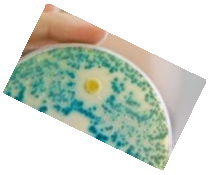
UBA Workshop

Brussels, 7 November 2018

Universitätsklinikum Leipzig
Medizin ist unsere Berufung.

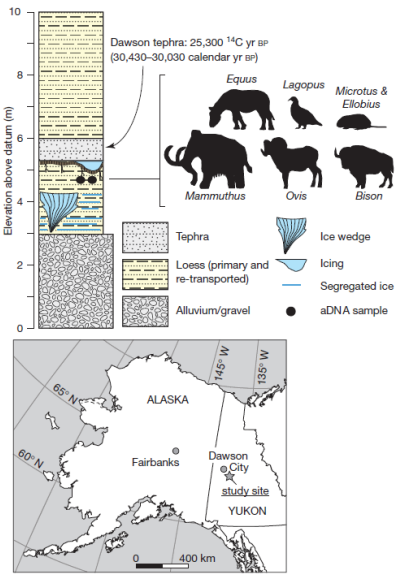
ZENTRUM FÜR INFEKTIONSMEDIZIN

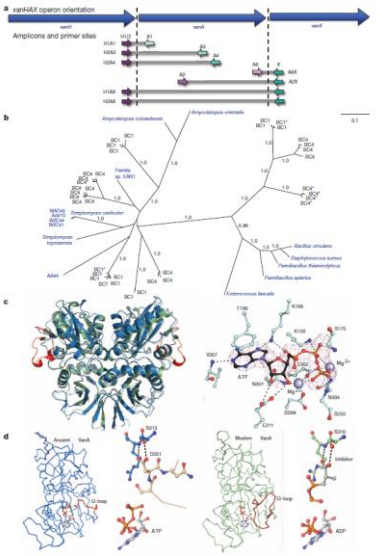
Multi-drug resistance as a growing global problem and its impact in Germany



Prof. Christoph Lübbert, MD, PhD, DTM&H
Head, Division of Infectious Diseases and Tropical Medicine
Department of Gastroenterology
Leipzig University Hospital, Germany

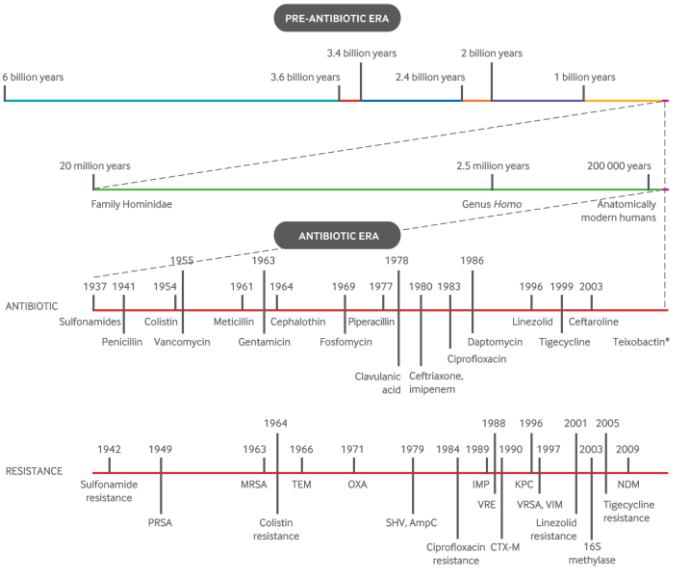
Antibiotic resistance is ancient





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

Timeline of antimicrobial resistance



Iredell J et al. BMJ 2015; 351: h6420

PLOS ONE

RESEARCH ARTICLE

Antimicrobial Resistance: The Major Contribution of Poor Governance and Corruption to This Growing Problem

Peter Collignon[1,2]*, Prema-chandra Athukorala[3,4], Sanjaya Senanayake[5,6], Fahad Khan[3]

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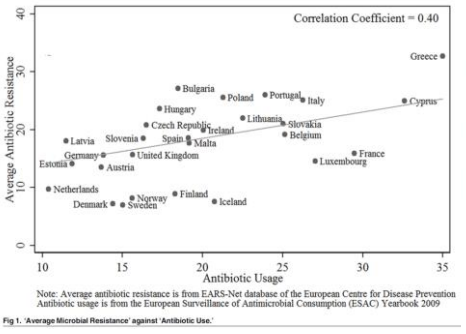
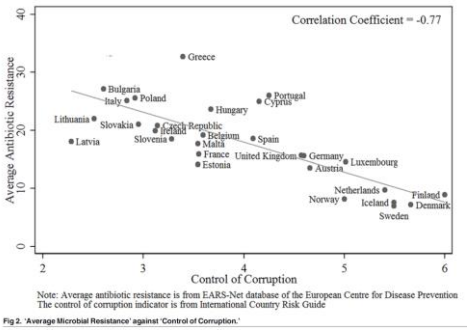


Note: Average antibiotic resistance is from EARS-Net database of the European Centre for Disease Prevention Antibiotic usage is from the European Surveillance of Antimicrobial Consumption (ESAC) Yearbook 2009

Fig 1. 'Average Microbial Resistance' against 'Antibiotic Use.'



Note: Average antibiotic resistance is from EARS-Net database of the European Centre for Disease Prevention The control of corruption indicator is from International Country Risk Guide

Fig 2. 'Average Microbial Resistance' against 'Control of Corruption.'

Collignon PR et al. PLoS ONE 2015

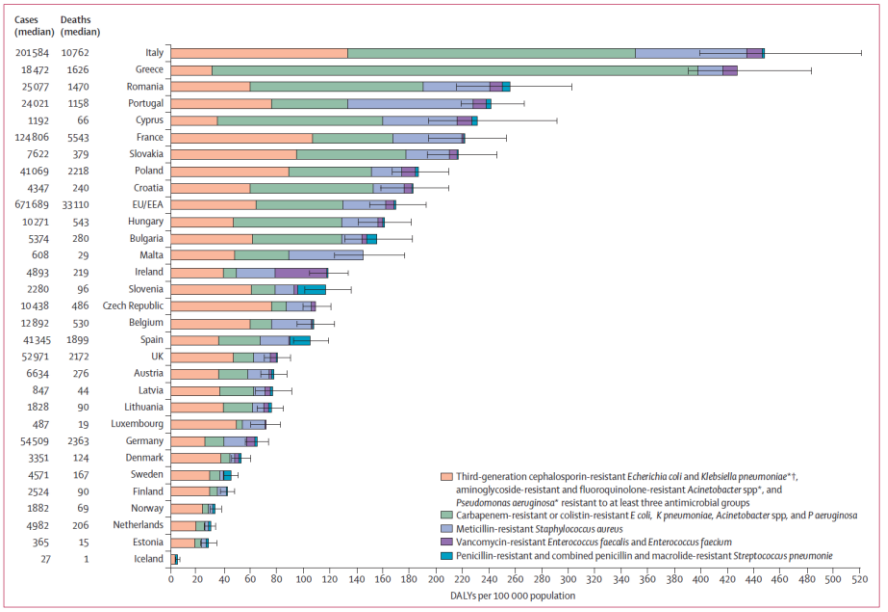
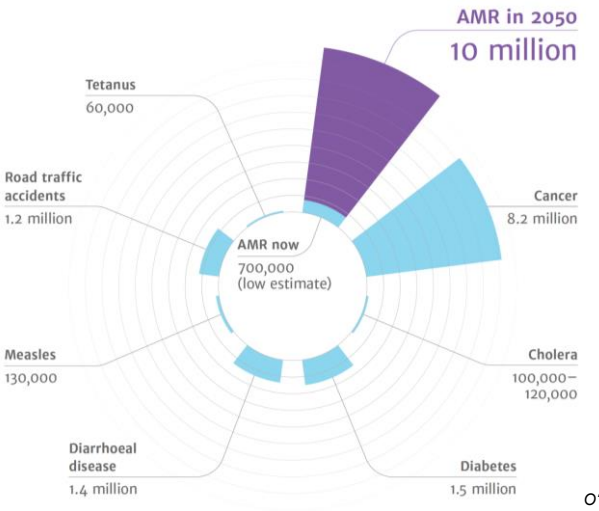


