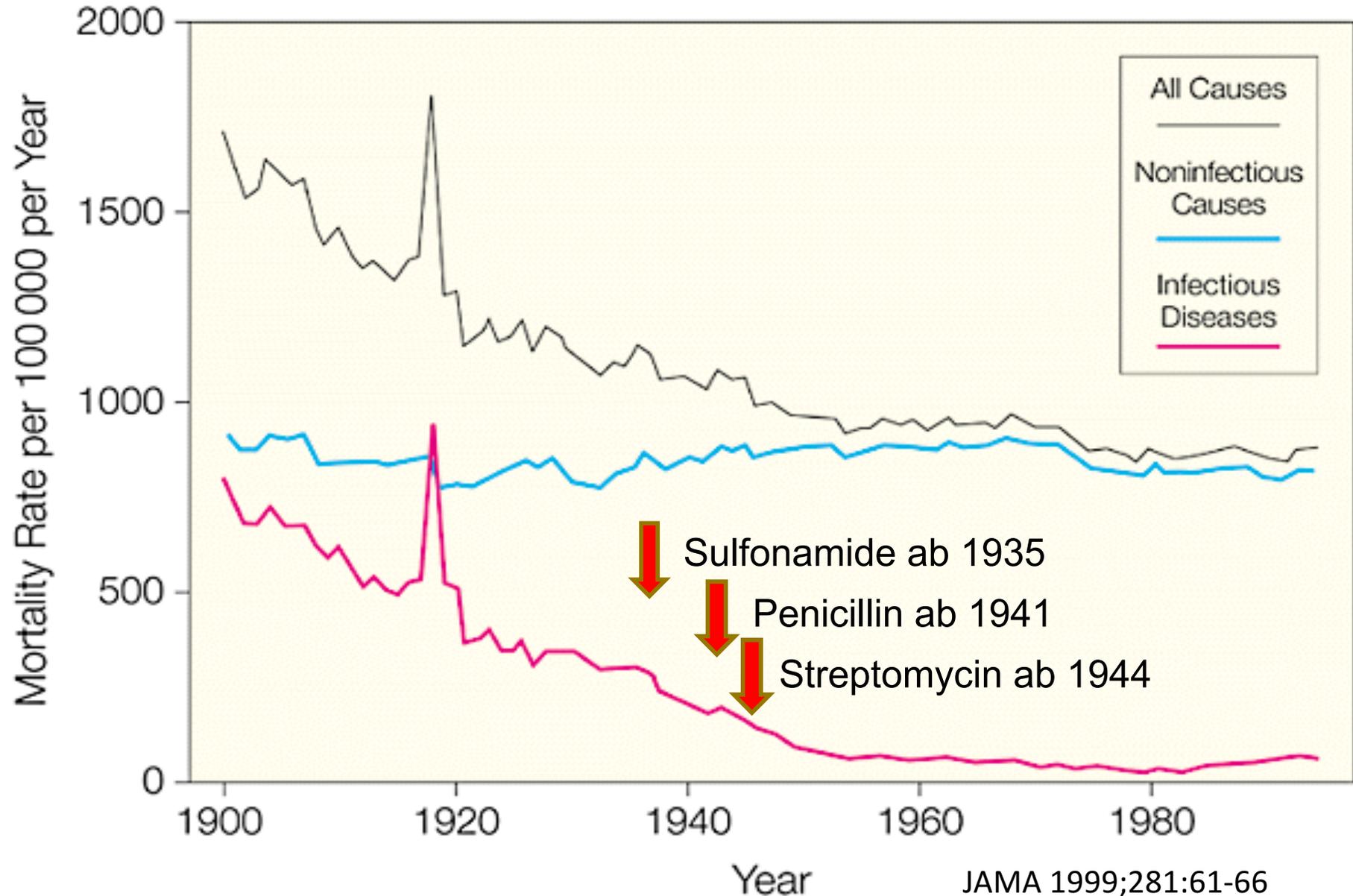


Problembewusstsein Antibiotikaresistenz: ...aus Sicht der Mikrobiologie

Burkhard Springer

Institut für Medizinische Mikrobiologie und Hygiene Graz

Sterberaten in den USA 1900-1996



Antibiotikaresistenz ist ein natürliches Phänomen

Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome

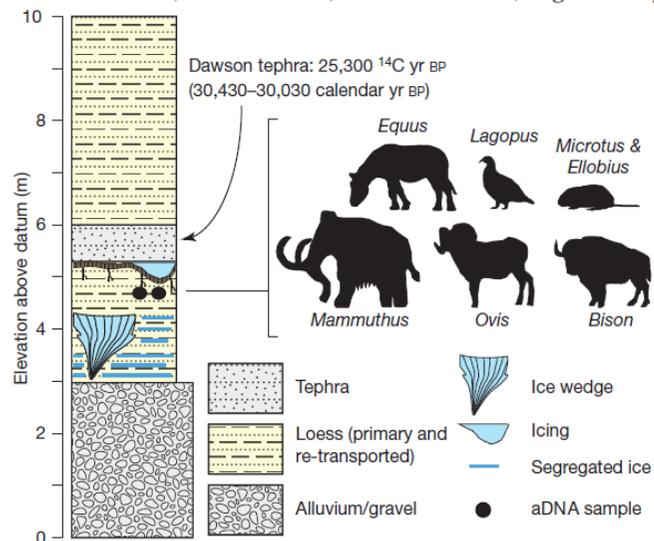
Kirandeep Bhullar¹, Nicholas Waglechner¹, Andrew Pawlowski¹, Kalinka Koteva¹, Eric D. Banks², Michael D. Johnston², Hazel A. Barton², Gerard D. Wright^{1*}

