Joining the Dots

Brussels, 30 January 2018

Universitätsklinikum Leipzig
Medizin ist unsere Berufung.
ZENTRUM FÜR INFEKTIONSMEDIZIN

The Global Rise of Multi-Drug Resistant Bacteria and Implications for Patients

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Head, Division of Infectious Diseases and Tropical Medicine
Department of Gastroenterology and Rheumatology
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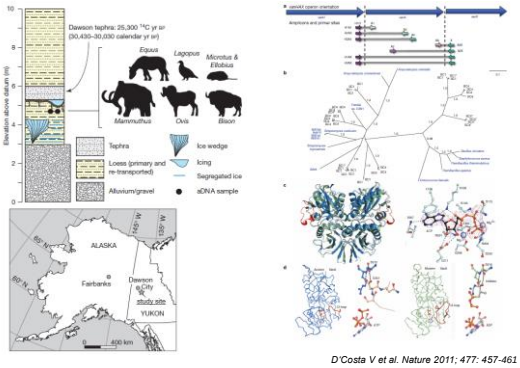
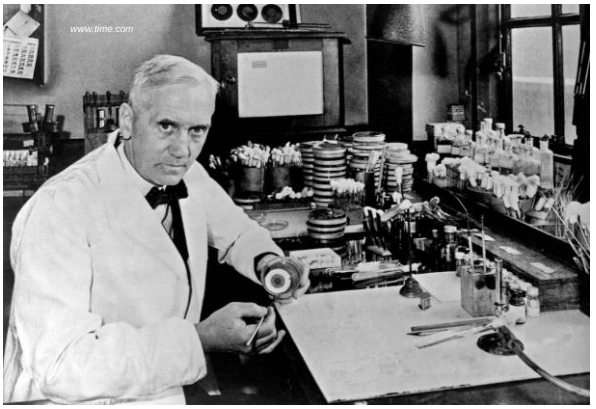
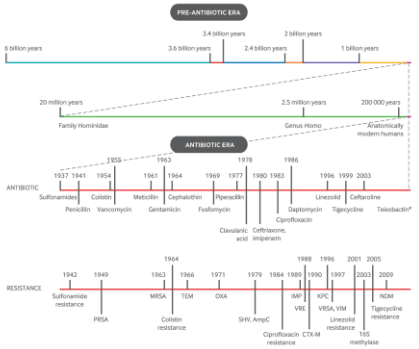
Antibiotic resistance is ancient



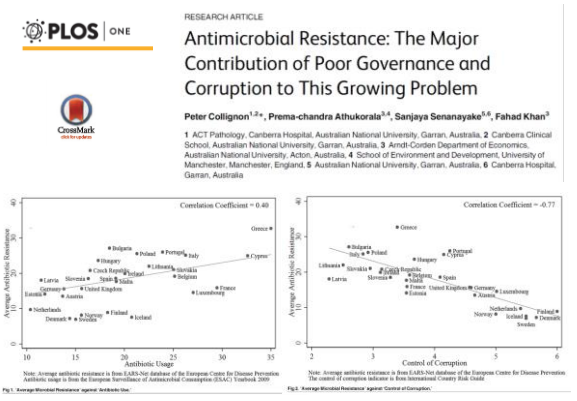
D'Costa V et al. Nature 2011; 477: 457-461



Timeline of antimicrobial resistance

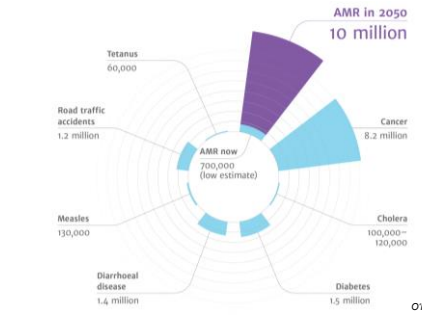


Iredell J et al. BMJ 2015; 351: h6420



Collignon PR et al. PLoS ONE 2015

AMR causes extra deaths



O'Neill, May 2016

Main drivers of AMR

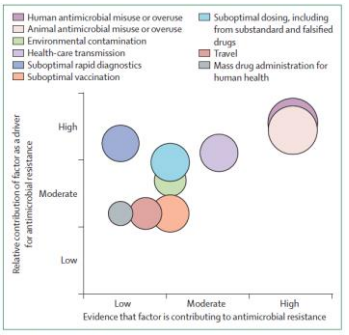


Figure 3: Role of modifiable drivers for antimicrobial resistance: a conceptual framework

Holmes AH et al. Lancet 2016

What is the problem?

The qualitative and quantitative use of antibiotics is equivalent to the development of resistance.

This is a natural law!