Figure 3: **Burden of infections with antibiotic-resistant bacteria in DALYs, EU and European Economic Area, 2015**
Error bars are 95% uncertainty intervals. Greece did not report data on *S pneumoniae* isolates to the European Antimicrobial Resistance Surveillance Network in 2015. DALY rates are age-standardised to limit the effect of demographic differences across countries; numbers of cases and deaths are not age-standardised. DALYs=disability-adjusted life-years. *Excludes those resistant to carbapenem or colistin. †In 2015, most of the third-generation cephalosporin-resistant *E coli* (88·6%) and *K pneumoniae* (85·3%) isolates reported to the European Antimicrobial Resistance Surveillance Network produced an extended-spectrum β-lactamase.[9]

Cassini A et al. Lancet Infect Dis 2018 (ePub ahead of print)

AMR causes extra deaths



O'Neill, May 2016

Sources:
Diabetes: www.whi.int/mediacentre/factsheets/fs312/en/ Cancer: www.whi.int/mediacentre/factsheets/fs297/en/
Cholera: www.whi.int/mediacentre/factsheets/fs107/en/ Diarrhoeal disease: www.sciencedirect.com/science/article/pii/S0140673612617280
Measles: www.sciencedirect.com/science/article/pii/S0140673612617280 Road traffic accidents: www.whi.int/mediacentre/factsheets/fs358/en/
Tetanus: www.sciencedirect.com/science/article/pii/S0140673612617280

Review on Antimicrobial Resistance

Main drivers of AMR

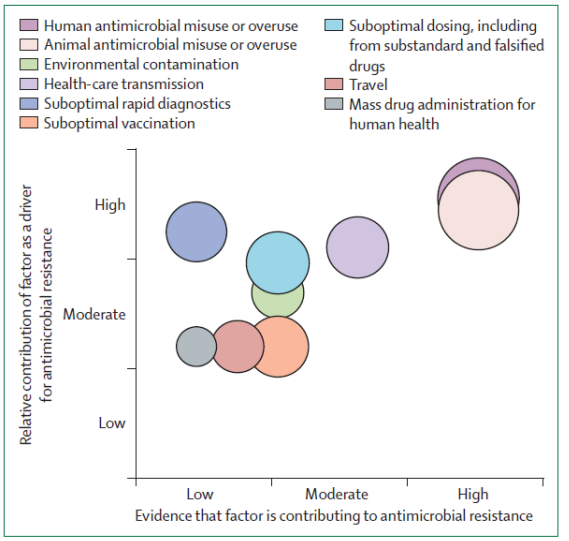


Figure 3: **Role of modifiable drivers for antimicrobial resistance: a conceptual framework**

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

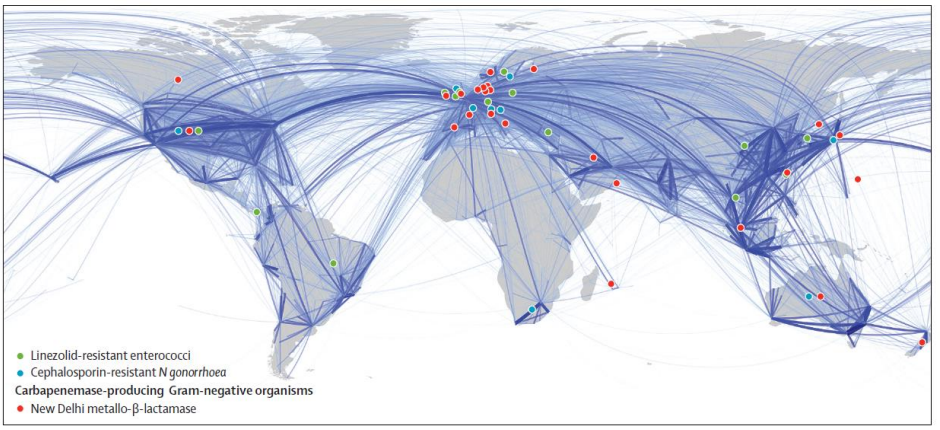
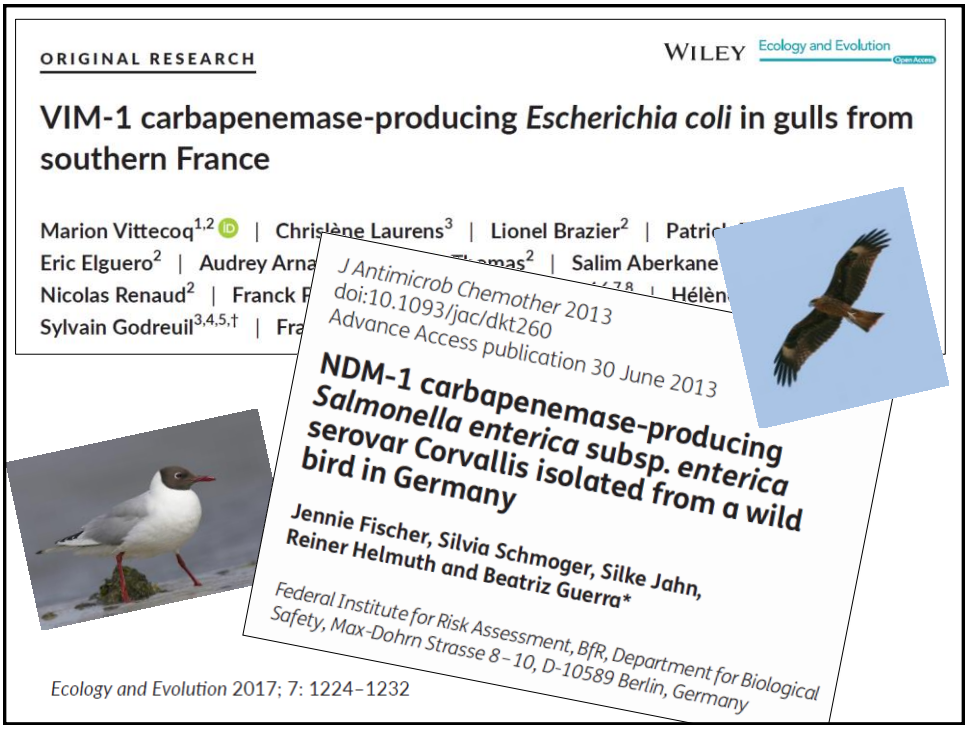


