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# **Pandemia da Enterobatteri carbapenem-resistenti**

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

A.-P. Magiorakos<sup>1</sup>, A. Srinivasan<sup>2</sup>, R. B. Carey<sup>2</sup>, Y. Carmeli<sup>3</sup>, M. E. Falagas<sup>4,5</sup>, C. G. Giske<sup>6</sup>, S. Harbarth<sup>7</sup>, J. F. Hindler<sup>8</sup>, G. Kahlmeter<sup>9</sup>, B. Olsson-Liljequist<sup>10</sup>, D. L. Paterson<sup>11</sup>, L. B. Rice<sup>12</sup>, J. Stelling<sup>13</sup>, M. J. Struelens<sup>1</sup>, A. Vatopoulos<sup>14</sup>, J. T. Weber<sup>2</sup> and D. L. Monnet<sup>1</sup>

**TABLE 6.** Definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria

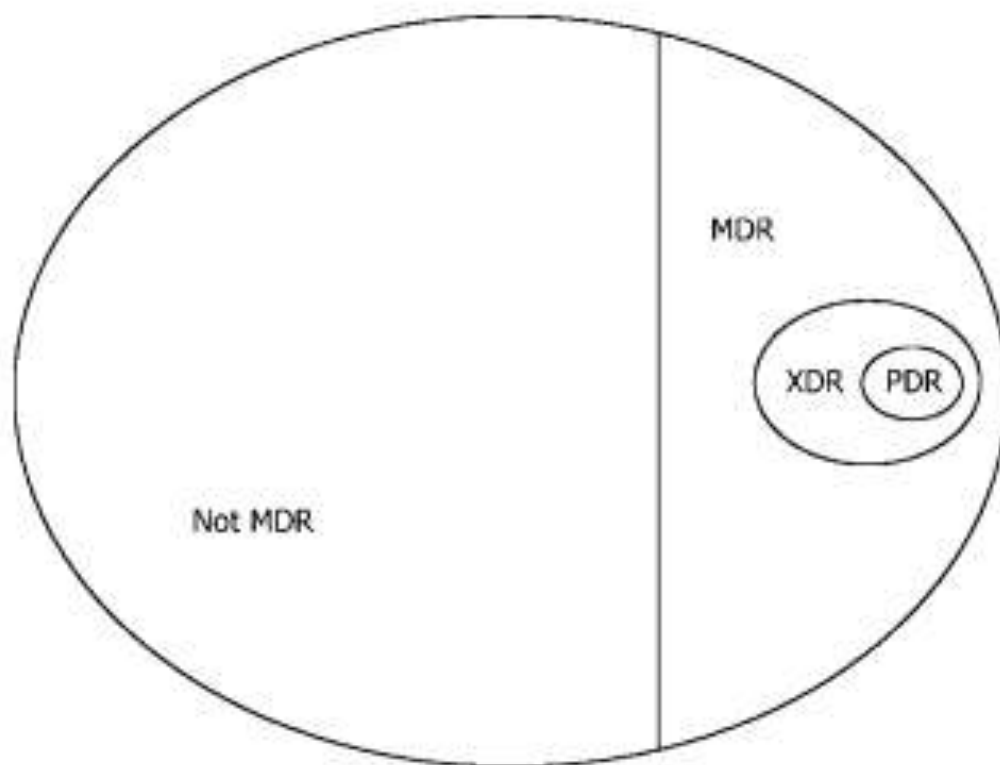
Bacterium	MDR	XDR	PDR
<i>Staphylococcus aureus</i>	The isolate is non-susceptible to at least 1 agent in $\geq 3$ antimicrobial categories listed in Table 1 <sup>a</sup>	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1.	Non-susceptibility to all agents in all antimicrobial categories for each bacterium in Tables 1–5
<i>Enterococcus</i> spp.	The isolate is non-susceptible to at least 1 agent in $\geq 3$ 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.	
<i>Enterobacteriaceae</i>	The isolate is non-susceptible to at least 1 agent in $\geq 3$ 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.	
<i>Pseudomonas aeruginosa</i>	The isolate is non-susceptible to at least 1 agent in $\geq 3$ 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.	
<i>Acinetobacter</i> spp.	The isolate is non-susceptible to at least 1 agent in $\geq 3$ 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.	

<sup>a</sup>All MRSA isolates are defined as MDR because resistance to oxacillin or cefoxitin predicts non-susceptibility to all categories of  $\beta$ -lactam antimicrobials listed in this document, with the exception of the anti-MRSA cephalosporins (i.e. all categories of penicillins, cephalosporins,  $\beta$ -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](http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx).

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

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

# MDR organisms in the healthcare setting: from ESKAPE to ESCAPE

- We are currently facing new microbiological, infection control and clinical issues, and the epidemiologic variations observed in the last years highlighted the need of a change from the initial proposed acronym:
- “ESKAPE”  
*E. faecium*  
*S. aureus*  
*K. pneumoniae*  
*A. baumannii*  
*P. aeruginosa*  
*Enterobacter* species
- 
- “ESCAPE”  
*E. faecium*  
*S. aureus*  
*C. difficile*  
*A. baumannii*  
*P. aeruginosa*  
Enterobacteriaceae



