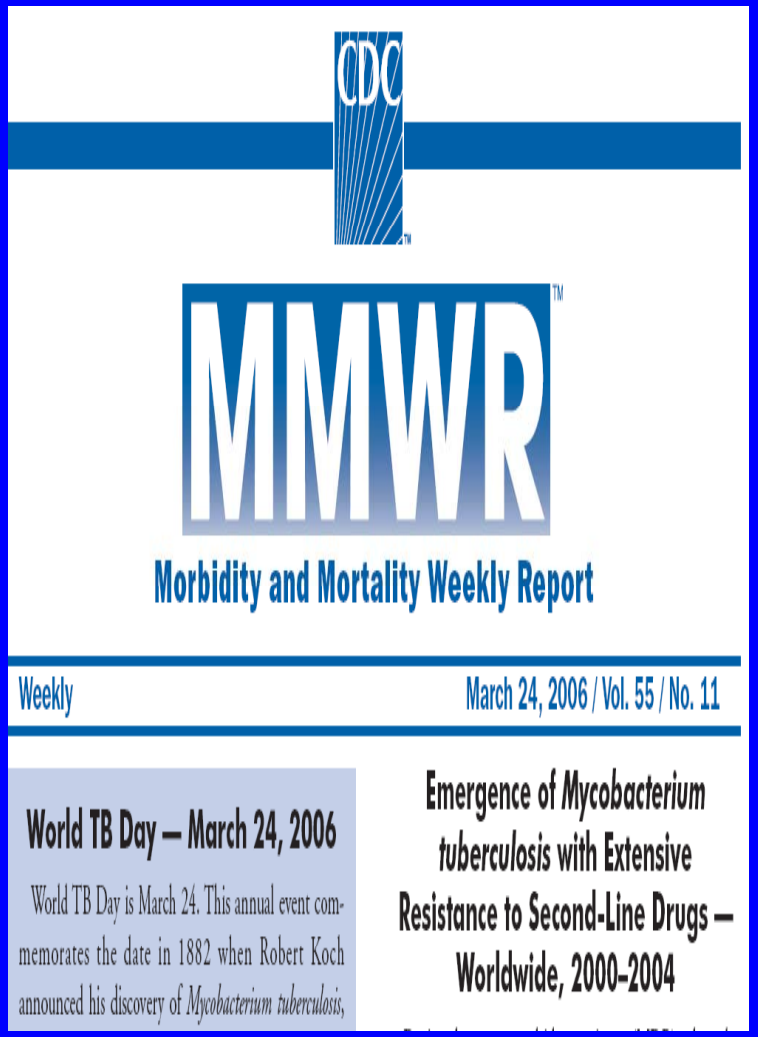
INH **and** RIF

(MDR)

and at least to

3 of the 6 main classes of second line drugs

("first definition")


CDC

MMWR

Morbidity and Mortality Weekly Report

Weekly March 24, 2006 / Vol. 55 / No. 11

World TB Day – March 24, 2006

World TB Day is March 24. This annual event commemorates the date in 1882 when Robert Koch announced his discovery of *Mycobacterium tuberculosis*,

Emergence of *Mycobacterium tuberculosis* with Extensive Resistance to Second-Line Drugs – Worldwide, 2000-2004

Main antituberculous drugs for MDR

Ethambutol*

Pyrazinamide

Ethionamide* (R peut être croisée INH)

Aminoglycosides

Fluoroquinolones

PAS

Cycloserine

Thiacetazone

Revised Definition XDR-TB October 2006

XDR = resistance to :

INH and RIF (MDR-TB)

and

amikacin, kanamycin or capreomycin

(injectable agents other than streptomycin)

and

fluroquinolones

Outcome (%) of MDR et XDR Lithuania (old and new definitions)

	cure*	**failure**
MDR	67	**13**
XDR (old definition**)	58	**30**
XDR (new definition***)	28	**55**