Figure 2: **Worldwide travel routes and emergence of antimicrobial resistance**

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,[52] linezolid-resistant enterococci,[53] and reported cefixime/ceftriaxone treatment failures for *Neisseria gonorrhoea*.[54] 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

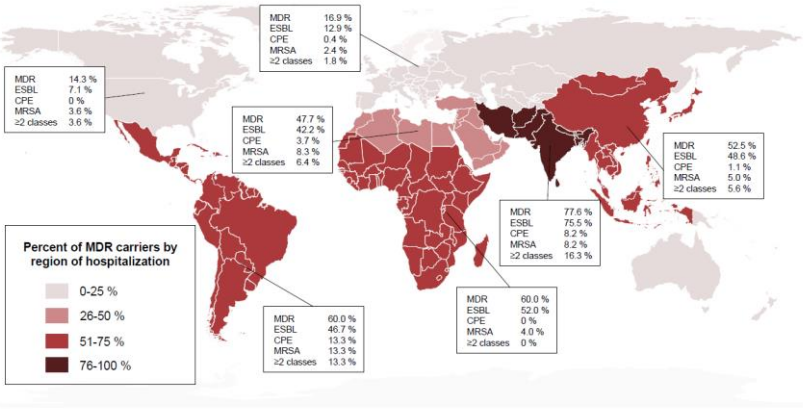
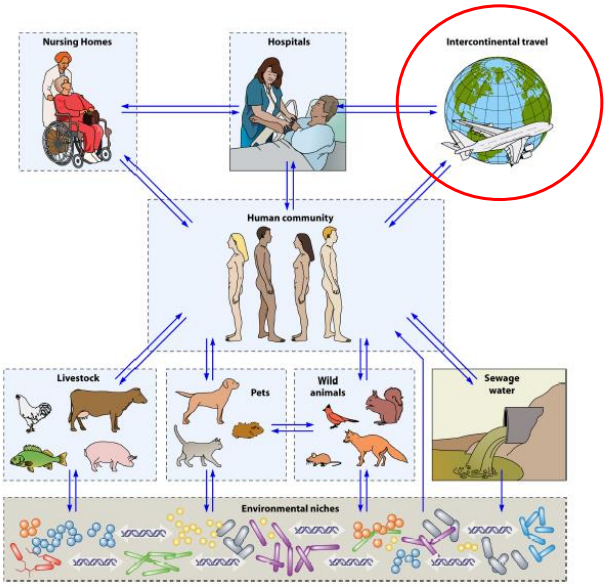


Fig. 1. Prevalence of multidrug-resistant bacteria carriage in returning patients according to the geographic region of their prior hospitalization. Abbreviations: MDR, multidrug-resistant bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; ESPL-PE, extended-spectrum β-lactamase-producing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

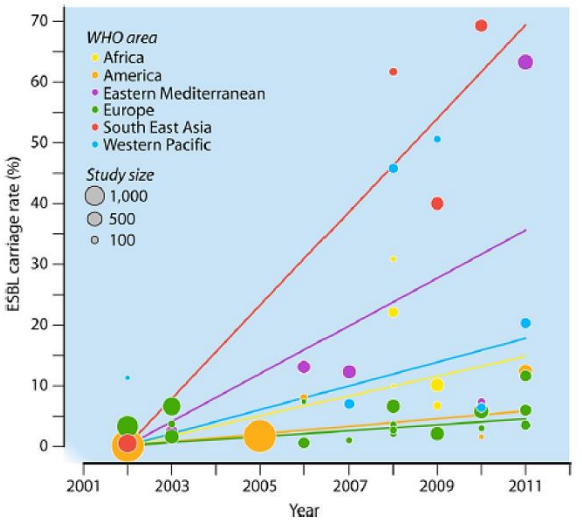
Khawaha T et al. Clin Microbiol Infect 2017

MDRO and their reservoirs



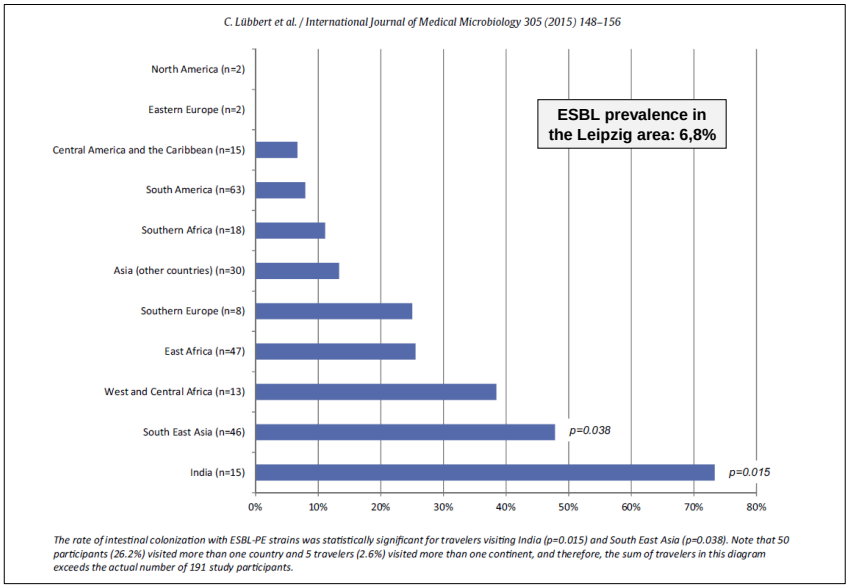
Wörther PL et al. Clin Microbiol Rev 2013