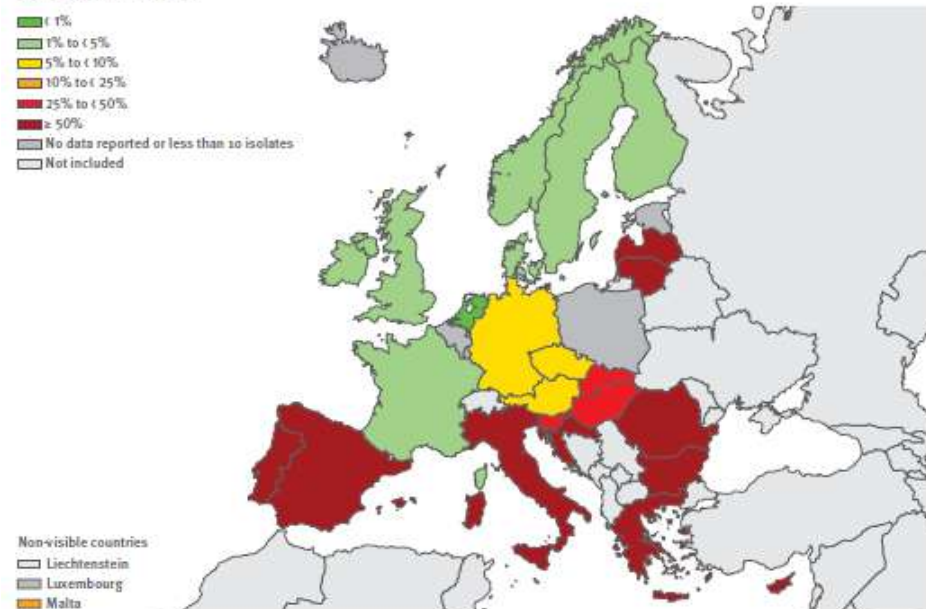
**Figure 3-9. *Klebsiella pneumoniae*.** Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2014



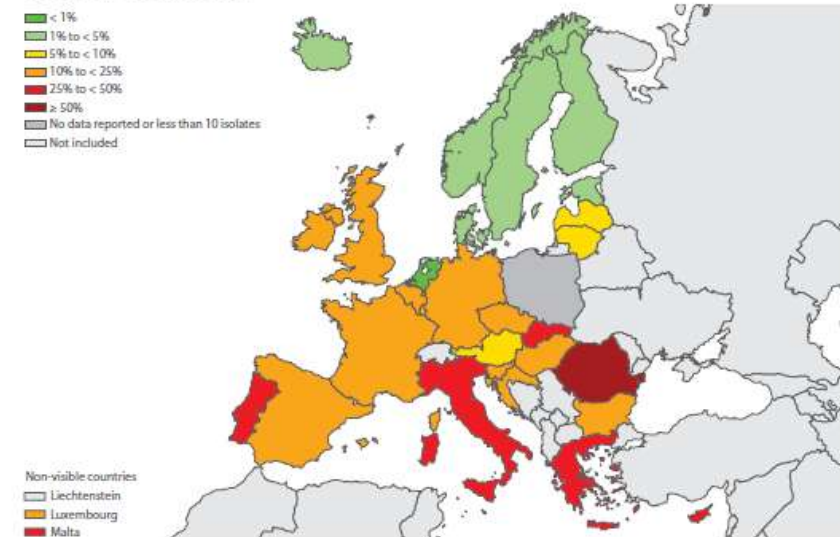
**Figure 3-15. *Pseudomonas aeruginosa*.** Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2014