- completed treatment

** R to 3 2nd line drugs

*** R to FQs and 1 injectable

Lemaine UICT 2006

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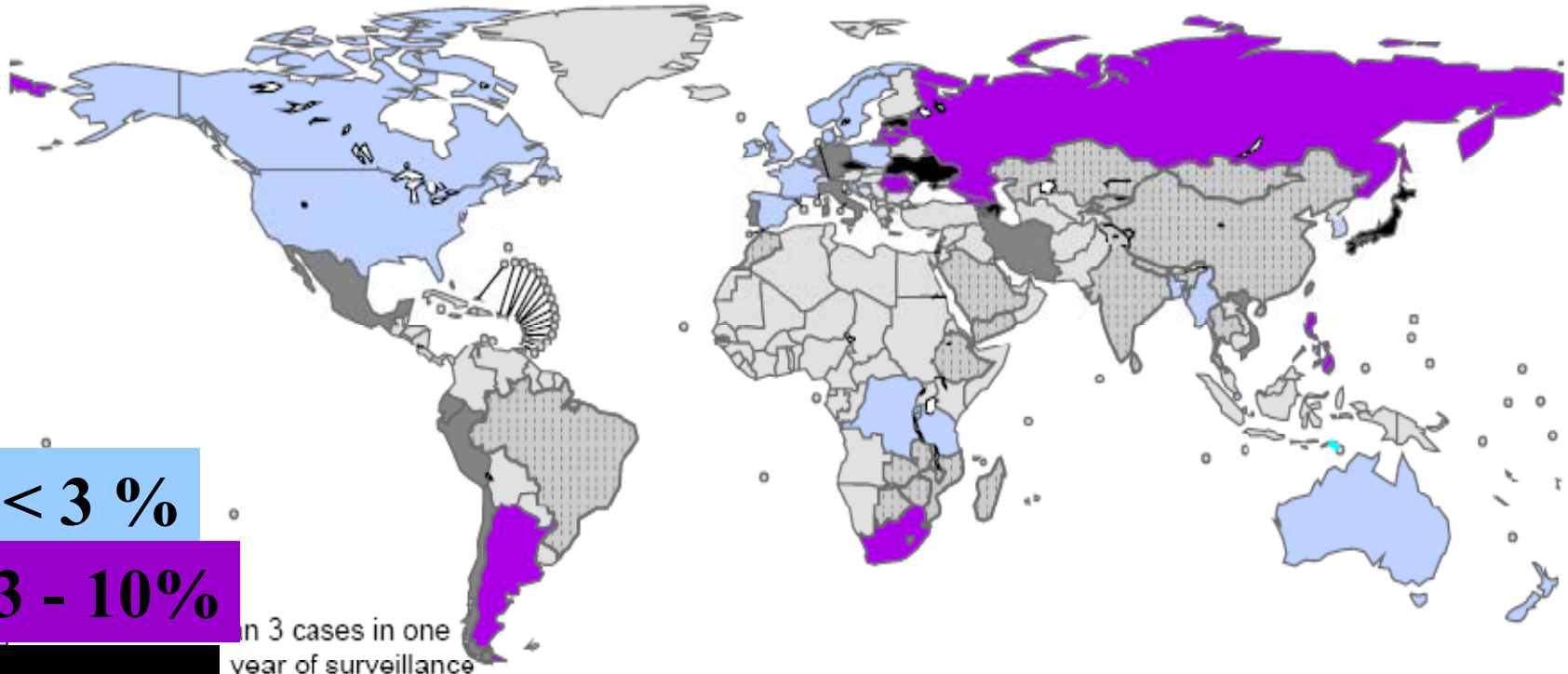
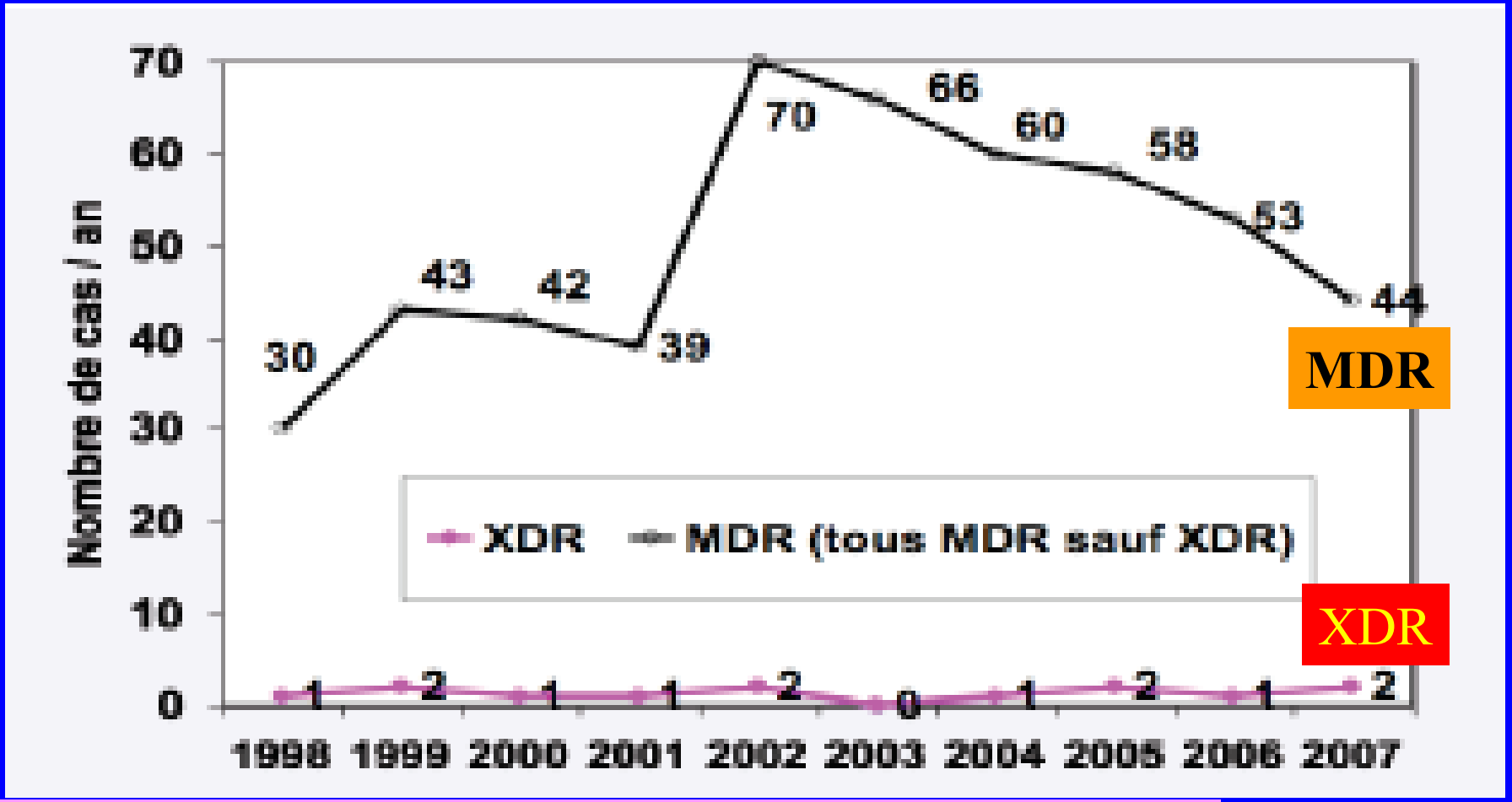
XDR-TB (new definition)
in % of MDR cases