ESBL producing Enterobacteria – global dynamics

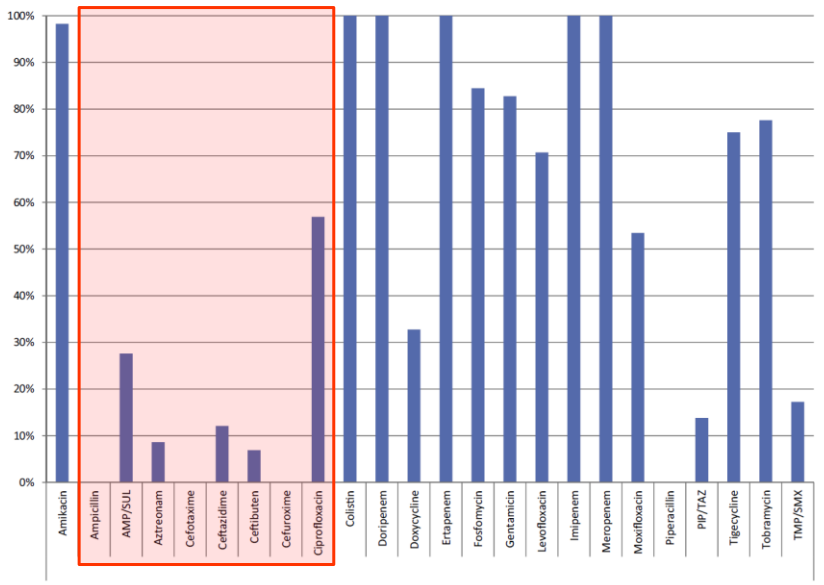


Wörther PL et al. Clin Microbiol Rev 2013

Import of ESBL producers by travelers



Lübbert C et al. Int J Med Microbiol 2015



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

Lübbert C et al. Int J Med Microbiol 2015

Import of ESBL producers by travelers

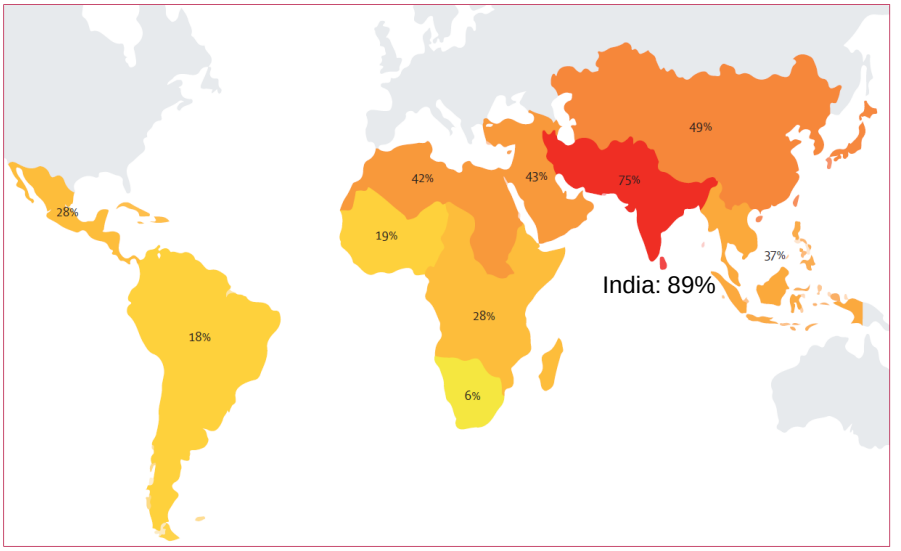


Figure 1: Percentages of travellers that acquired β-lactamase-producing Enterobacteriaceae per subregion, according to the United Nations geoscheme

Arcilla MS et al. Lancet Infect Dis 2016

Acquisition of ESBL producing Enterobacteria 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.

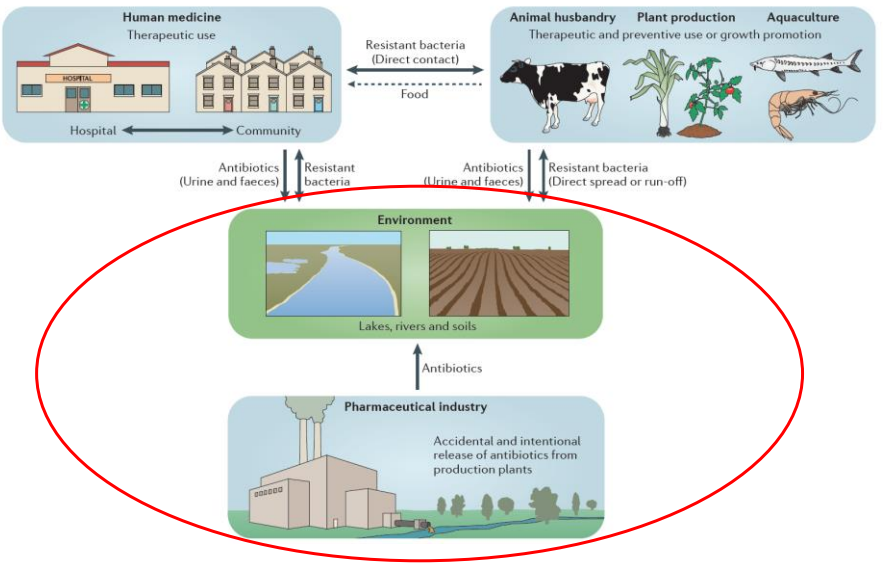
Lübbert C et al. Int J Med Microbiol 2015; 305: 148-56

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.

Arcilla MS et al. Lancet Infect Dis 2016

The One Health Approach



Andersson DI & Hughes D. Nature Rev Microbiol 2014

Big Pharma in India ...

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NACHRICHTEN

Pharmastandort Deutschland: Apotheke der Welt war einmal

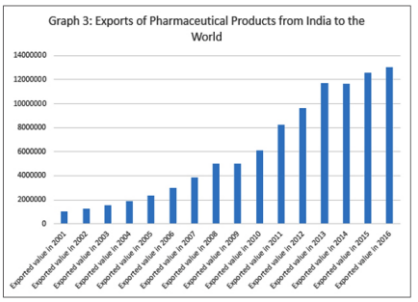
Deutschland ist heute nicht mehr die Apotheke der Welt. Darauf machte Professor Dr. Andreas Busch (Foto) von Bayer HealthCare beim Kongress des Weltapothekerverbandes FIP in Düsseldorf aufmerksam. Unter den 49 in Deutschland neu auf den Markt gebrachten Wirkstoffen im vergangenen Jahr befänden sich nur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

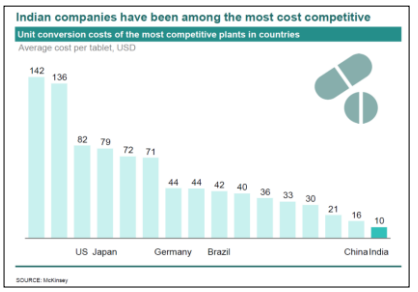
Hierzulande wird dem Apotheker zufolge zwar mehr in Forschung und Entwicklung investiert als in jedem anderen europäischen Land. Im internationalen Vergleich ist es aber dennoch wenig. «Die pharmazeutische Industrie in den USA gibt mehr als zehnmal so viel dafür aus.»

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 60 Prozent mit «Ja» geantwortet.