LETTER

doi:10.1038/nature10388

Antibiotic resistance is ancient

Vanessa M. D'Costa^{1,2*}, Christine E. King^{3,4*}, Lindsay Kalan^{1,2}, Mariya Morar^{1,2}, Wilson W. L. Sung⁴, Carsten Schwarz³, Duane Froese⁵, Grant Zazula⁶, Fabrice Calmels⁵, Regis Debruyne⁷, G. Brian Golding⁴, Hendrik N. Poinar^{1,3,4} & Gerard D. Wright^{1,2}



The samples were collected from a part of Lechuguilla Cave in Carlsbad Cavern National Park in New Mexico that has been cut off from any input from the surface for four million to seven million years. (Max Wisshak/speleo-foto.de/McMaster University)

Das ideale Antibiotikum

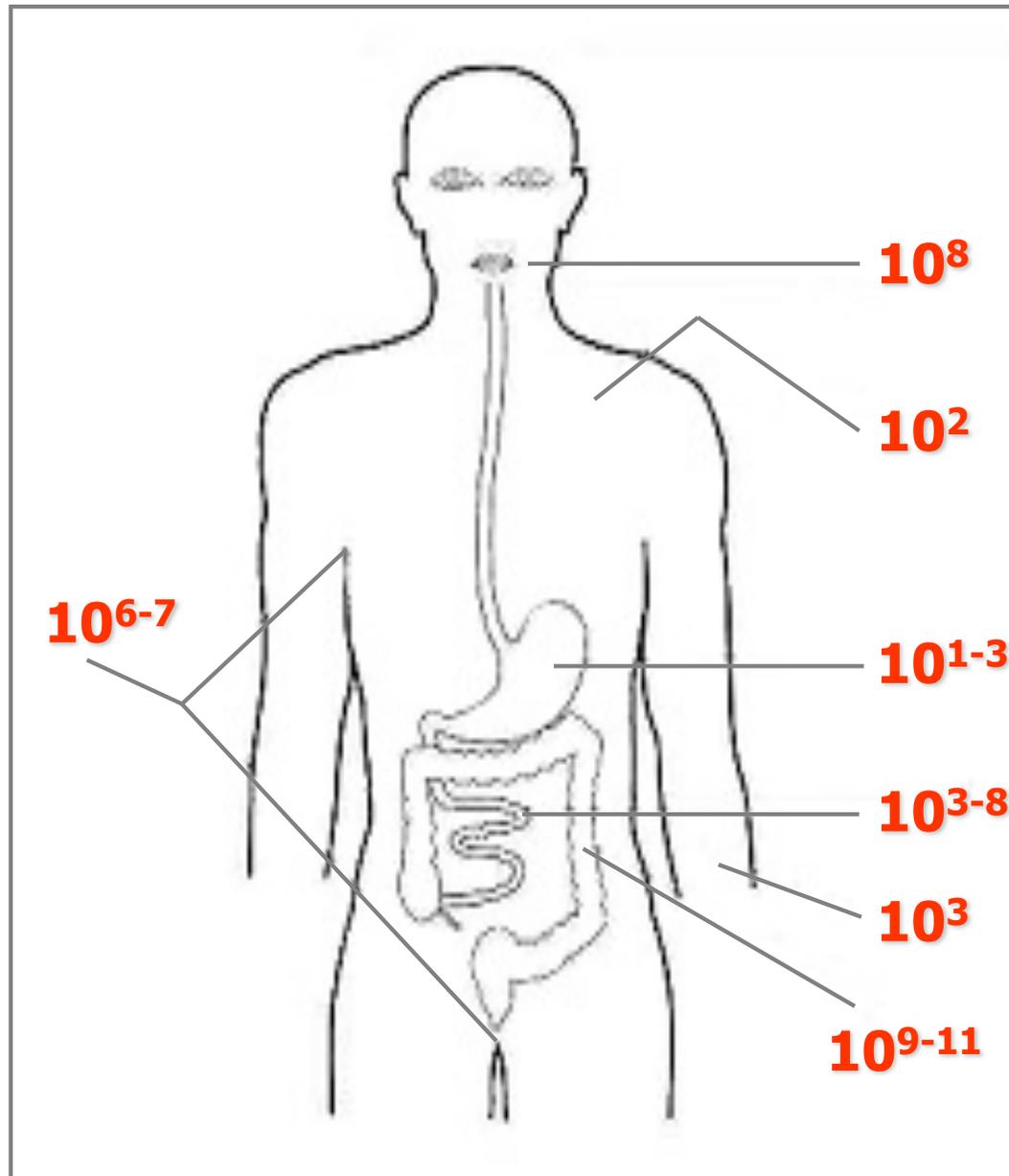
gibt es nicht!