WHO 4th Report 2008

* Sub-national averages applied to Russia



MDR-TB and XDR-TB in France 1998 - 2007



In 10 years :
517 MDR and 13 XDR (1 to 2 XDR per year)

Kanitz 2010
submitted

MDR-XDR (new) definitions for Mtb

- Usable ? → YES (simple and clear)
- Workable ?

  i.e. fitting prerequisites for :

  – therapeutic decisions ?

    → helps but not enough

  – outcome ? → YES

  – infection control programmes ? → YES

MDR, XDR

in other bacterial species ?

→ no consensus to date

→ ECDC proposal (2008-2011)

ECDC target

"Adopting standardized international terminology to define organisms that are resistant to a significant number of antibiotics 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."

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ECDC target

"To convey to the public and to policy makers about the rising threat of MDROs to public health"

General methods (1)

- A bacterial isolate is considered non-susceptible to an antibiotic when resistant or intermediate
- Only acquired antimicrobial resistance is taken into consideration
- Intrinsic resistance is not addressed

General methods (2)

- Panels of antibiotics for each organism or organism group that could be used by clinical, reference, and public health microbiology laboratories that perform DST
- Designed to be comprehensive and to reflect current antibiotic and testing practices

General methods (3)

- Antibiotic added or removed based on : EUCAST's Expert Rules and specific inclusion and exclusion criteria
- Inclusion criteria :
  - ATB currently approved in humans by EMA or FDA
  - breakpoints established by EUCAST, CLSI, FDA
- Exclusion criteria :
  - therapeutic concentrations only in urine (e.g. nitrofurantoin)
  - widespread acquired resistance (e.g. penicillin *S. aureus*)