The resistance equation

Resistance genes + selection pressure

= Resistance problem

adapted from Werner Witte, Robert Koch Institute, Germany

Resistance genes and globalization

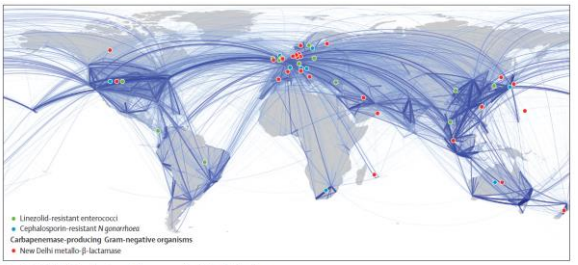
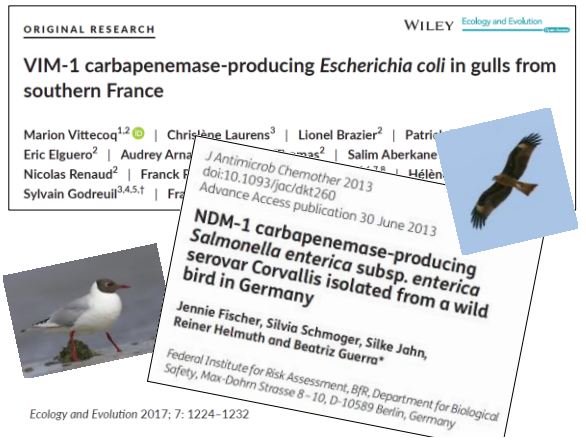


Figure 2: Worldwide travel routes and emergence of antimicrobial resistance

Although extended-spectrum β-lactamase-producing *Enterobacteriaceae* and MRSA are now nearly ubiquitous, certain novel types of resistance, among both Gram-negative and Gram-positive organisms, are of particular concern. The mechanisms of human-to-human transmission for these organisms are likely to be complex, but include association with travel. Data shown includes NDM-positive bacteria from patients with an epidemiological link to the Indian subcontinent,[42] linezolid-resistant enterococci,[43] and reported cefixime/ceftriaxone treatment failures for *Neisseria gonorrhoeae*.[44] Flight path data developed by Dr Jonathan Read and Professor Tom Solomon, based on the number of commercial flight bookings made (number of travellers might be higher).

Holmes AH et al. Lancet 2016



Import of MDRO through patients hospitalized abroad

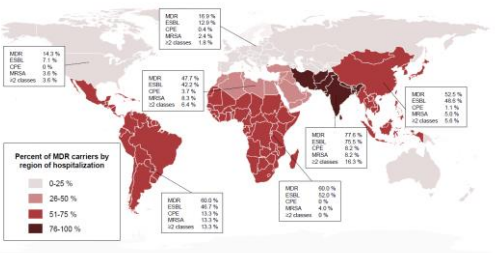
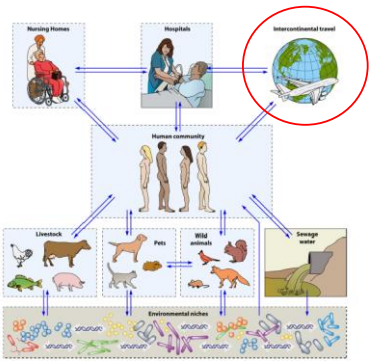


Fig. 1. Prevalence of multidrug-resistant bacteria carriage in returning patients according to the geographic region of their prior hospitalization. Abbreviations: MDR, multidrug-resistant bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; ESPL-PE, extended-spectrum β-lactamase-producing *Enterobacteriaceae*; CPE, carbapenemase-producing *Enterobacteriaceae*.

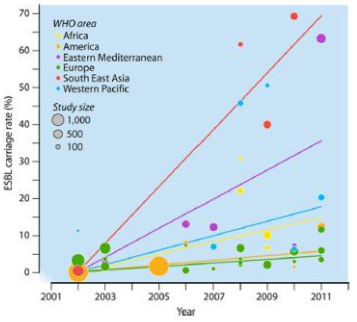
Khawaha T et al. Clin Microbiol Infect 2017

MDRO and their reservoirs



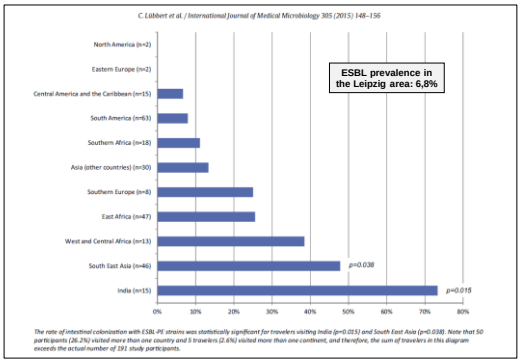
Wörther PL et al. Clin Microbiol Rev 2013