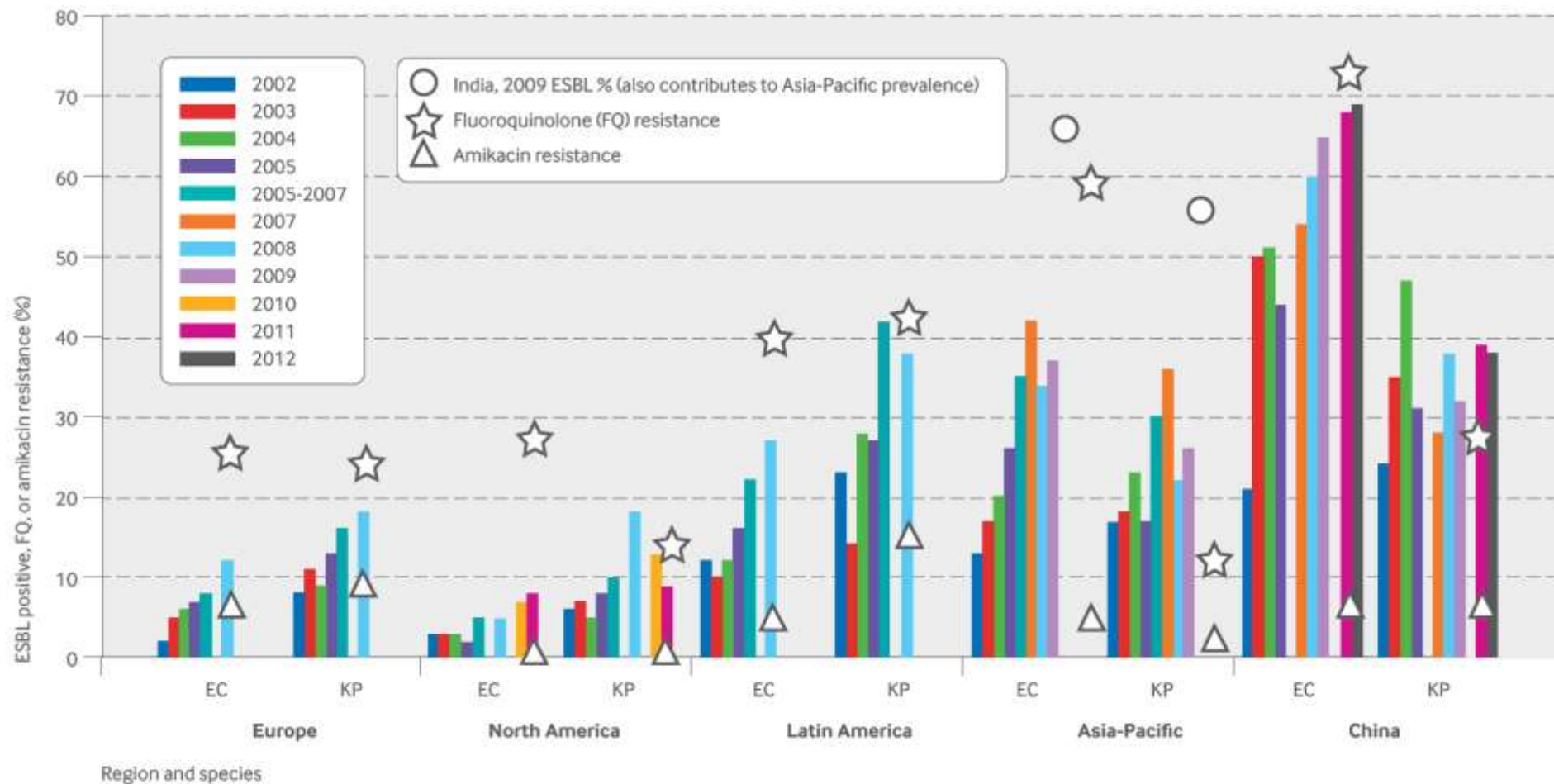


**Figure 3-19. *Achromobacter* spp.** Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2014



**Figure 3-23. *Staphylococcus aureus*.** Percentage (%) of invasive isolates with resistance to meticillin (MRSA), by country, EU/EEA countries, 2014





**Fig 2|Antibiotic resistance by region.** Increasing rates of extended spectrum  $\beta$  lactamase (ESBL) carriage in *Klebsiella pneumoniae* (KP) and *Escherichia coli* (EC) and high rates of fluoroquinolone resistance are seen in all regions, whereas amikacin resistance remains relatively rare. Data were collated from the SMART studies of intra-abdominal and urinary tract infection.<sup>9-26</sup> Fluoroquinolone and aminoglycoside resistance data for the Asia-Pacific region come from Mendes and colleagues<sup>27</sup>

# **CDC: Action needed now to halt spread of deadly bacteria**

**“CRE are nightmare bacteria. Our strongest antibiotics don’t work and patients are left with potentially untreatable infections,” said CDC Director Tom Frieden, M.D., M.P.H.**

**“Doctors, hospital leaders, and public health, must work together now to implement CDC’s “detect and protect” strategy and stop these infections from spreading.”**

# Determinants of Carbapenem-Resistance

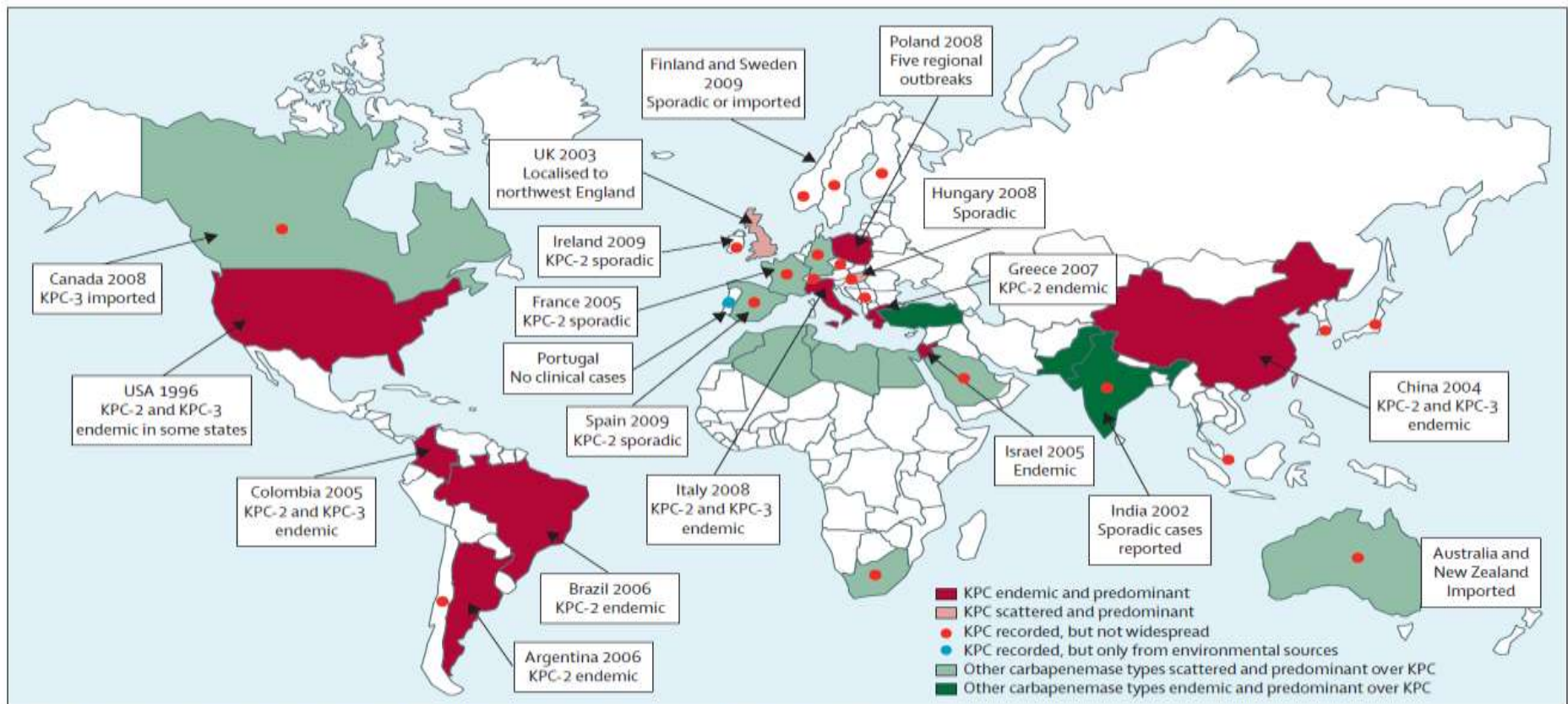
**Table 1. Classification and activities of the more common acquired carbapenemases**