General method (4)

- Cross-resistance (EUCAST, CLSI) applied to the panels to minimize the number of ATB
- Examples :
  - *E. coli* non-susceptible to ciprofloxacin : non-susceptible to all fluoroquinolones
  - *S. aureus* non-susceptible to clindamycin : non-susceptible to all lincosamides
- When full cross-resistance in an antibiotic category, 1 agent only from that category is proposed for DST

General methods (5)

- Isolate is considered non-susceptible to an antibiotic category when it is "non-susceptible to ≥ 1 agent in this category"
- Resistance to only 1 agent within a category is a crude indicator of antimicrobial resistance to the entire category

Methods for MDR

- Most frequent definition : “resistant to ≥ 3 antibiotic classes”
- Creating an acronym for a bacterium based on a specific traits (e.g. MRSA, ESBL…) immediately highlights its epidemiological significance; and has the advantage to be easily applied…
- … but often comes with cross or co-resistance to multiple classes of antimicrobials, making them MDR

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Methods for XDR

- Term XDR created for *M.tuberculosis* (XDR MTB)
- Definitions for other bacteria were constructed according to the principle underlying the XDR MTB definition : resistance profile which compromised most standard antimicrobial regimens
- 2 sets of criteria :
  - number of antibiotics/classes/subclasses to which a bacterium is resistant
  - resistant to key antimicrobial agents (e.g. MRSA)

ECDC process

- Proposal for MDR, XDR and PDR definitions presented to the ECDC Advisory Forum at the end of 2008
- Discussed at an ECDC joint meeting (AMR and HAI) in January 2009
- Posted on the internet for broad discussion, comments and further consultations by medical professional societies and other expert groups 22 July - 22 August, 2010
- Final release “soon”

General definitions

- **MDR** : non-susceptibility to ≥ 1 agent in ≥ 3 ATB categories
- **XDR** : non-susceptibility to ≥ 1 agent in all but ≤ 2 ATB categories (i.e. susceptible to only 1 or 2 categories)
- **PDR** : non-susceptibility to all ATB in all categories (i.e. no ATB tested as susceptible)

ATB list for *S.aureus*

Antimicrobial category	Antimicrobial agent
Aminoglycosides	Gentamicin
Ansamycins	Rifampin/rifampicin
Anti-staphylococcal β-lactams (or cephamycins)	Oxacillin (or cefoxitin)*
Fluoroquinolones	Ciprofloxacin
	Moxifloxacin
Folate pathway inhibitors	Trimethoprim-sulfamethoxazole
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

ATB list for *Enterococcus*

Antimicrobial category	Antimicrobial agent
Aminoglycosides (except streptomycin)	Gentamicin (High level)
Streptomycin	Streptomycin (High level)
Carbapenems	Imipenem Meropenem Doripenem
Fluoroquinolones	Ciprofloxacin Levofloxacin Moxifloxacin
Glycopeptides	Vancomycin Teicoplanin
Glycylcyclines	Tigecycline
Lipopeptides	Daptomycin
Oxazolidinones	Linezolid
Penicillins	Ampicillin
Streptogramins	Quinupristin-dalfopristin
Tetracycline	Doxycycline Minocycline

ATB list for *Enterobacteriaceae* (1)

Antimicrobial category	Antimicrobial agent
Aminoglycosides	Gentamicin
	Tobramycin
	Amikacin
	Netilmicin
Antipseudomonal penicillins + β-lactamase inhibitors	Ticarcillin-clavulanic acid
	Piperacillin-tazobactam
Carbapenems	Ertapenem
	Imipenem
	Meropenem
	Doripenem
Non-extended spectrum cephalosporins; 1st and 2nd generation cephalosporins	Cefazolin
	Cefuroxime
Extended-spectrum cephalosporins; 3rd and 4th generation cephalosporins	Cefotaxime or ceftriaxone
	Ceftazidime
	Cefepime
Cephamycins	Cefoxitin
	Cefotetan

ATB list for *Enterobacteriaceae* (2)