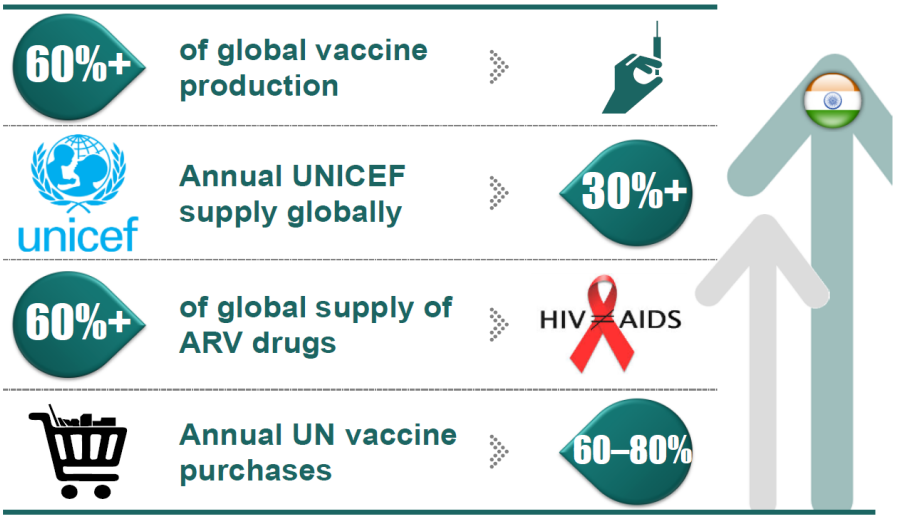
Die Gesellschaft müsse auch akzeptieren, dass die Industrie zum Beispiel mit Universitäten und akademischen Instituten heute stärker zusammenarbeitet. Grundsätzlich, so Busch, seien die Voraussetzungen für Forschung und Entwicklung in Deutschland exzellent. Als Beispiele führte er die umfassende Forschungslandschaft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

29.09.2015 I PZ
Foto: PZ/Alois Müller





Indian industry's contribution to drug access, both in India and globally



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


North German Broadcasting Corporation (NDR)
Department of Investigative Journalism
November 2016
Tilo Gummel, ARD
Christine Adelhardt, NDR
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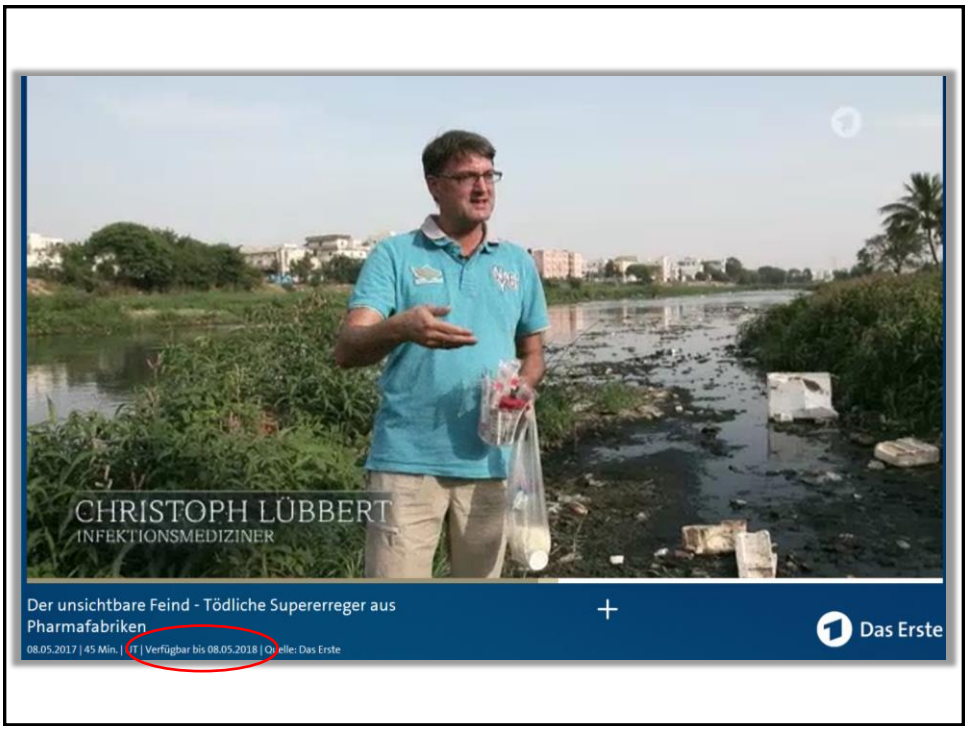
Christoph Lübbert, UKL


CHRISTOPH LÜBBERT
INFEKTIONSMEDIZINER
Der unsichtbare Feind - Tödliche Supererreger aus Pharmafabriken
08.05.2017 | 45 Min. | | Verfügbar bis 08.05.2018 | Quelle: Das Erste
Das Erste

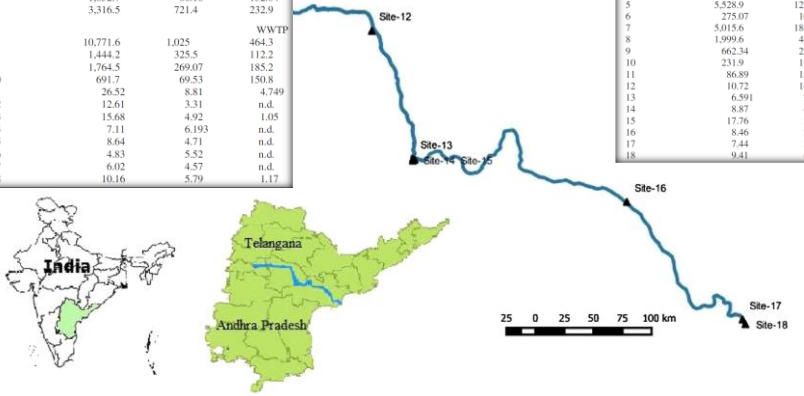
Occurrence of High Levels of Fluoroquinolones in Aquatic Environment due to Effluent Discharges from Bulk Drug Manufacturers

Table 3. Fluoroquinolone Concentrations in Sediment Samples

Site number	CIP	ENR	NOR
1	5.58	4.47	n.d.
2	n.d.	7.83	n.d.
3	49.23	13.99	22.34
4	1,052.7	66.16	132.04
5	3,316.5	721.4	232.9
6			WWTP
7	10,771.6	1,025	464.3
8	1,444.2	325.5	112.2
9	1,764.5	269.07	185.2
10	691.7	69.53	150.8
11	26.52	8.81	4.749
12	12.61	3.31	n.d.
13	15.68	4.92	1.05
14	7.11	6.193	n.d.
15	8.64	4.71	n.d.
16	4.83	5.52	n.d.
17	6.02	4.57	n.d.
18	10.16	5.79	1.17

Table 2. Fluoroquinolone Concentrations in Water Samples

Site number	CIP	ENR	NOR
1	27.31	3.77	26.68
2	18.39	6.63	16.77
3	43.76	12.46	58.91
4	245.55	14.78	112.9
5	5,528.9	123.4	217.5
6	275.07	10.07	63.27
7	5,015.6	181.6	251.13
8	1,999.6	44.38	148.54
9	662.34	22.07	92.98
10	231.9	13.73	79.37
11	86.89	15.82	49.41
12	10.72	14.67	31.84
13	6.591	2.75	19.98
14	8.87	4.73	16.86
15	17.76	3.24	19.0
16	8.46	2.26	18.21
17	7.44	3.55	16.45
18	9.41	4.05	16.14