ESBL producing Enterobacteriaceae Global dynamics

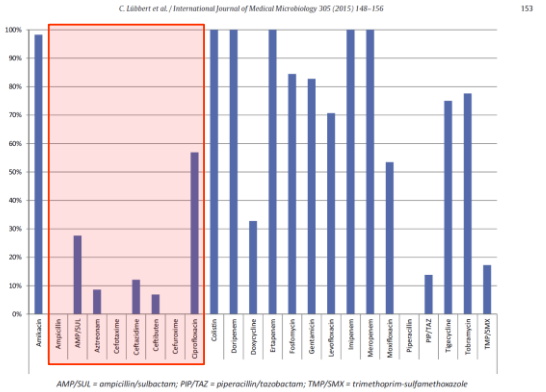


Wörther PL et al. Clin Microbiol Rev 2013

Import of ESBL producers by travelers



Lübbert C et al. Int J Med Microbiol 2015; 305: 148-56



AMP/SUL = ampicillin/sulbactam; PIP/TAZ = piperacillin/tazobactam; TMP/SMX = trimethoprim-sulfamethoxazole

Lübbert C et al. Int J Med Microbiol 2015; 305: 148-56

Import of ESBL producers by travelers

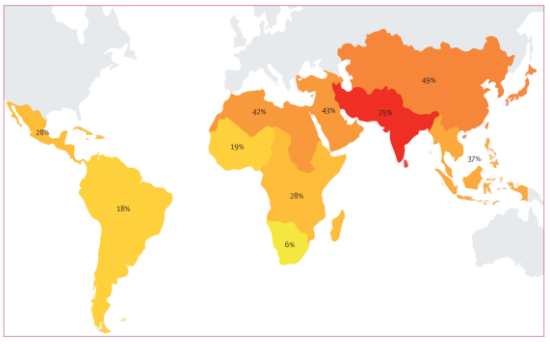


Figure 1: Percentages of travellers that acquired β-lactamase-producing Enterobacteriaceae per subregion, according to the United Nations geoscheme

Arcilla MS et al. Lancet Infect Dis 2016

Acquisition of ESBL producing Enterobacteriaceae by travelers – persistence and spread

packaged beverages showed no protective effect. The ESBL-PE persistence rate after 6 months was 8.6% (3/35). We conclude that global efforts are needed to address the further spread of ESBL-PE in the community. Active surveillance and contact isolation precautions may be recommended at admission to medical facilities especially for patients who traveled to India and South East Asia in the previous 6 months.

Lübbert C et al. Int J Med Microbiol 2015; 305: 148-56

Findings 633 (34·3%) of 1847 travellers who were ESBL negative before travel and had available samples after return had acquired ESBL-E during international travel (95% CI 32·1–36·5), with the highest number of acquisitions being among those who travelled to southern Asia in 136 of 181 (75·1%, 95% CI 68·4–80·9). Important predictors for acquisition of ESBL-E were antibiotic use during travel (adjusted odds ratio 2·69, 95% CI 1·79–4·05), traveller's diarrhoea that persisted after return (2·31, 1·42–3·76), and pre-existing chronic bowel disease (2·10, 1·13–3·90). The median duration of colonisation after travel was 30 days (95% CI 29–33). 65 (11·3%) of 577 remained colonised at 12 months. CTX-M enzyme group 9 ESBLs were associated with a significantly increased risk of sustained carriage (median duration 75 days, 95% CI 48–102, p=0·0001). Onward transmission was found in 13 (7·7%) of 168 household members. The probability of transmitting ESBL-E to another household member was 12% (95% CI 5–18).

Interpretation Acquisition and spread of ESBL-E during and after international travel was substantial and worrisome. Travellers to areas with a high risk of ESBL-E acquisition should be viewed as potential carriers of ESBL-E for up to 12 months after return.

Marcilla MS et al. Lancet Infect Dis 2016

RESEARCH

Overdevest I et al. EID 2011

Extended-Spectrum β-Lactamase Genes of *Escherichia coli* in Chicken Meat and Humans, the Netherlands

Ilse Overdevest, Ina Willemsen, Martine Rijnsburger, Andrew Eustace, Li Xu, Peter Hawkey, Max Heck, Paul Savelkoul, Christina Vandenbroucke-Grauls, Kim van der Zwaluw, Xander Huijsdens, and Jan Kluytmans

ESBL Genes of *E. coli* in Chicken Meat and Humans

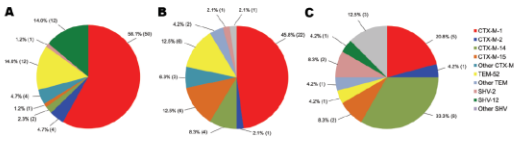
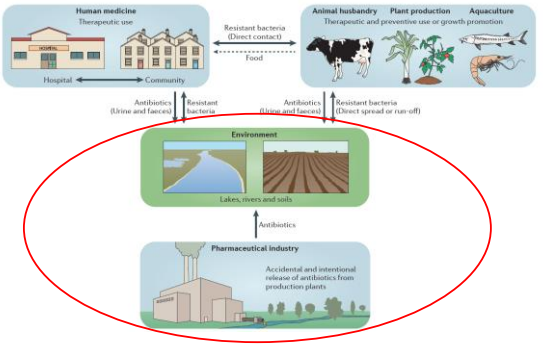


Figure 1. Distribution of extended-spectrum β-lactamase genes in chicken meat (A), human rectal swabs (B), and human blood cultures (C), the Netherlands. Values in parentheses are no. positive.