Fluoroquinolones	Ciprofloxacin
Folate pathway inhibitors	Trimethoprim-sulfamethoxazole
Glycylcyclines	Tigecycline
Monobactams	Aztreonam
Penicillins	Ampicillin
Penicillins + β-lactamase inhibitors	Amoxicillin-clavulanic acid
	Ampicillin-sulbactam
Phenicols	Chloramphenicol
Phosphonic acids	Fosfomycin
Polymyxins	Colistin
Tetracyclines	Tetracycline
	Doxycycline
	Minocycline

ATB list for *P.aeruginosa*

Antimicrobial category	Antimicrobial agent
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

Limitations cited by ECDC (1)

- MDR isolates can have **many different resistance profiles** since non-susceptibility to a single agent in only 3 antibiotic categories defines MDR
- **Further characterization of resistance in MDR**, based on the agents to which they are resistant, is **beyond the scope** of the ECDC document

Examples of MDR in *S.aureus*

1. Any MRSA…still susceptible to ≥ 2 ATB such as : vancomycin, linezolid, fosfomycin
2. GISA (e.g. *vanA*), R to all other ATB but linezolid, fosfomycin

Examples of MDR in *Enterococci*

- R to ampicillin, streptomycin (HL), cyclines but susceptible to glycopeptides, gentamicin (HL), moxifloxacin, tigecycline, linezolid
- VRE, R to ampicillin, streptomycin (HL), gentamicin (HL), cyclines, moxifloxacin … but susceptible to tigecycline, linezolid

Examples of MDR in *E.coli*

1. R to ampicillin, cotrimoxazole, cyclines
2. ESBL, R to cefoxitin, TNA, cotrimoxazole, cyclines, phenicols, ciprofloxacin… but susceptible to Pip-Taz, carbapenems, fosfomycin, tigecycline, colistin
3. carbapemenase (VIM, KPC…), R to GTNA, cotrimoxazole, cyclines, phenicols ciprofloxacin … but susceptible to tigecycline, fosfomycin, colistin

Examples of MDR in *P.aeruginosa*

1. R to Pip-Taz, tobramycin, ciprofloxacin… but susceptible to ceftazidime, aztreonam, carbapenems, amikacin, fosfomycin, colistin
2. R to ceftazidime, aztreonam, carbapenems, tobramycin, amikacin, ciprofloxacin… but susceptible to, fosfomycin, colistin

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Limitations cited by ECDC (2)

- Definitions are for public health use and epidemiological purposes only
- **Definitions do not intend** :
  - to replace clinical judgment
  - to contribute to therapeutic decision-making
  - to offer guidance in infection control practices
- These areas are **beyond the scope** of the ECDC document and remain the **responsability of clinical specialists, local and national health authorities**

Are the ECDC MDR-XDR definitions

- **Usable** ? → YES (simple and clear)
- **Workable** ?

  i.e. fitting prerequisites for
  - therapeutic decisions ?
  - infection control programmes ?

→ NO….