- breites Spektrum
 - führt nicht zur Resistenzamplifikation
 - ist selektiv toxisch, hat keine Nebenwirkungen
 - schont die Normalflora
-
- In der Human- und Veterinärmedizin werden identische bzw. strukturell verwandte Antibiotika eingesetzt
 - Selektion von Bakterien mit Ko- oder Kreuzresistenz gegenüber den in der Humanmedizin eingesetzten Antibiotika
 - Jeder Einsatz von Antibiotika kann zu einer Selektion von resistenten Bakterien führen

Besiedlung des Menschen

Wir beherbergen mehr Bakterien als körpereigene Zellen



Normalflora

Anzahl Organismen pro
Gramm Gewebe/Flüssigkeit
bzw. cm² Hautoberfläche

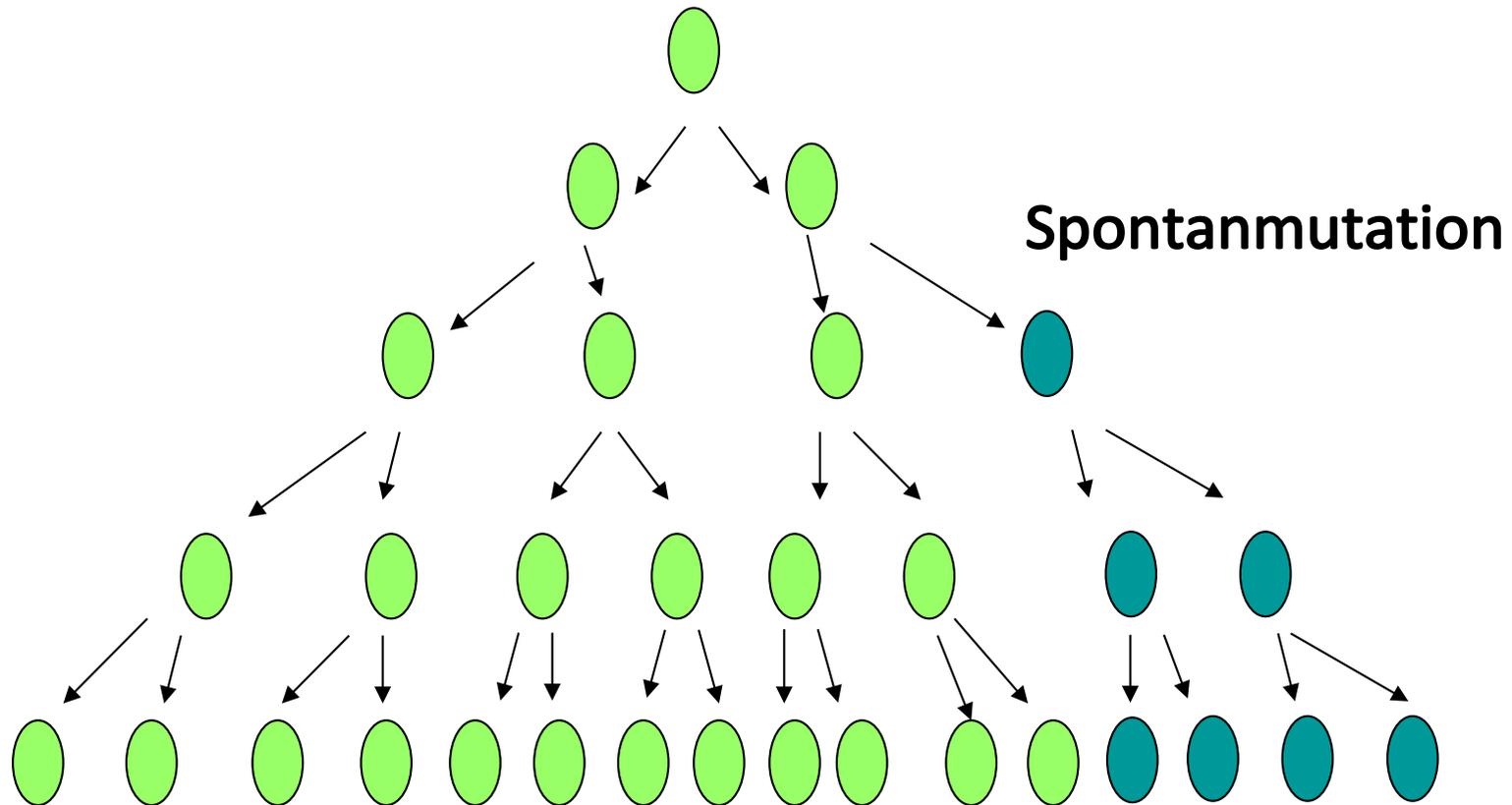
Der menschliche Körper
besteht aus:

30 Billionen Körperzellen

und beherbergt:

40 Billionen Bakterienzellen

Resistenz durch Mutation

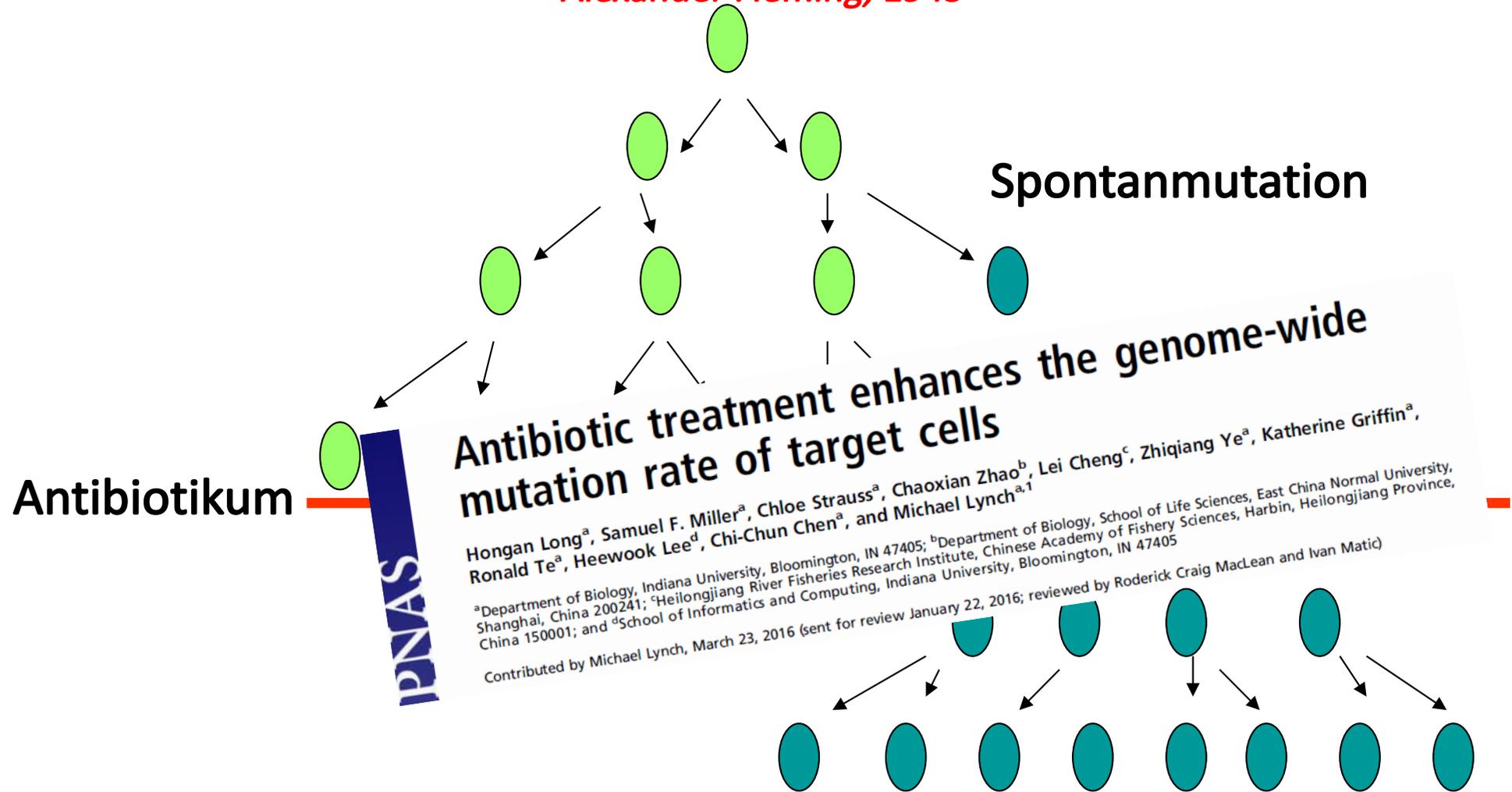


Resistenzamplifikation durch Selektion



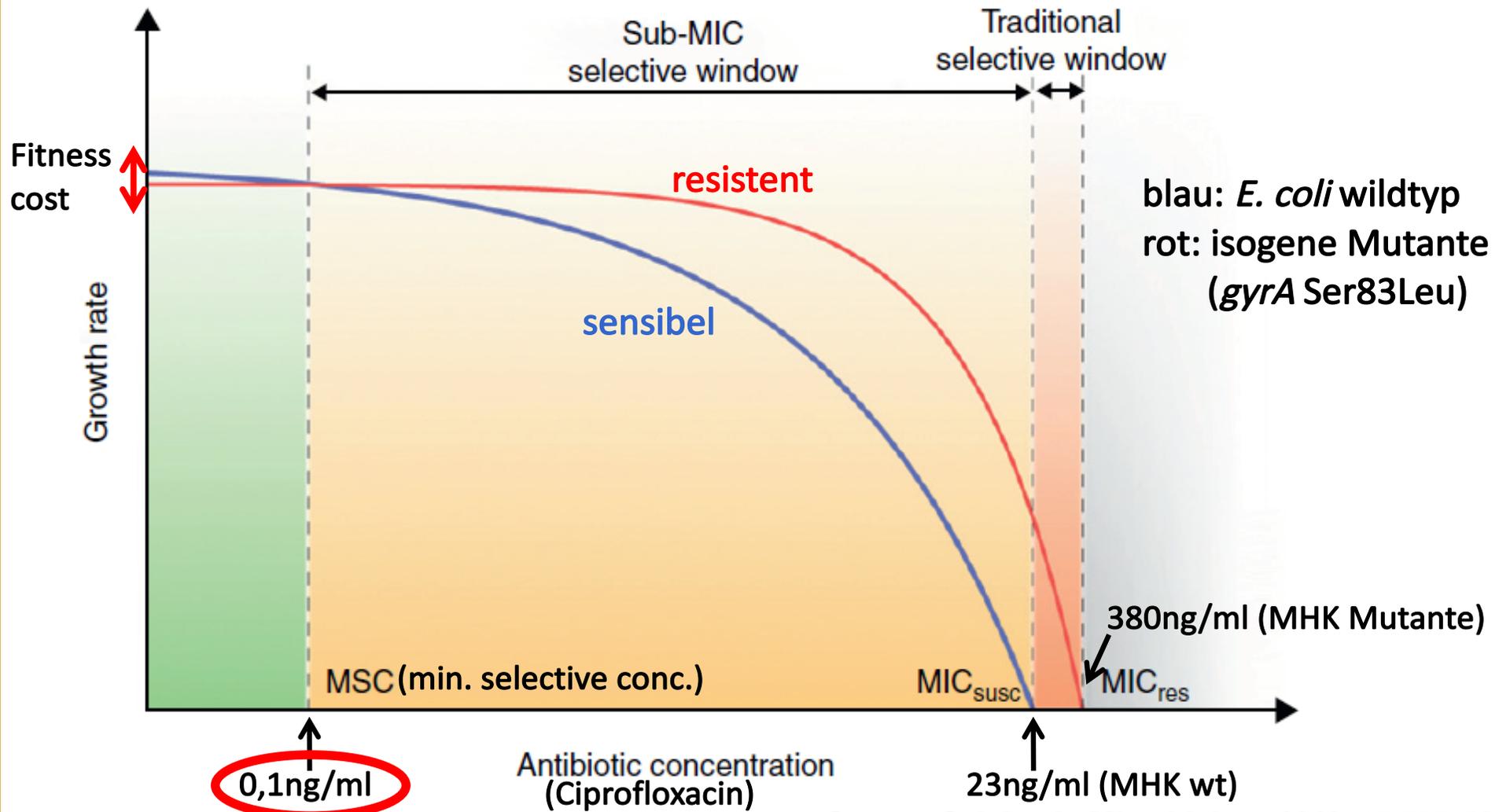
„It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficiently to kill them, and the same thing occasionally happened in the body....“