One health approach



Andersson DI & Hughes D. Nature Rev Microbiol 2014

Table 1. Studies on treated industrial effluents, waterways, river sediment, soil and groundwater where pollution with APIs from manufacturing is documented.

country	pharmaceuticals detected	matrices/max. concentration	year	references
China	oxytetracycline—antibiotic	effluent: 1065 mg l^{-1}	1988	[6]
India	salicylic acid—anti-inflammatory	effluent: 2270 mg l^{-1}	1993	[7]
Denmark	sulfonamide antibiotics and intermediates/ metabolites	groundwater: sulfaquinoxaline 1.6 mg l^{-1}	1995	[2]
Germany	phenazone and metabolites	groundwater: phenazone 3.95 µg l^{-1} tap water: phenazone 0.4 µg l^{-1}	2002	[3]
Germany	phenazone and metabolites	groundwater: phenazone 2.5 µg l^{-1} tap water: phenazone 0.25 µg l^{-1}	2004	[4]
Switzerland	venlafaxine—antidepressant	surface water: 0.8 µg l^{-1}	2004	[8]
Norway	bactracin—antibiotic	effluent: up to 250 kg per discharge	2005	[9]
China	oestrogenic sex steroids	effluent: ethinylestradiol 53 ng l^{-1}	2006	[10]
India	many, including fluoroquinolone antibiotics	effluent: ciprofloxacin 31 mg l^{-1}	2007	[11]
China	oxytetracycline—antibiotic	effluent: 19.5 mg l^{-1} surface water: 712 µg l^{-1}	2008	[12]
China/Taiwan	many	surface water: diclofenac 27 µg l^{-1}	2008	[13]
Croatia	sulfonamide antibiotics	effluent: sulfaguanidine more than 1.1 mg l^{-1}	2008	[14]
China	penicillin G and its metabolites	effluent: penilloic acid* 44 mg l^{-1} surface water: penilloic acid* 11.6 mg l^{-1}	2008	[15]
China/Taiwan	sulfonamides, NSAIDs and other drugs	effluent: sulfamethoxazole 1.34 mg l^{-1}; ibuprofen 1.5 mg l^{-1}	2009	[16]
India	many, including fluoroquinolone antibiotics	effluent: ciprofloxacin 14 mg l^{-1} groundwater: ofloxacin 20 µg l^{-1} surface water: ciprofloxacin 6.5 mg l^{-1}	2009	[17]
Switzerland	metformin—antiviral	surface water: 980 ng l^{-1}	2010	[18]
USA	narcotic opioids	effluent: metoxalone 1.8 mg l^{-1}	2010	[19]
India	fluoroquinolone antibiotics	river sediment: ciprofloxacin 494 mg kg^{-1} organic material	2011	[20]
Korea	lincomycin—antibiotic	effluent: 43.9 mg l^{-1}	2011	[21]
Israel	venlafaxine and metabolites	effluent: venlafaxine 91.2 µg l^{-1}	2012	[22]
Israel	carbamazepine and venlafaxine	effluent: venlafaxine 10.7 mg l^{-1}	2013	[23]
Pakistan	several antibiotics	surface water: sulfamethoxazole 49 µg l^{-1}	2013	[24]
India	fluoroquinolone antibiotics	groundwater: ciprofloxacin 770 mg l^{-1} soil: ciprofloxacin 7.2 µg g^{-1} organic matter	2014	[25]
Spain	venlafaxine	effluent: 2.6 µg l^{-1}	2014	[26]

*Metabolite. Levels of penilloilic G were in the ng l^{-1} range.

Larsson DGJ. Phil Trans R Soc B 2014; 369: 20130571


PHARMAZEUTISCHE ZEITUNG online

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NACHRICHTEN

Pharmastandort Deutschland: Apotheke der Welt war einmal

Deutschland ist heute nicht mehr die Apotheke der Welt. Darauf machte Professor Dr. Andreas Busch (Foto) von Bayer HealthCare beim Kongress des Wirtschaftsverbandes FVF in Düsseldorf aufmerksam. Unter den 49 in Deutschland neu auf den Markt gebrachten Wirkstoffen im vergangenen Jahr befänden sich nur fünf von deutschen Unternehmen.