Enzyme type	Ambler enzyme class	Spectrum of activity	Organism(s)
KPC	A	All $\beta$ -lactams (isolates with these enzymes can test susceptible to carbapenems, cefepime, and cephamycins)	<i>Enterobacteriaceae</i> , <i>P. aeruginosa</i>
SME	A	Carbapenems and aztreonam, but not extended-spectrum cephalosporins	<i>S. marcescens</i>
NMC-A, IMI	A	Same as for the SME family	<i>Enterobacter</i> spp.
GES	A	Imipenem and extended-spectrum cephalosporins	<i>P. aeruginosa</i> , <i>Enterobacteriaceae</i>
IMP, VIM	B (metallo- $\beta$ -lactamases)	All $\beta$ -lactams (isolates with these enzymes can test susceptible to aztreonam)	<i>Pseudomonas</i> spp., <i>Acinetobacter</i> spp., <i>Enterobacteriaceae</i>
OXA	D	Carbapenems (weak activity)	<i>A. baumannii</i> , <i>P. aeruginosa</i> , and rare reports in <i>Enterobacteriaceae</i>

**Patel JB et al. Clin Microb Newsletter 2009;  
31:55-62**



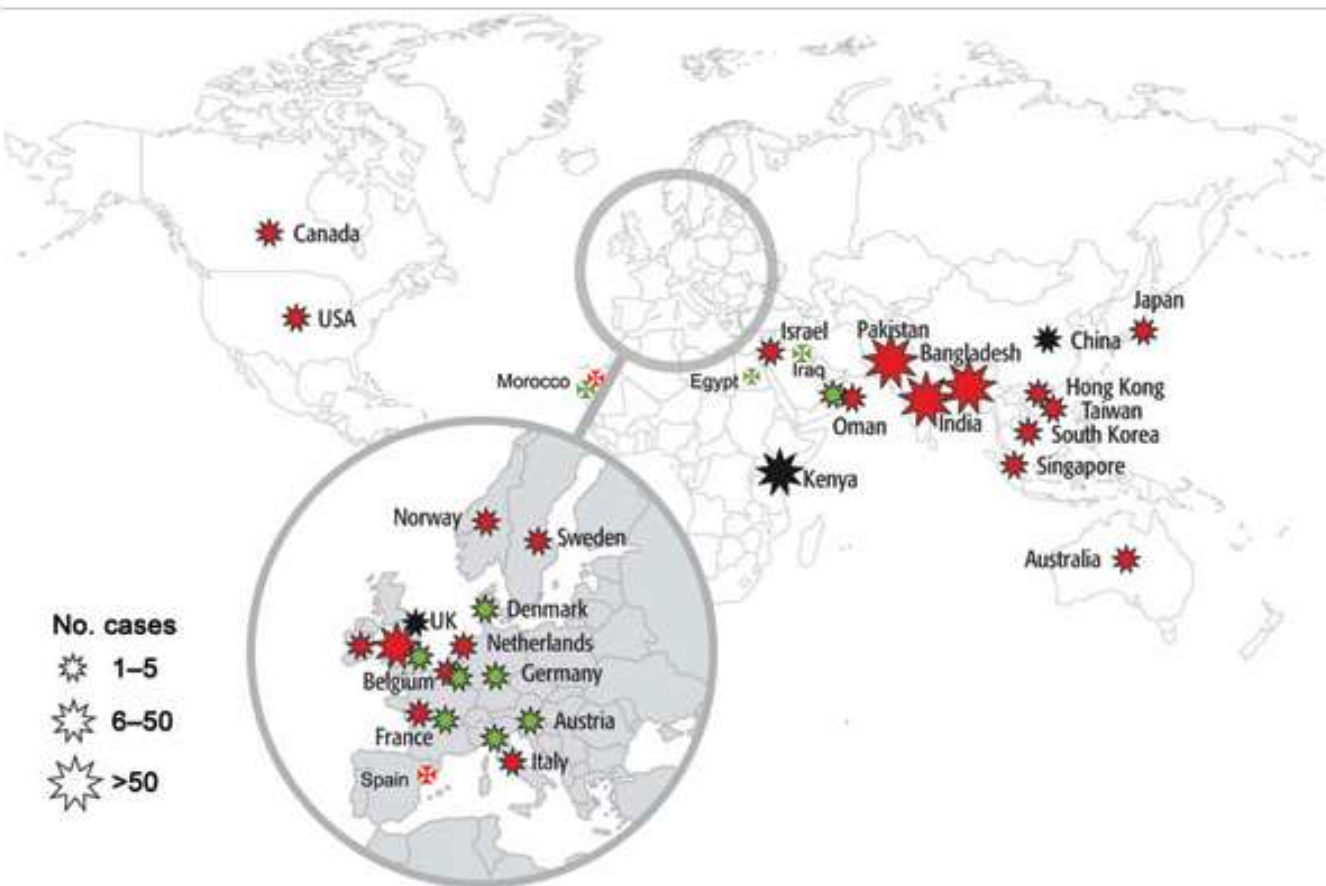
# Epidemiology of Carbapenem-Resistance



**Figure:** Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin  
Other carbapenemase types include VIM, OXA-48, or NDM. KPC=*Klebsiella pneumoniae* carbapenemase.

# *Carbapenemases other than KPC*

- SME (class A) → restricted to the chromosome of *Serratia marcescens*; does not hydrolyze ceftazidime;
- Metallo-beta-lactamases (MBLs), or class B beta-lactamases, such as NDM (New Delhi metallo-beta-lactamase), VIM (Verona Integron Mediated MBL), and IMP (initially found in imipenem-resistant *S. marcescens*) → potent carbapenemases and cephalosporinases. They do not hydrolyze the monobactam aztreonam.
- OXA-48 enzyme (class D), difficult to detect mechanism of resistance; relative inactivity against cephalosporins.