-Alexander Fleming, 1945-



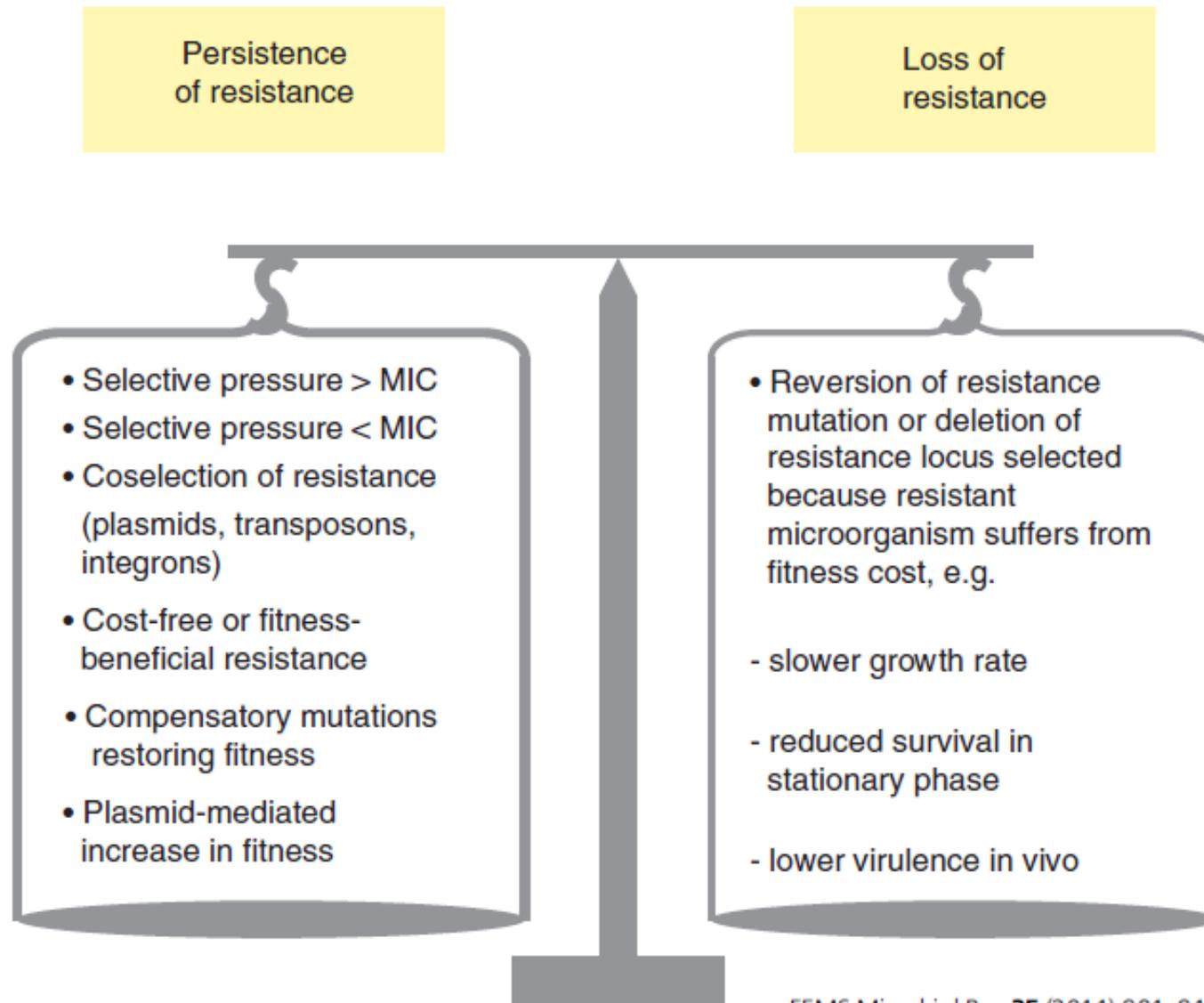
Resistenzamplifikation durch Selektion

...auch durch subletale Dosen!



Verschiedene Selektionskräfte

führen zum Verlust oder der Persistenz der Resistenz



Antibiotika als Leistungsförderer bei Tier und Mensch?



Antibiotic Exposure in Infancy and Risk of Being Overweight in the First 24 Months of Life

PEDIATRICS Volume 135, number 4, April 2015

Antti Saari, MD^{a,b}, Lauri J. Virta MD, PhD^c, Ulla Sankilampi MD, PhD^b, Leo Dunkel MD, PhD^d, Harri Saxen MD, PhD^e