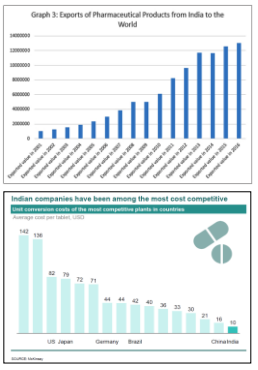
Hierzulande wird dem Apotheker zufolge zwar mehr in Forschung und Entwicklung investiert als in jedem anderen europäischen Land. Im internationalen Vergleich ist es aber dennoch wenig. »Die pharmazeutische Industrie in den USA gibt mehr als zehnmal so viel dafür aus.«

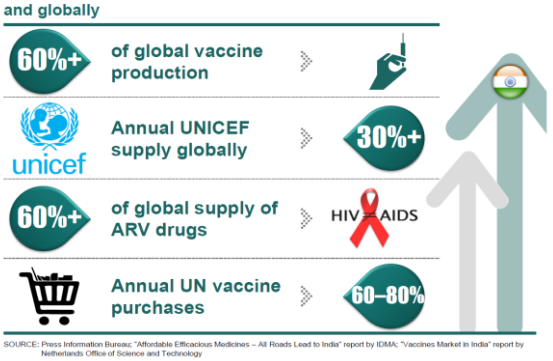
Um Forschung und Entwicklung in Deutschland wieder attraktiver zu machen, schlug Busch Steuervergünstigungen für Unternehmen vor, die sich in diesem Bereich engagieren. Er kritisierte, dass die bestehenden Datenschutzregeln für Forschung und Entwicklung von Arzneimitteln in Deutschland eine höhere Hürde darstellten als in jedem anderen Land. Zudem betonte er, dass man insbesondere in Deutschland für eine höhere Akzeptanz von Innovationen sorgen müsse. Auf die Frage, ob Wissenschaft und Technik das Leben gesünder und einfacher machten, hätten bei einer Befragung hierzulande nur 69 Prozent mit »Ja« geantwortet.

Die Gesellschaft müsse auch akzeptieren, dass die Industrie zum Beispiel mit Universitäten und akademischen Instituten heute stärker zusammenarbeitet. Grundsätzlich, so Busch, seien die Voraussetzungen für Forschung und Entwicklung in Deutschland exzellent. Als Beispiele führte er die umfassende Forschungslandschaft an, das große Knowhow im Bereich Technik und Herstellung sowie die hohe Dichte an Krankenhäusern, welche für klinische Studien wichtig sind. (ks)

29.09.2015 | PZ
Foto: PZ/Alois Müller

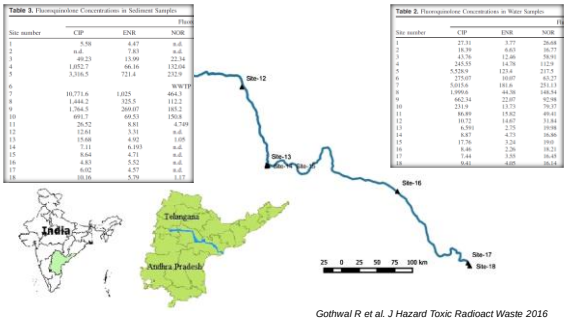
Big Pharma in India ...



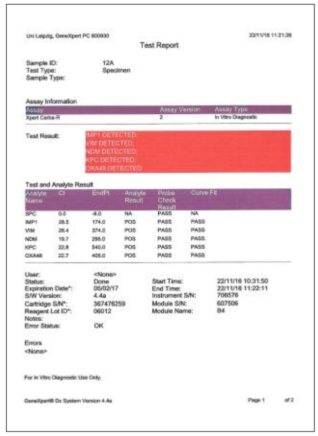


SOURCE: Press Information Bureau; "Affordable Efficacious Medicines – All Roads Lead to India" report by IDMA; "Vaccines Market in India" report by Netherlands Office of Science and Technology

Occurrence of High Levels of Fluoroquinolones in Aquatic Environment due to Effluent Discharges from Bulk Drug Manufacturers



Gothwal R et al. J Hazard Toxic Radioact Waste 2016



Uni Leipzig, GeneXpert PC 800930 — 22/11/16 11:21:28

Test Report

Sample ID: 12A
Test Type: Specimen
Sample Type:

Assay Information

Assay	Assay Version	Assay Type
Xpert Carba-R	2	In Vitro Diagnostic

Test Result: IMP1 DETECTED; VIM DETECTED; NDM DETECTED; KPC DETECTED; OXA48 DETECTED

Test and Analyte Result

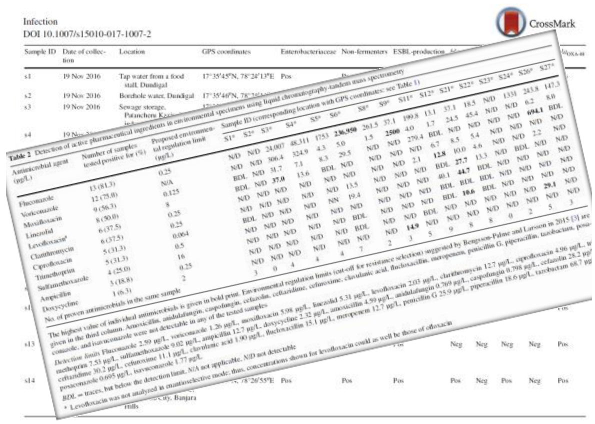
Analyte Name	Ct	EndPt	Analyte Result	Probe Check Result	Curve Fit
SPC	0.0	-6.0	NA	PASS	NA
IMP1	28.5	174.0	POS	PASS	PASS
VIM	28.4	374.0	POS	PASS	PASS
NDM	19.7	295.0	POS	PASS	PASS
KPC	22.8	540.0	POS	PASS	PASS
OXA48	22.7	405.0	POS	PASS	PASS

User: <None>
Status: Done — Start Time: 22/11/16 10:31:50
Expiration Date*: 05/02/17 — End Time: 22/11/16 11:22:11
S/W Version: 4.4a — Instrument S/N: 706576
Cartridge S/N*: 367476259 — Module S/N: 607506
Reagent Lot ID*: 06012 — Module Name: B4
Notes:
Error Status: OK

Errors
<None>

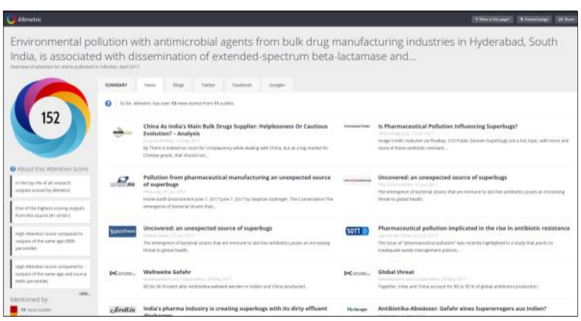
For In Vitro Diagnostic Use Only.

GeneXpert® Dx System Version 4.4a — Page 1 of 2



Lübbert C et al. Infection 2017

Attention Scores – Altmetric
May - December 2017



Hyderabad, 6 October 2017
Gandi Lake in Sangareddy District

www.gettyimages.com

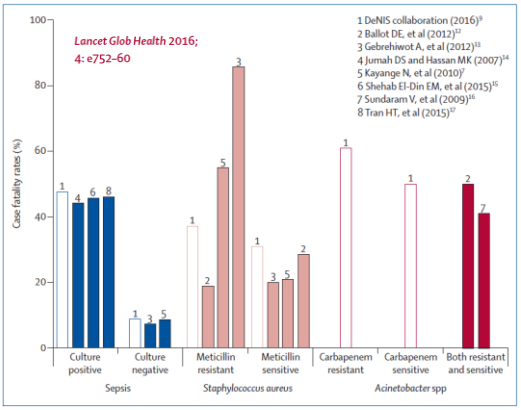
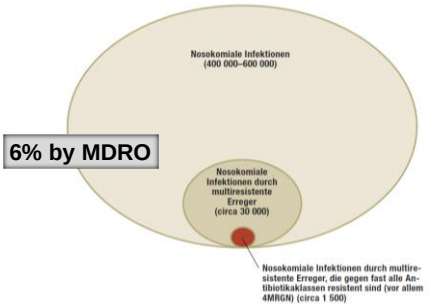


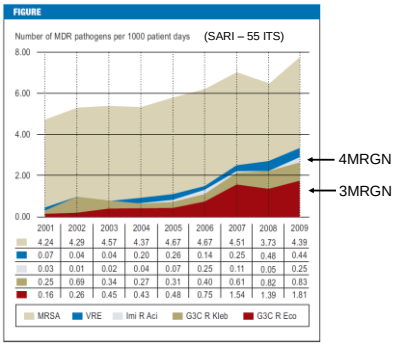
Figure: Case fatality rates from the DeNIS study (unshaded) compared with earlier studies (in solid colours)

Nosocomial infections in Germany by MDRO – size relation



Gastmeier P & Fätkenheuer G. Dtsch Ärztebl 2015; 112: A674

MDRO – How bad is it really in Germany?



Mattner F et al. Dtsch Ärztebl Int 2012; 109: 39-45

Detection of carbapenemases in Germany – results from the NRC

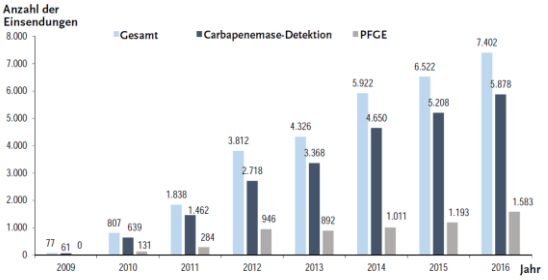


Abb. 1: Anzahl der jährlichen Einsendungen an das NRZ für gramnegative Krankenhauserreger; 2009–2016

Pfennigwerth N et al. Epi Bull 26/2017

Bad Bugs ...