**Figure 4.** Geographic distribution of New Delhi metallo-β-lactamase-1 producers, July 15, 2011. Star size indicates number of cases reported. Red stars indicate infections traced back to India, Pakistan, or Bangladesh, green stars indicate infections traced back to the Balkan states or the Middle East, and black stars indicate contaminations of unknown origin. (Most of the information corresponds to published data; other data are from P. Nordmann.)

# Isolation of NDM-1-producing *Pseudomonas aeruginosa* sequence type ST235 from a stem cell transplant patient in Italy, May 2013

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Susceptibility pattern of NDM-1-positive *Pseudomonas aeruginosa* isolated from blood cultures and perianal abscess, Rome, May 2013

Euro Surveill 2013; 18:46

Antibiotics	MIC (µg/mL), Interpretation result <sup>a</sup>
Amikacin	>16, R
Aztreonam	=16, R
Cefepime	>8, R
Ceftazidime	>8, R
Ciprofloxacin	>1, R
Colistin	≤1, S
Gentamicin	>4, R
Imipenem	>8, R
Levofloxacin	>2, R
Meropenem	>8, R
Piperacillin	>16, R
Piperacillin/tazobactam	>16/4, R
Tobramycin	>4, R

MIC: minimum inhibitory concentration R: resistant: S: susceptible

We describe the first isolation of an NDM-1-producing *Pseudomonas aeruginosa* in Italy. In May 2013, a patient with acute lymphoblastic leukaemia and history of prior hospitalisation in Belgrad, Serbia, underwent stem cell transplantation at a tertiary care hospital in Rome, Italy. After transplantation, sepsis by NDM-1-producing *P. aeruginosa* occurred, leading to septic shock and fatal outcome.



# High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality

A. Capone<sup>1</sup>, M. Giannella<sup>1</sup>, D. Fortini<sup>2</sup>, A. Giordano<sup>3</sup>, M. Meledandri<sup>4</sup>, M. Ballardini<sup>4</sup>, M. Venditti<sup>5</sup>, E. Bordi<sup>6</sup>, D. Capozzi<sup>7</sup>, M. P. Balice<sup>8</sup>, A. Tarasi<sup>9</sup>, G. Parisi<sup>10</sup>, A. Lappa<sup>10</sup>, A. Carattoli<sup>2</sup>, N. Petrosillo<sup>1</sup> and on behalf of the SEERBIO-GRAB network<sup>†</sup>

*Clin Microbiol Infect* 2013; **19**: E23–E30

**TABLE 4.** Multivariate analysis of risk factors for in-hospital mortality in patients with infection due carbapenem-resistant *Klebsiella pneumoniae* (CR-KP), adjusted for appropriate antibiotic treatment, combination therapy and removal of the infectious source

	OR (95% CI)	p
Charlson comorbidity score	1.42 (1.15–1.76)	0.001
Hospitalization in intensive-care unit	18.05 (3.90–83.51)	<0.001
Bloodstream infection	4.92 (1.35–17.28)	0.01
Infection due to a colistin-resistant strain	4.15 (1.17–14.74)	0.02



**Table 3. Metallo- $\beta$ -lactamases.**

Enzyme	First isolated (year)	Organism	Geographic distribution	Location	Ref.
IMP 1–26	1988	Enterobacteriaceae <i>Pseudomonas</i> spp. <i>Acinetobacter</i> spp.	Worldwide	Plasmid or chromosomal	[63]
VIM 1–23	1997	Enterobacteriaceae <i>Pseudomonas</i> spp. <i>Acinetobacter</i> spp.	Worldwide	Plasmid or chromosomal	[64,65]
SPM-1	2001	<i>Pseudomonas aeruginosa</i>	Brazil <sup>†</sup>	Chromosomal	[72,77]
GIM-1	2002	<i>P. aeruginosa</i>	Germany	Plasmid	[71]
SIM-1	2003–2004	<i>Acinetobacter baumannii</i>	Korea	Chromosomal	[73]
NDM-1	2006	<i>Acinetobacter</i> spp. Enterobacteriaceae	Worldwide (FIGURE 2)	Plasmid	[78,86]
NDM-2	2011	<i>Acinetobacter</i> spp.	Egypt	Chromosomal	[196]
AIM-1	2007	<i>P. aeruginosa</i>	Australia		[74]
KHM-1	1997	<i>Citrobacter freundii</i>	Japan	Plasmid	[76]
DIM-1	2007	<i>Pseudomonas stutzeri</i>	The Netherlands	Plasmid	[75]

<sup>†</sup>Single report of an isolate of SPM-1 in Europe in a patient who had received healthcare in Brazil [77].