Gothwal R et al. J Hazard Toxic Radioact Waste 2016

Infection
DOI 10.1007/s15010-017-1007-2

CrossMark

Sample ID	Date of collection	Location	GPS coordinates	Enterobacteriaceae	Non-fermenters	ESBL-production	bla_{OXA-48}
s1	19 Nov 2016	Tap water from a food stall, Dundigal	17°35′45″N, 78°24′13″E	Pos			
s2	19 Nov 2016	Borehole water, Dundigal	17°35′46″N, 78°24′				
s3	19 Nov 2016	Sewage storage, Patancheru K…	17°…				
s4	19 Nov…	…	…				
…							
s13						Neg	Neg
s14		…ny, Banjara	…, 78°26′55″E	Pos	Pos	Pos	Pos

Table 2 Detection of active pharmaceutical ingredients in environmental specimens using liquid chromatography-tandem mass spectrometry

Antimicrobial agent (μg/L)	Number of samples tested positive for (%)	Proposed environmental regulation limit (μg/L)	Sample ID (corresponding location with GPS coordinates: see Table 1)														
			S1*	S2*	S3*	S4*	S5*	S6*	S8*	S9*	S11*	S12*	S21*	S22*	S23*	S24*	S26*	S27*
Fluconazole	13 (81.3)	0.25	N/D	N/D	24,007	48,311	1753	**236,950**	261.5	37.1	199.8	13.1	37.1	18.5	N/D	1331	243.8	147.3
Voriconazole	12 (75.0)	N/A	N/D	N/D	306.4	324.9	4.3	5.0	1.5	**2500**	4.0	1.7	24.5	45.4	N/D	N/D	6.2	8.0
Moxifloxacin	9 (56.3)	0.125	BDL	N/D	31.7	7.1	8.3	29.5	N/D	N/D	279.4	BDL	N/D	N/D	N/D	N/D	**694.1**	BDL
Linezolid	8 (50.0)	8	BDL	N/D	**37.0**	13.6	BDL	N/D	N/D	N/D	N/D	6.7	8.5	5.4	N/D	N/D	N/D	N/D
Levofloxacin[a]	6 (37.5)	0.25	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	**12.8**	10.0	4.6	N/D	N/D	2.2	N/D
Clarithromycin	5 (31.3)	0.25	N/D	N/D	N/D	N/D	N/D	13.5	N/D	N/D	N/D	2.1	**27.7**	13.3	N/D	BDL	N/D	N/D
Ciprofloxacin	5 (31.3)	0.064	BDL	N/D	N/D	N/D	NN	19.4	N/D	N/D	N/D	BDL	**44.7**	BDL	N/D	N/D	N/D	N/D
Trimethoprim	4 (25.0)	0.5	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	40.1	BDL	BDL	N/D	N/D	N/D	N/D
Sulfamethoxazole	3 (18.8)	16	N/D	N/D	N/D	N/D	N/D	BDL	N/D	N/D	N/D	BDL	BDL	**10.6**	BDL	N/D	N/D	**29.1**
Ampicillin	1 (6.3)	0.25	N/D	N/D	N/D	N/D	N/D	BDL	N/D	N/D	N/D	BDL	N/D	N/D	N/D	N/D	N/D	N/D
Doxycycline		2	3	0	4	4	4	7	2	3	**14.9**	N/D	N/D	9	8	8	0	2	5	3

No. of proven antimicrobials in the same sample

The highest value of individual antimicrobials is given in bold print. Environmental regulation limits (cut-off for resistance selection) suggested by Bengsson-Palme and Larsson in 2015 [3] are given in the third column. Amoxicillin, anidulafungin, caspofungin, cefazolin, ceftazidine, cefuroxime, clavulanic acid, flucloxacillin, meropenem, penicillin G, piperacillin, tazobactam, posaconazole, and isavuconazole were not detectable in any of the tested samples

Detection limits Fluconazole 2.59 μg/L, voriconazole 1.26 μg/L, moxifloxacin 5.98 μg/L, linezolid 5.31 μg/L, levofloxacin 2.03 μg/L, clarithromycin 12.7 μg/L, ciprofloxacin 4.96 μg/L, trimethoprim 7.53 μg/L, sulfamethoxazole 9.02 μg/L, ampicillin 12.7 μg/L, doxycycline 2.32 μg/L, amoxicillin 4.59 μg/L, anidulafungin 0.769 μg/L, caspofungin 0.798 μg/L, cefazolin 28.2 μg/L, ceftazidime 30.2 μg/L, cefuroxime 11.1 μg/L, clavulanic acid 1.90 μg/L, flucloxacillin 15.1 μg/L, meropenem 12.7 μg/L, penicillin G 25.9 μg/L, piperacillin 18.6 μg/L, tazobactam 68.7 μg/L, posaconazole 0.695 μg/L, isavuconazole 1.77 μg/L

BDL = traces, but below the detection limit, *N/A* not applicable, *N/D* not detectable

[a] Levofloxacin was not analyzed in enantioselective mode; thus, concentrations shown for levofloxacin could as well be those of ofloxacin

Lübbert C et al. Infection 2017

Selection of a Multidrug Resistance Plasmid by Sublethal Levels of Antibiotics and Heavy Metals

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E.G. and L.M.A. contributed equally to this article.

ABSTRACT How sublethal levels of antibiotics and heavy metals select for clinically important multidrug resistance plasmids is largely unknown. Carriage of plasmids generally confers substantial fitness costs, implying that for the plasmid-carrying bacteria to be maintained in the population, the plasmid cost needs to be balanced by a selective pressure conferred by, for example, antibiotics or heavy metals. We studied the effects of low levels of antibiotics and heavy metals on the selective maintenance of a 220-kbp extended-spectrum β-lactamase (ESBL) plasmid identified in a hospital outbreak of *Klebsiella pneumoniae* and *Escherichia coli*. The concentrations of antibiotics and heavy metals required to maintain plasmid-carrying bacteria, the minimal selective concentrations (MSCs), were in all cases below (almost up to 140-fold) the MIC of the plasmid-free susceptible bacteria. This finding indicates that the very low antibiotic and heavy metal levels found in polluted environments and in treated humans and animals might be sufficiently high to maintain multiresistance plasmids. When resistance genes were moved from the plasmid to the chromosome, the MSC decreased, showing that MSC for a specific resistance conditionally depends on genetic context. This finding suggests that a cost-free resistance could be maintained in a population by an infinitesimally low concentration of antibiotic. By studying the effect of combinations of several compounds, it was observed that for certain combinations of drugs each new compound added lowered the minimal selective concentration of the others. This combination effect could be a significant factor in the selection of multidrug resistance plasmids/bacterial clones in complex multidrug environments.