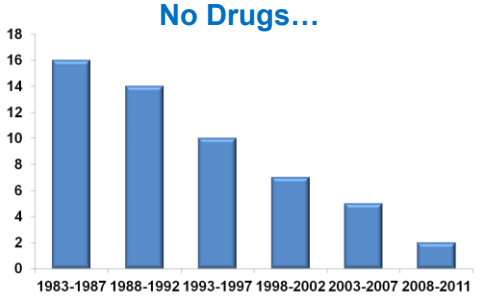
Attention!

This is a KPC producing strain

Institute for Medical Microbiology
Leipzig University Hospital, 2012

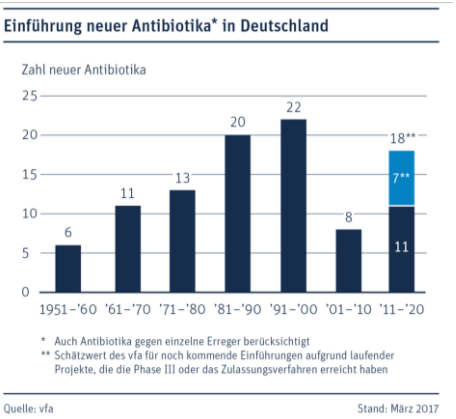
Antibiogramm	1	
Ampicillin	>32	R
Ampicillin+Sulbactam	>32	R
Piperacillin	>64	R
Piperacillin+Tazobac	>64	R
Ceftibuten	>4	R
Cefuroxim	>32	R
Cefotaxim/Ceftriaxon	>8	R
Ceftazidim	>32	R
Aztreonam	>16	R
Imipenem	>16	R
Meropenem	>16	R
Ertapenem	>4	R
Doripenem	=16	R
Gentamicin	=2	S
Amikacin	=32	R
Tobramycin	>16	R
Colistin	=8	R
Fosfomycin	>128	R
Levofloxacin	>8	R
Ciprofloxacin	>4	R
Moxifloxacin	>4	R
Doxycyclin	=4	*
Tigecyclin	=0.5	S

No Drugs…



➡ On the threshold of a post-antibiotic era

IDSA Public Policy. Clin Infect Dis 2009; 48: 1-12



Known endemic areas of KPC producing *Klebsiella* (2013)

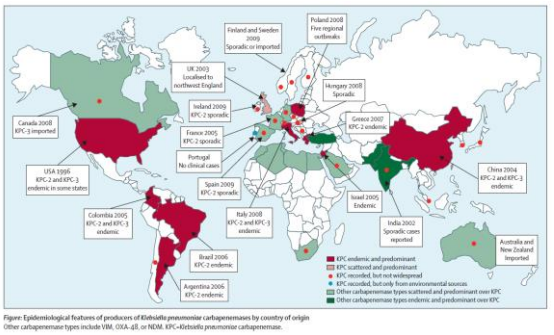
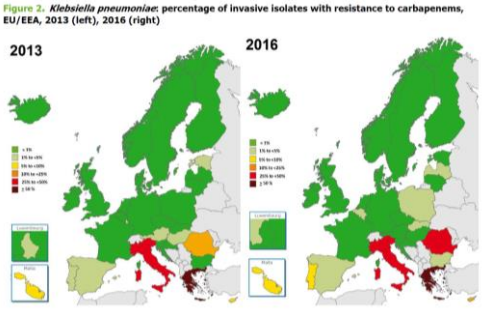


Figure: Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin
Other carbapenemase types include VIM, OXA-48, or NDM. KPC=*Klebsiella pneumoniae* carbapenemase.

Munoz-Price LS P et al. Lancet Infect Dis 2013; 13: 785-96

Epidemiology of carbapenem-resistant *Klebsiella pneumoniae* in Europe



https://ecdc.europa.eu/sites/portal/files/documents/AMR-surveillance-Europe-2016.pdf

Süddeutsche.de Panorama

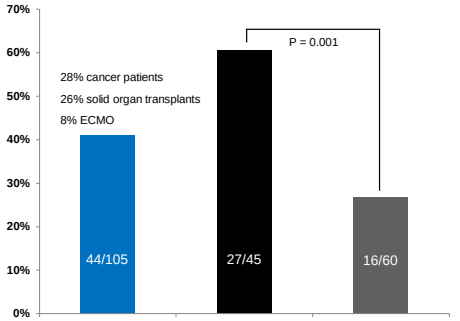
7. Juni 2012, 12:00 Uniklinikum Leipzig

30 Tote nach Keimbefall

Es ist der größte bekannte Ausbruch dieser Art: Im Leipziger Universitätsklinikum haben sich in den vergangenen zwei Jahren 63 Menschen mit einem multiresistenten Erreger infiziert. Wie jetzt bekannt wurde, ist knapp die Hälfte dieser Patienten gestorben.