**Patel G et al. *Expert Rev Anti Infect Ther* 2011; 9: 555–570**

# **Hospital and Societal Costs of Antimicrobial-Resistant Infections (ARIs)**

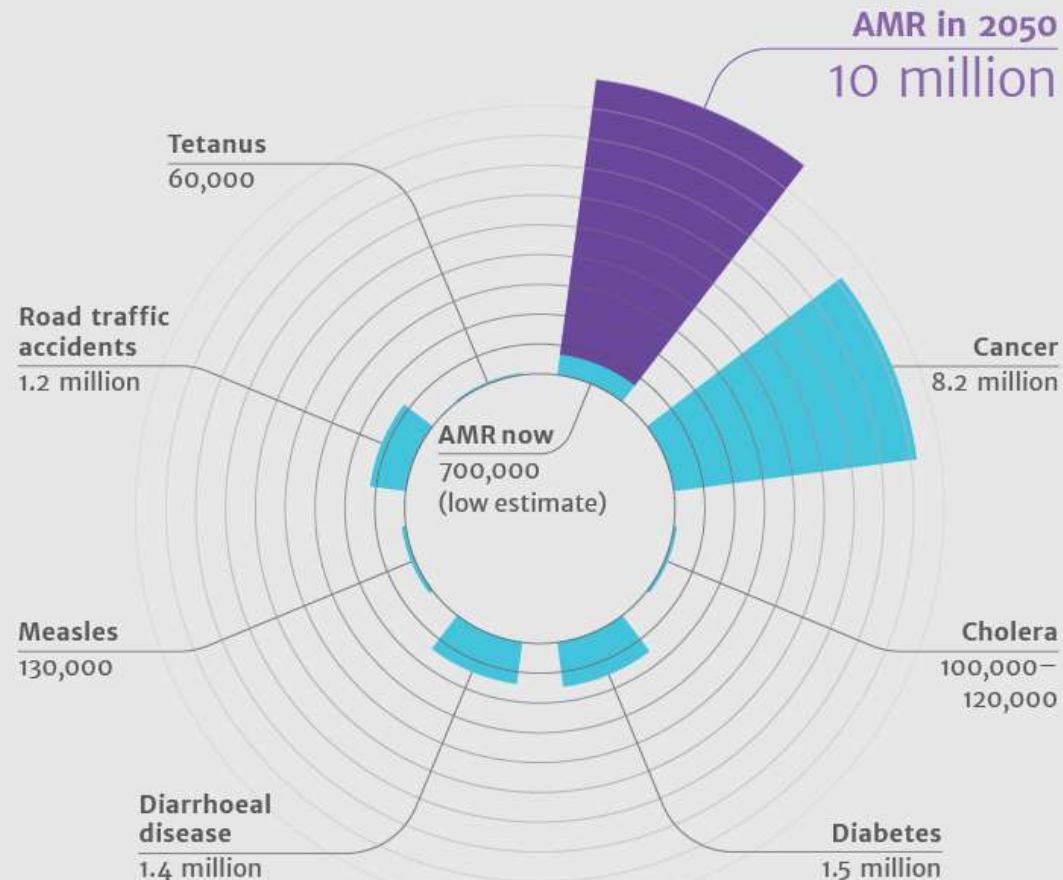
**An economic analysis of the  
Chicago Antimicrobial Resistant Project  
dataset:**

**188 / 1391 patients (13.5%) with ARI**

<b>Medical costs attributable to ARI</b>	<b>\$18,588 - \$29,069 / patient</b>
<b>Excess LOS</b>	<b>6.4 – 12.7 days</b>
<b>Attributable mortality</b>	<b>6.5%</b>
<b>Societal costs</b>	<b>\$10.7 - \$15.0 million</b>

Bacteria that already show concerning resistance levels	Broader public health issues for which resistance is a concern
<b>Klebsiella pneumonia</b>	<b>HIV</b>
<b>Escherichia coli (E. coli)</b>	<b>Tuberculosis (TB)</b>
<b>Staphylococcus aureus</b>	<b>Malaria</b>

# Deaths attributable to AMR every year compared to other major causes of death



**The Review on Antimicrobial Resistance  
Chaired by Jim O'Neill  
December 2014**

## Sources

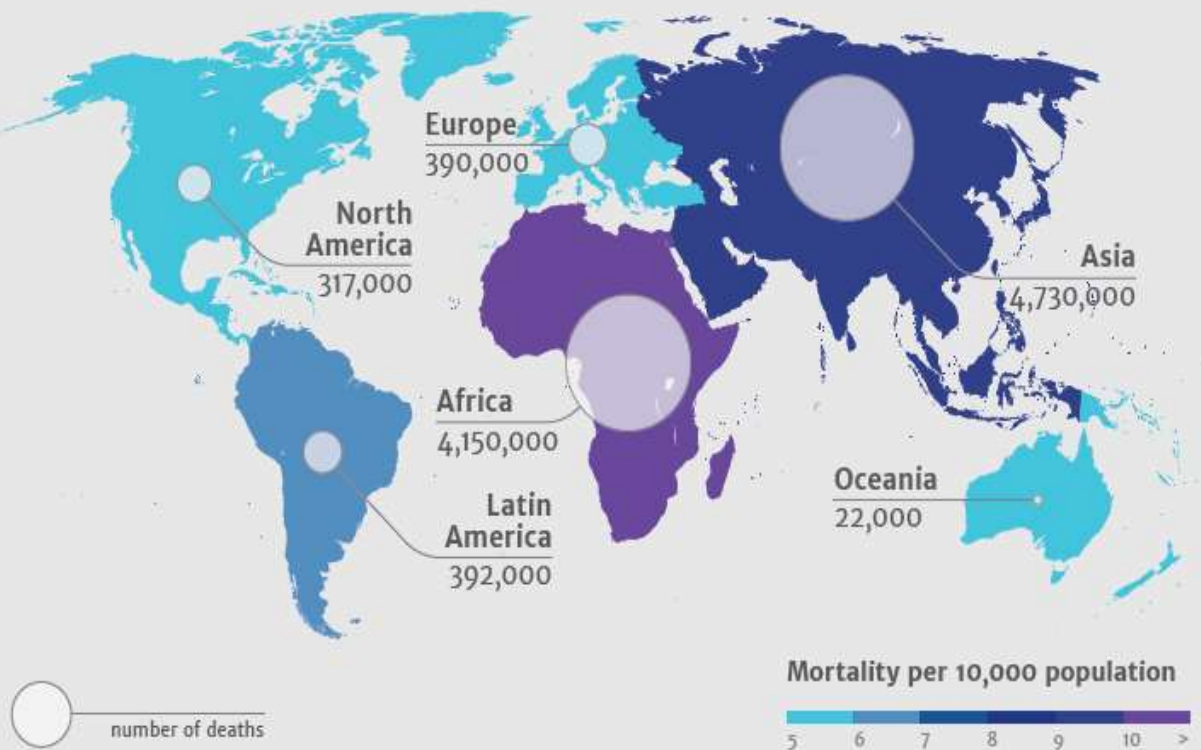
Diabetes  
Cancer  
Cholera  
Diarrhoeal disease