Limitations to be workable

Differences between MDR and XDR

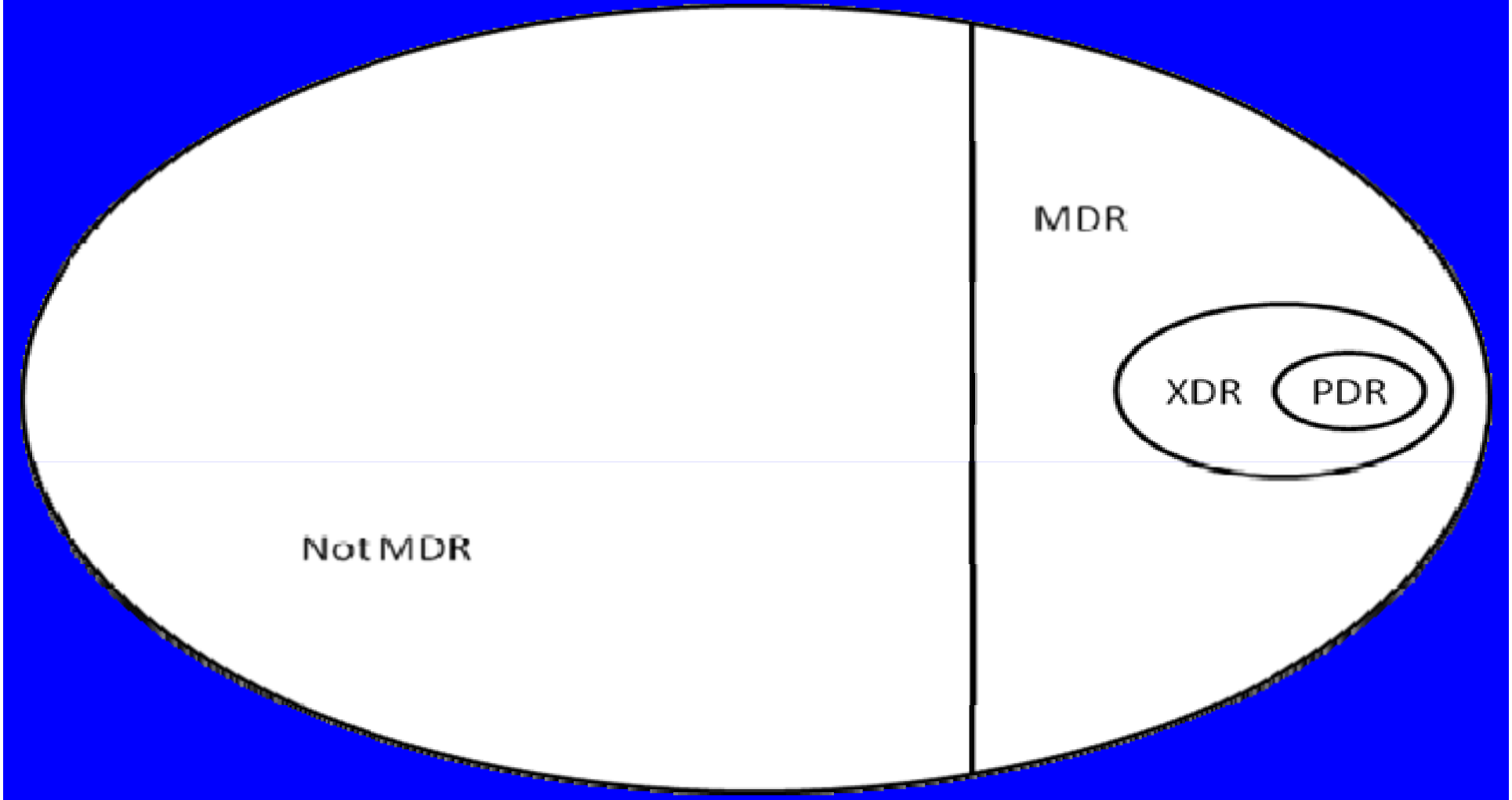
R can be tiny, e.g. :

- Carbapemenase producing *E.coli* or *K.pneumoniae* :
  - S only to fosfomycin, tigecycline, colistin = **MDR**
  - S only to tigecycline, colistin = **XDR**
- VRE :
  - S only to linezolid, tigecycline, daptomycin = **MDR**
  - S only to tigecycline, daptomycin = **XDR**

Limitations to be workable

- **MDR – XDR** differentiation not accurate
- **MDR** does not take into account, by definition, resistant traits that immediately highlights epidemiological significance (ESBL, carbapemenase, VRE) except MRSA
- **XDR** = good specificity but poor sensibility
- **PDR** = clear, providing that all drugs of the panels are tested

MDR-XDR-PDR scheme adopted by ECDC



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MDR-XDR-PDR scheme not adopted by ECDC

MDR → XDR → PDR

As a help to understand the process to go from resistance to therapeutical dead end and to establish resistance control programmes

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Conclusions

- Interesting for XDR and PDR
- Confusing for MDR
- If come into use in France, we will have :
  - to keep “MDR targets” : MRSA, VRE, ESBL producing *Enterobacteriaceae*, carbapemenase producing *Enterobacteriaceae* for the purpose of our infection control and surveillance programmes
  - to avoid confusion and possible indirect deleterious effects

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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.	

- 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

MDR, XDR in other bacterial species ?

No consensus

- “multidrug-resistant” (MDR)
- “extensively drug- resistant” (XDR)
- “pandrug-resistant” (PDR)

ECDC rationale (2)

"MDROs, highly-resistant Gram- bacteria require special mention : can be resistant to all currently available antibiotics or remain susceptible only to older, potentially more toxic antibiotics like the polymyxins, leaving limited and suboptimal options for treatment"

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.	

ECDC rationale (1)

"Infections with MDROs can lead to inadequate or delayed antimicrobial therapy, and are associated with poorer patient outcomes"