IMPORTANCE Antibiotic resistance is in many pathogenic bacteria caused by genes that are carried on large conjugative plasmids. These plasmids typically contain multiple antibiotic resistance genes as well as genes that confer resistance to biocides and heavy metals. In this report, we show that very low concentrations of single antibiotics and heavy metals or combinations of compounds can select for a large plasmid that carries resistance to aminoglycosides, β-lactams, tetracycline, macrolides, trimethoprim, sulfonamide, silver, copper, and arsenic. Our findings suggest that the low levels of antibiotics and heavy metals present in polluted external environments and in treated animals and humans could allow for selection and enrichment of bacteria with multiresistance plasmids and thereby contribute to the emergence, maintenance, and transmission of antibiotic-resistant disease-causing bacteria.

Gullberg E et al. MBio 2014

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
Expiration Date*: 05/02/17
S/W Version: 4.4a
Cartridge S/N*: 367476259
Reagent Lot ID*: 06012
Notes:
Error Status: OK

Start Time: 22/11/16 10:31:50
End Time: 22/11/16 11:22:11
Instrument S/N: 706576
Module S/N: 607506
Module Name: B4

Errors
<None>

For In Vitro Diagnostic Use Only.

GeneXpert® Dx System Version 4.4a Page 1 of 2


http://indiapollutionproject.weebly.com


S.S. MEDICAL GENERAL STORES
& GENERAL STORES

Hyderabad, 6 October 2017
Gandi Lake in Sangareddy District

Hyderabad Lake Throws Up Over 23 Lakh (2,3 Mio) Dead Fish, Locals Accuse Pharma Companies
Indische Medien Oktober 2017

www.gettyimages.com

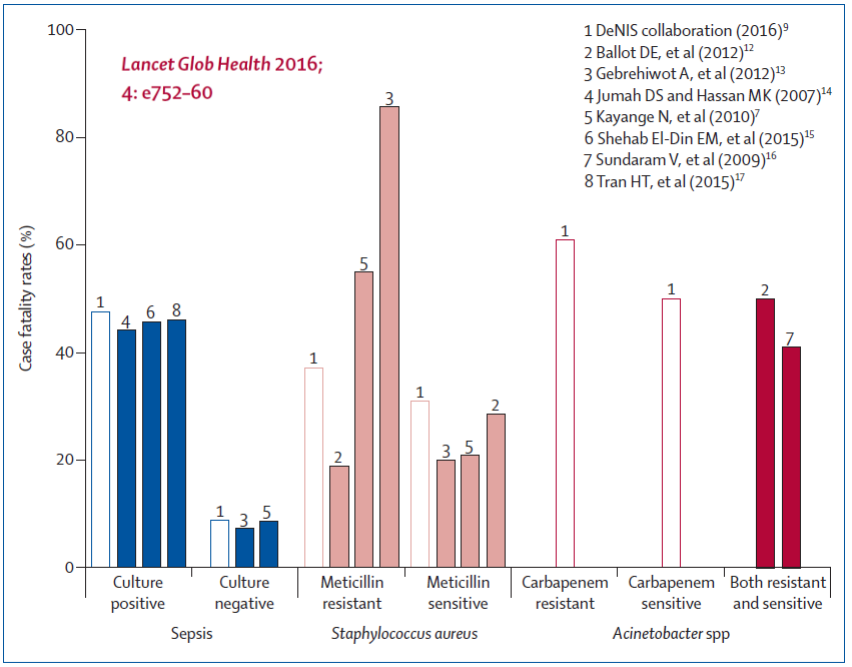
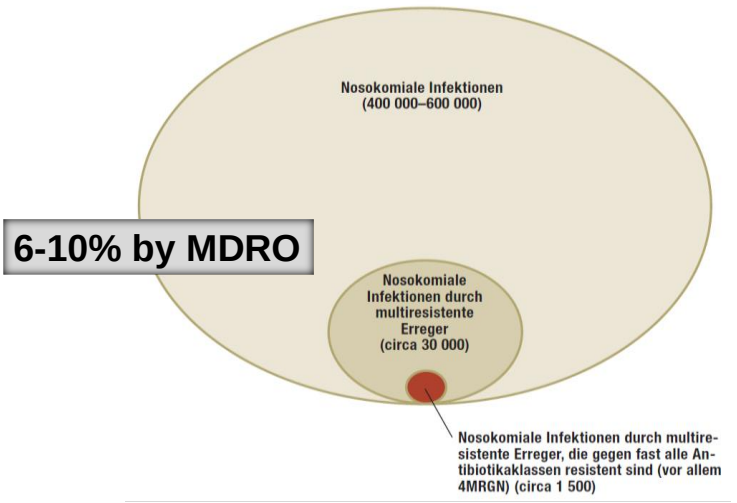


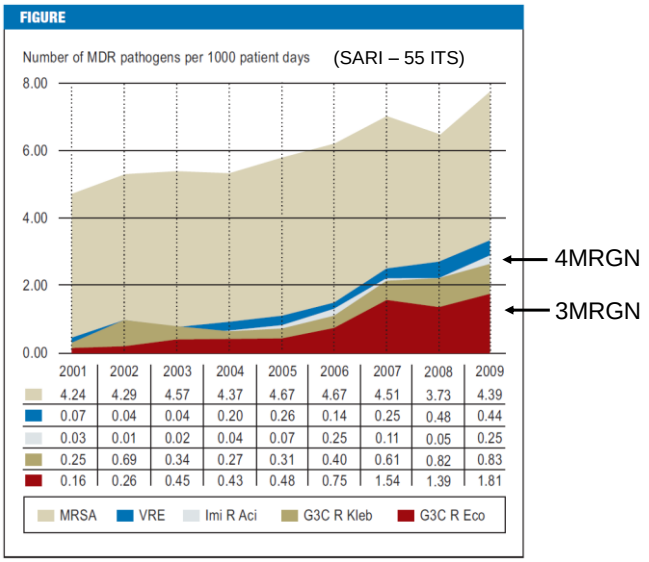
Figure: Case fatality rates from the DeNIS study (unshaded) compared with earlier studies (in solid colours)

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

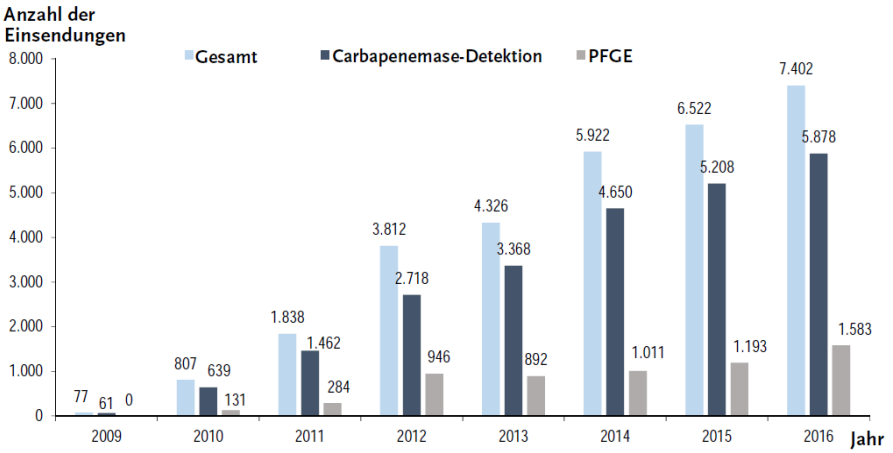


Abb. 1: Anzahl der jährlichen Einsendungen an das NRZ für gramnegative Krankenhauserreger; 2009–2016