[www.who.int/mediacentre/factsheets/fs312/en/](http://www.who.int/mediacentre/factsheets/fs312/en/)  
[www.who.int/mediacentre/factsheets/fs297/en/](http://www.who.int/mediacentre/factsheets/fs297/en/)  
[www.who.int/mediacentre/factsheets/fs107/en/](http://www.who.int/mediacentre/factsheets/fs107/en/)  
[www.sciencedirect.com/science/article/pii/S0140673612617280](http://www.sciencedirect.com/science/article/pii/S0140673612617280)

Measles  
Road traffic accidents  
Tetanus

[www.sciencedirect.com/science/article/pii/S0140673612617280](http://www.sciencedirect.com/science/article/pii/S0140673612617280)  
[www.who.int/mediacentre/factsheets/fs358/en/](http://www.who.int/mediacentre/factsheets/fs358/en/)  
[www.sciencedirect.com/science/article/pii/S0140673612617280](http://www.sciencedirect.com/science/article/pii/S0140673612617280)

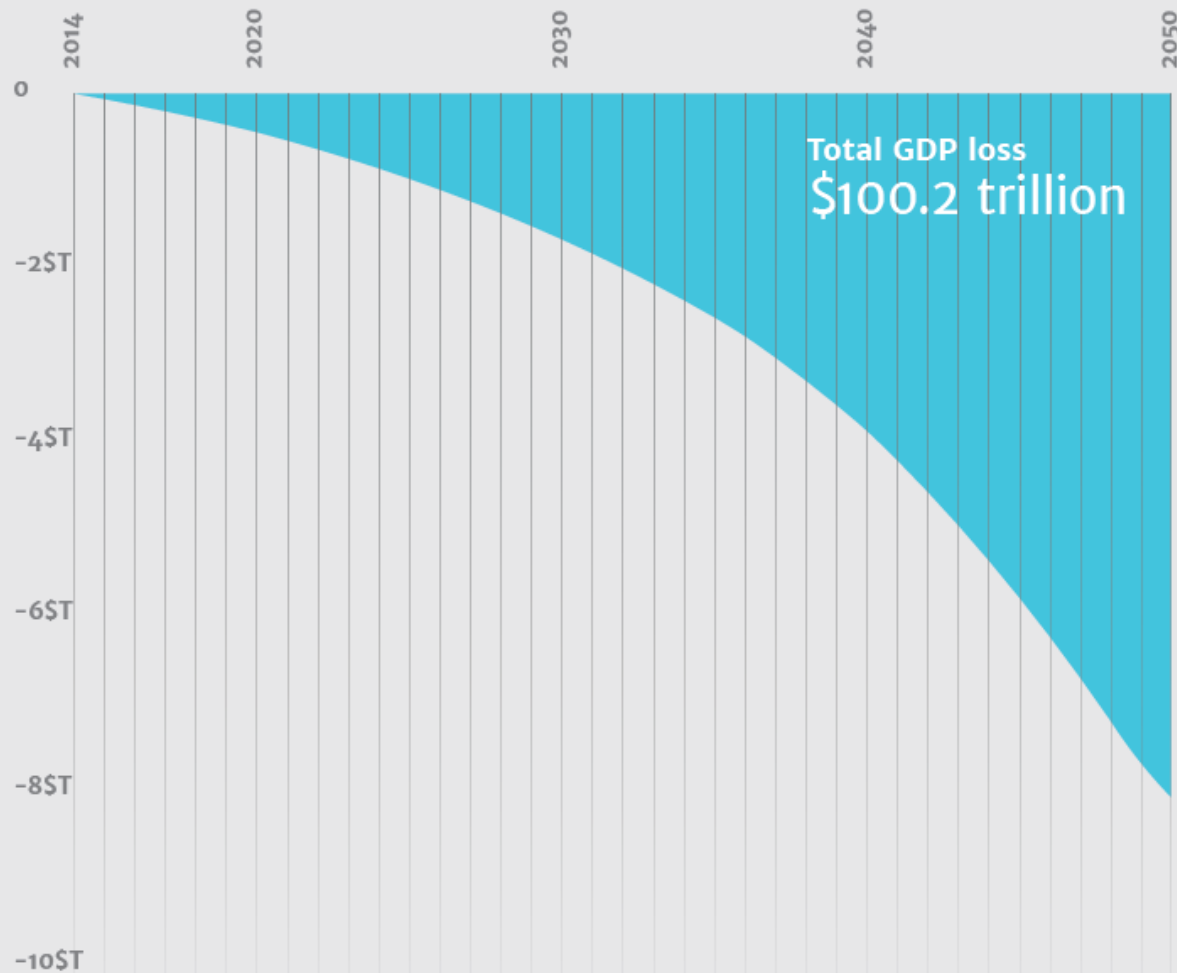
# Deaths attributable to AMR every year by 2050





# AMR's impact on World GDP

in trillions of USD



# The secondary health effects of AMR: a return to the *dark age* of medicine?

- **Less surgery for the risk of AMR**
  - **Caesarean sections contribute about 2% to world GDP**
  - **Joint replacements add about 0.65%**
  - **Organ transplant add about 0.1%**
- **These are just a small number of the areas in modern medicine that risk being undermined if we do not have effective antibiotics in the future**
- **Concerns for international travels → less trade affecting mainly developing countries**

Left unchecked, the current trend in rising drug resistance is a crisis of global scale