Original Investigation

Association of Antibiotics in Infancy With Early Childhood Obesity

L. Charles Bailey, MD, PhD; Christopher B. Forrest, MD, PhD; Peixin Zhang, PhD; Thomas M. Richards, MS;
Alice Livshits, BS; Patricia A. DeRusso, MD, MS

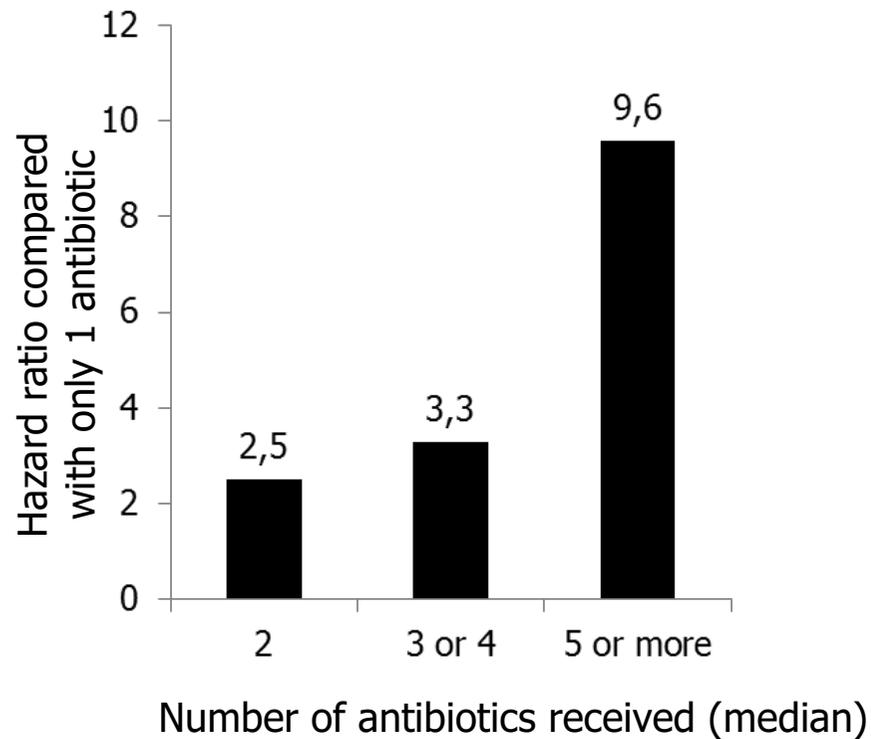
JAMA Pediatrics November 2014 Volume 168, Number 11

Room

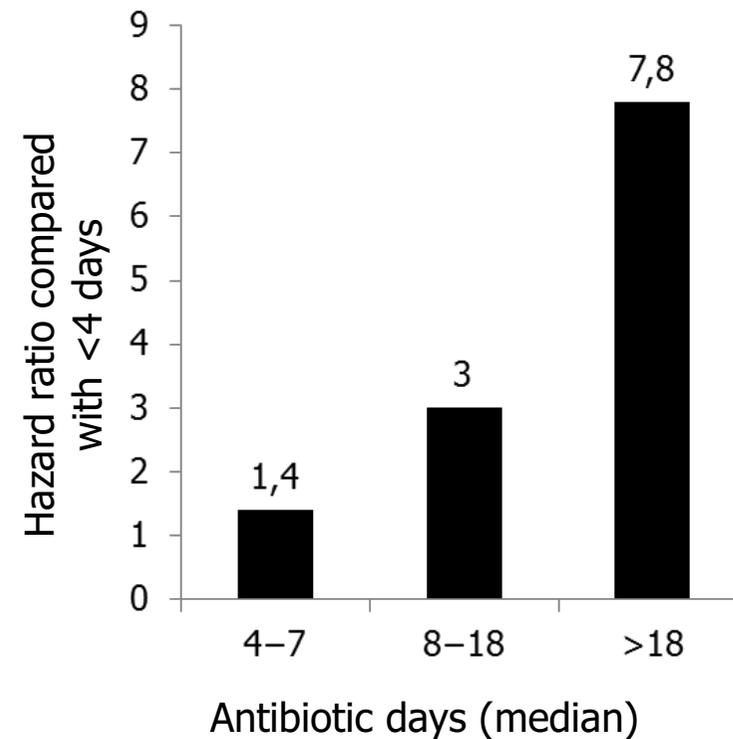
Antibiotic dose-dependent elevation in *Clostridium difficile* infection risk