Eingeschleppt wurden die Erreger nach Erkenntnissen der Klinikleitung 2010 von einem deutschen Patienten, der auf Rhodos im Krankenhaus gewesen war. Er litt an

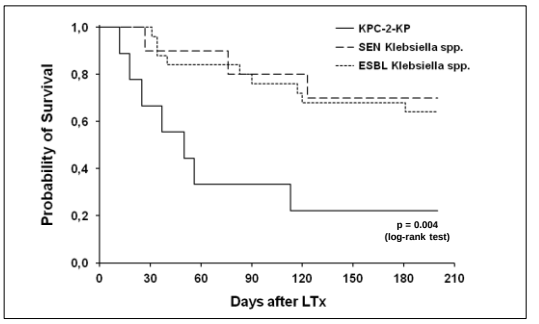
KPC-2-KP outbreak at the Leipzig University Hospital (2010-13)



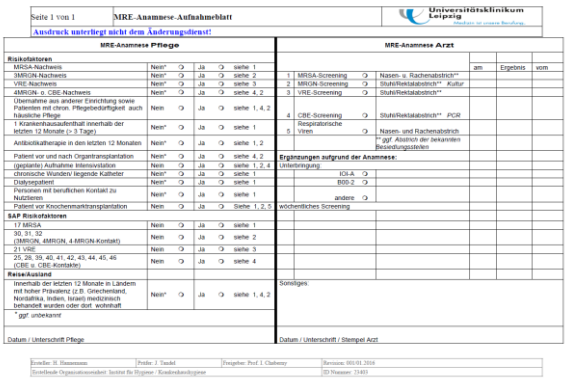
Lübbert C et al. Am J Infect Control 2014; 42: 376-80

Patients with immunosuppression

Effect of KPC-2-KP in liver transplant recipients



Lübbert C et al. Liver Transplantation 2014; 20: 736-8



Seite 1 von 1 — MRE-Anamnese-Aufnahmeblatt — Universitätsklinikum Leipzig

Ausdruck unterliegt nicht dem Änderungsdienst!

MRE-Anamnese Pflege

Risikofaktoren					am	Ergebnis	vom
MRSA-Nachweis	Nein*	Ja	siehe 1				
3MRGN-Nachweis	Nein*	Ja	siehe 2				
VRE-Nachweis	Nein*	Ja	siehe 3				
4MRGN- o. CBE-Nachweis	Nein*	Ja	siehe 4, 2				
Übernahme aus anderer Einrichtung sowie Patienten mit chron. Pflegebedürftigkeit auch häusliche Pflege	Nein	Ja	siehe 1, 4, 2				
1 Krankenhausaufenthalt innerhalb der letzten 12 Monate (> 3 Tage)	Nein*	Ja	siehe 1				
Antibiotikatherapie in den letzten 12 Monaten	Nein*	Ja	siehe 1, 2				
Patient vor und nach Organtransplantation	Nein*	Ja	siehe 4, 2				
(geplante) Aufnahme Intensivstation	Nein	Ja	siehe 1, 2, 4				
chronische Wunden/ liegende Katheter	Nein*	Ja	siehe 1				
Dialysepatient	Nein*	Ja	siehe 1				
Personen mit beruflichen Kontakt zu Nutztieren	Nein*	Ja	siehe 1				
Patient vor Knochenmarktransplantation	Nein	Ja	Siehe 1, 2, 5				
SAP Risikofaktoren							
17 MRSA	Nein	Ja	siehe 1				
30, 31, 32 (3MRGN, 4MRGN, 4-MRGN-Kontakt)	Nein	Ja	siehe 2				
21 VRE	Nein	Ja	siehe 3				
25, 28, 39, 40, 41, 42, 43, 44, 45, 46 (CBE o. CBE-Kontakte)	Nein	Ja	siehe 4				
Reiseclusland							
Innerhalb der letzten 12 Monate in Ländern mit hoher Prävalenz (z B. Griechenland, Nordafrika, Indien, Israel) medizinisch behandelt wurden oder dort wohnhaft	Nein*	Ja	siehe 1, 4, 2				

* ggf. unbekannt

Datum / Unterschrift Pflege

MRE-Anamnese Arzt

1	MRSA-Screening	☐	Nasen- u. Rachenabstrich**
2	MRGN-Screening	☐	Stuhl/Rektalabstrich** Kultur
3	VRE-Screening	☐	Stuhl/Rektalabstrich**
4	CBE-Screening	☐	Stuhl/Rektalabstrich** PCR
5	Respiratorische Viren	☐	Nasen- und Rachenabstrich

** ggf. Abstrich der bekannten Besiedlungsstellen

Ergänzungen aufgrund der Anamnese:

Unterbringung:
- IOI-A ☐
- B00-2 ☐
- andere ☐

wöchentliches Screening

Sonstiges:

Datum / Unterschrift / Stempel Arzt

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