Content	Key guidance	Example of jurisprudence
A right to medical care	Persons deprived of liberty have the right to access the health services available in the country without discrimination based on their legal situation	Mandela Rules (rules 24–35) UN principles of medical ethics (principle 1) European prison rules (article 40.3) European CPT standards Principles and best practices on the protection of persons deprived of liberty in the Americas (principle 10)  Van Rijn and Others vs The Minister of Correctional Services (Cape of Good Hope Provincial Division, South Africa, 1997): prisoners on ART at the time of incarceration have a right to continued medication. EN and Others vs The Government of the RSA and Others (Durban and Local Coast Division, South Africa, 2005): prisoners have a right to ART Odufe and Others vs Attorney-General and Others (High Court of Nigeria, 2004): failure to provide HIV treatment violates African Charter on Human and Peoples' Rights
A right to timely medical attention	Individuals in detention have the right to access timely medical attention. Medical care for individuals deprived of liberty is only compliant with international law if it is available when needed	Mandela Rules (rules 24–35) Body of principles for the protection of all persons under any form of detention or imprisonment (principle 24) European CPT Principles and best practices on the protection of persons deprived of liberty in the Americas (principles 9, 10)  Khudobin vs Russia (ECHR, 2006): failure to provide timely medical assistance and independent examination of prisoner with mental illness and HIV amounts to degrading treatment
A right to preventive health	Individuals deprived of liberty must be provided with measures to prevent the transmission of disease	Mandela Rules (rules 24–35) UN rules for the protection of juveniles deprived of their liberty (paragraph 49) CPT standards (paragraphs 52–63)  Concluding Observations on Moldova (UN Human Rights Committee, 2002): failure to address rapid spread of disease could be violation of right to liberty and security of the person Concluding Observations on Moldova (UN Committee on Economic, Social and Cultural Rights, 2003): state must ensure availability of tuberculosis medicines and adequate sanitary conditions in prisons Panbe vs Romania (ECHR, 2005): authorities must take practical preventive measures to protect the physical integrity and the health of prisoners Stoykov vs Bulgaria (ECHR, 2006): denial of prevention and treatment for tuberculosis amounts to inhuman and degrading treatment
A right to mental health care	Individuals deprived of liberty have a right to access psychiatric and mental health services. Given the unique vulnerability of persons with mental illness in detention, the State's positive obligations to ensure their humane treatment, and to protect their wellbeing, are heightened	Mandela Rules (rules 24–35) European prison rules (article 47) European CPT standards Principles and best practices on the protection of persons deprived of liberty in the Americas (principle 3)  Sehadath vs Trinidad and Tobago (UN Human Rights Committee, 2002): government has obligation to provide appropriate psychiatric care Herczegfalvy vs Austria (ECHR, 1992) and Victor Rosario Congo v Ecuador (Inter-American Court 1999): a prisoner's mental illness heightens government obligation to ensure prisoner wellbeing
A right to a professional standard of care	Individuals deprived of liberty have a right to a professional standard of health service provided by qualified medical personnel	Mandela Rules (rules 24–35) European prison rules (article 41.1) UN principles of medical ethics (principle 1) European CPT standards Principles and best practices on the protection of persons deprived of liberty in the Americas (principle 10)  Teste vs Croatia (ECHR, 2007): lack of medical attention to chronic hepatitis C infection and inadequate prison conditions violates rights to dignity and to be free from humiliation
A right to informed consent and to refuse treatment	Individuals deprived of liberty have a right to consent and a right to refuse treatment. These rights are subject to some specific limitations, subject to due process of law	Mandela Rules (rule 32) UN body of principles for the protection of all persons under any form of detention or imprisonment (principle 25) UN rules for the protection of juveniles deprived of their liberty (paragraph 55) UN Committee on Economic, Social and Cultural Rights (general comment 14: right to be free from non-consensual medical treatment) CPT standards (paragraphs 46–49) Principles and best practices on the protection of persons deprived of liberty in the Americas (principle 10) European CPT standards  C vs Minister of Correctional Services (South Africa, 1996): HIV testing without consent is a violation of rights
A right to adequate living space	Persons deprived of liberty have the right to an amount of living space sufficient to safeguard their health	Mandela Rules (rules 12–17) European CPT standards Principles and best practices on the protection of persons deprived of liberty in the Americas (principle 12)  Concluding Observations, Georgia (UN Human Rights Committee, 1997): crowding increases spread of infectious disease and alarming mortality rate Concluding Observations, Mongolia (UN Human Rights Committee, 2000): lack of adequate spaces damages prisoners' health
A right to hygienic living conditions	The failure of the State to provide proper toilet or washing facilities, or clean living conditions, can contribute to a violation of international law	Mandela Rules (rules 12–17) European CPT standards (paragraph 53) Principles and best practices on the protection of persons deprived of liberty in the Americas (principle 12)  Pedro Orlando Ubaque vs Director, National Model Prison (Colombia, 1994): lack of sanitary and environmental conditions violates rights to health and life of prisoner with HIV Malawi African Association and Others vs Mauritania (African Commission on Human and Peoples Rights 2000): inadequate hygiene is a violation of prisoners' rights
A right to food and water	The failure to provide safe and adequate food and drinking water contributes to violations of international law in all human rights systems	Mandela Rules (rule 22) European CPT standards Principles and best practices on the protection of persons deprived of liberty in the Americas (principle 11)  Malawi African Association and Others vs Mauritania (African Commission on Human and Peoples Rights 2000): failure to provide sufficient food is a violation of right to health Alver vs Estonia (ECHR, 2005): prisoners have a right to food
Inadequate health care or denial of medical treatment as inhumane treatment or torture	In some circumstances, an inadequate level of health care or the denial of health care can lead to situations that are tantamount to inhuman and degrading treatment or torture	Mandela Rules (rules 32) CPT standards (paragraph 30)  Khudobin vs Russia (ECHR, 2006): absence of qualified and timely medical assistance and refusal to allow an independent medical examination created such a strong feeling of insecurity that, with inmate's physical suffering, amounts to degrading treatment Odufe and Others vs Attorney-General and Others (AHRIR 205 [NHC, 2004]): failure to provide treatment for HIV is a violation of rights

Rubenstein LS et al. Lancet 2016; 388: 1202-14