Number of antibiotics



Days on antibiotic



Number of CDI events, N=241;
240 patients

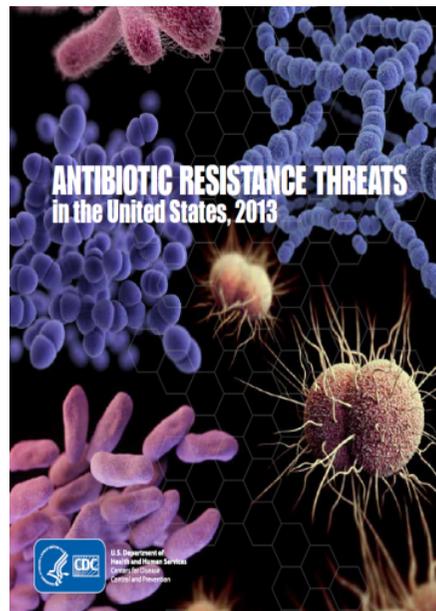
Stevens V, et al. Clin Infect Dis 2011;53:42-8.

Clostridium difficile

Infektionen in Europa und USA

USA

- 453 000 CDI/Jahr¹
- 29 500 Tote
- urgent threat (CDC)



Europa

- 172 000 CDI/Jahr
- 9% Mortalität (direkt oder indirekt)



¹Lessa, NEJM 2015, 372, 825; ² Magill SS, NEJM 2014; 370, 1198-208:

<http://www.ecdc.europa.eu/en/publications/publications/healthcare-associated-infections-antimicrobial-use-pps.pdf>

Österreich:

11.360 CDI-Fälle

740 †

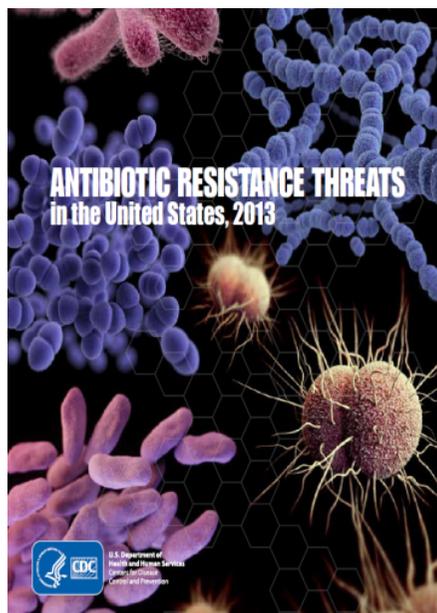


2.709 CDI-Fälle

244 †

USA

- 453 000 CDI/Jahr¹
- 29 500 Tote
- urgent threat (CDC)



Europa

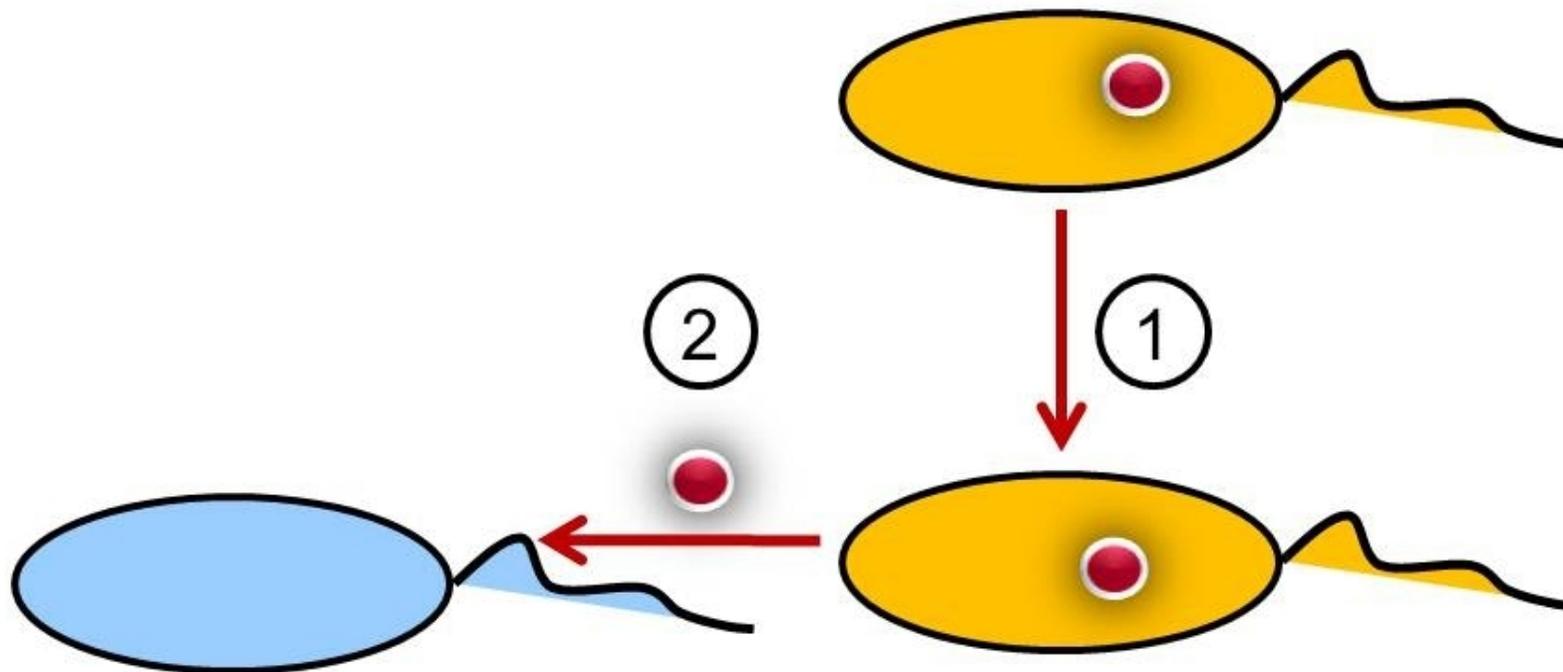
- 172 000 CDI/Jahr
- 9% Mortalität (direkt oder indirekt)