Pfennigwerth N et al. Epi Bull 26/2017

Bad bugs ... no drugs

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

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

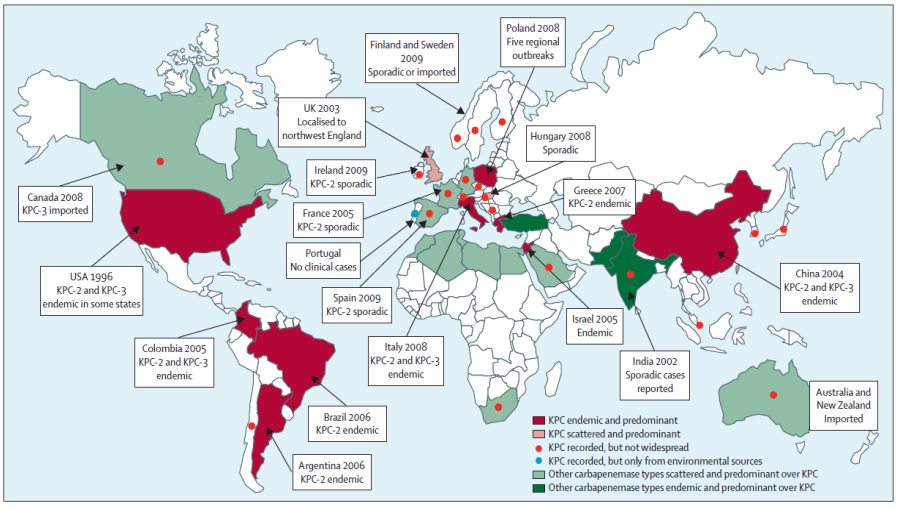
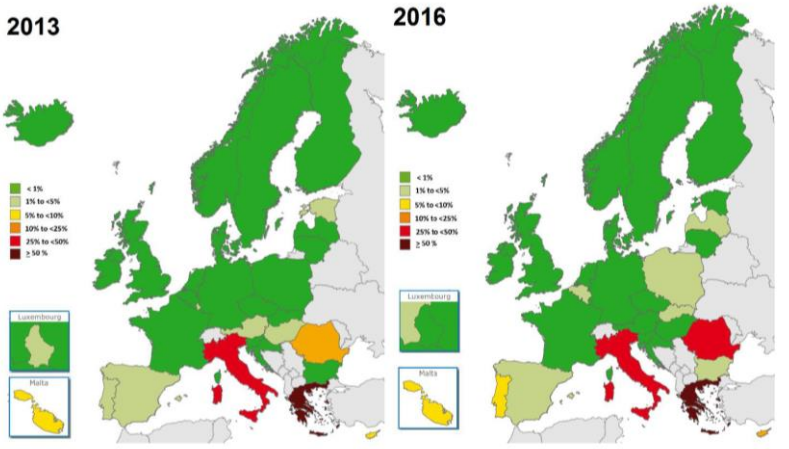


Figure: **Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin**
Other carbapenemase types include VIM, OXA-48, or NDM. KPC=*Klebsiella pneumoniae* carbapenemase.

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

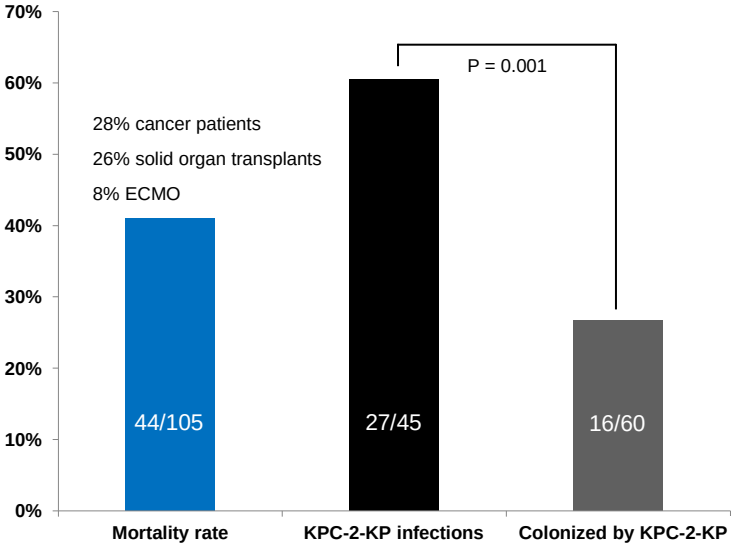
Epidemiology of carbapenem-resistant *Klebsiella pneumoniae* in Europe

Figure 2. ***Klebsiella pneumoniae***: percentage of invasive isolates with resistance to carbapenems, EU/EEA, 2013 (left), 2016 (right)



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

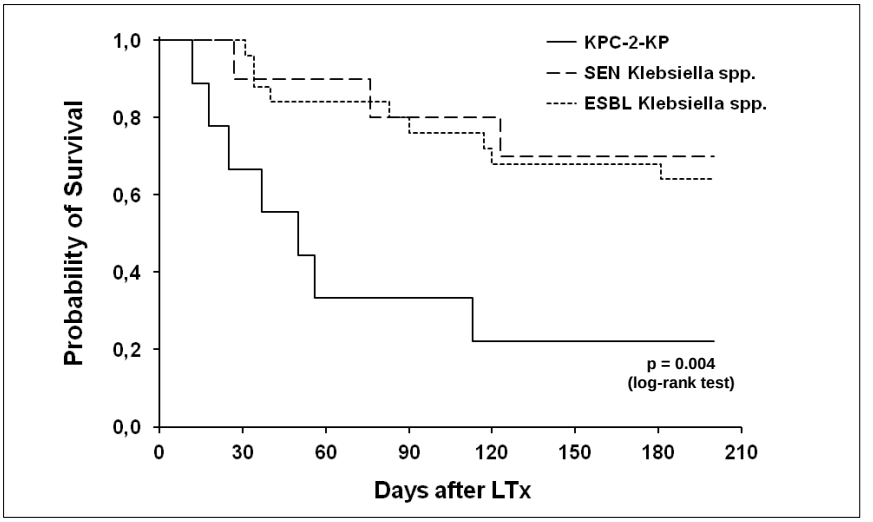
KPC-2-KP outbreak at the Leipzig University Hospital (2010-13)



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

What is my personal conclusion?

It cannot be fair that we are outsourcing dirty antibiotic manufacturing processes to the very fast emerging countries that already have the biggest resistance problems worldwide.

I appeal to the European Commission for its commitment to ensure that the pharmaceutical industry transparently discloses its supply chains and to strictly prevent the release of antibiotics into the environment.

In my opinion, this can only be achieved through a redefinition of the GMP criteria under the auspices of the WHO with the addition of globally harmonized environmental standards as part of the regulatory controls for pharmaceutical products, in particular antibiotics and chemotherapeutics.