¹Lessa , NEJM 2015, 372, 825; ² Magill SS, NEJM 2014; 370, 1198-208:

<http://www.ecdc.europa.eu/en/publications/publications/healthcare-associated-infections-antimicrobial-use-pps.pdf>

Resistenzübertragung



① vertikale Resistenzübertragung

② horizontale Resistenzübertragung

β-Laktamasen: Wirkungsmechanismus

Inaktivierung des Antibiotikums



No. 3713, DEC. 28, 1940

NATURE

837

LETTERS TO THE EDITORS

The Editors do not hold themselves responsible for opinions expressed by their correspondents. They cannot undertake to return, or to correspond with the writers of, rejected manuscripts intended for this or any other part of NATURE. No notice is taken of anonymous communications.

IN THE PRESENT CIRCUMSTANCES, PROOFS OF "LETTERS" WILL NOT BE SUBMITTED TO CORRESPONDENTS OUTSIDE GREAT BRITAIN.

An Enzyme from Bacteria able to Destroy Penicillin

FLEMING¹ noted that the growth of *B. coli* and a number of other bacteria belonging to the colityphoid group was not inhibited by penicillin. This observation has been confirmed. Further work has been done to find the cause of the resistance of these organisms to the action of penicillin.

An extract of *B. coli* was made by crushing a suspension of the organisms in the bacterial crushing mill of Booth and Green². This extract was found to contain a substance destroying the growth-inhibiting property of penicillin. The destruction took place on incubating the penicillin preparation with the bacterial extract at 37°, or at room temperature for a longer time. The following is a typical experiment showing the penicillin-destroying effect of *B. coli* extracts. A solution of 1 mgm. penicillin in 0.8 c.c. of water was incubated with 0.2 c.c. of centrifuged and dialysed bacterial extract at 37° for 3 hours, in the presence of ether, and a control solution of penicillin of equal concentration was incubated without enzyme for the same time. (The penicillin used was extracted from cultures of *Penicillium notatum* by a method to be described in detail later. It possessed a degree of purity similar to that of the samples used in the

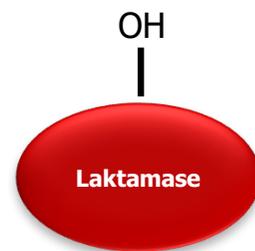
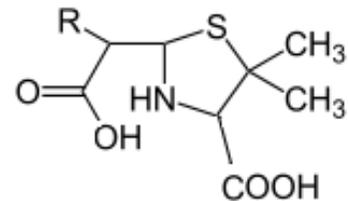
B. coli, it was not necessary to crush the organism in the bacterial mill in order to obtain the enzyme from it; the latter appeared in the culture fluid. The enzyme was also found in *M. lysodeikticus*, an organism sensitive to the action of penicillin, though less so than *Staphylococcus aureus*. Thus, the presence or absence of the enzyme in a bacterium may not be the sole factor determining its insensitivity or sensitivity to penicillin.

The tissue extracts and tissue autolysates that have been tested were found to be without action on the growth-inhibiting power of penicillin. Prof. A. D. Gardner has found staphylococcal pus to be devoid of inhibiting action, but has demonstrated a slight inhibition by the pus from a case of *B. coli* cystitis. The bacteriostatic action of the sulphonamide drugs is known to be inhibited in the presence of tissue constituents and pus.⁴ That the anti-bacterial activity of penicillin is not affected under these conditions gives this substance a definite advantage over the sulphonamide drugs from the chemotherapeutic point of view. The fact that a number of bacteria contain an enzyme acting on penicillin points to the possibility that this substance may have a function in their metabolism.

E. P. ABRAHAM.
E. CHAIN.

β -Laktamasen: Wirkungsmechanismus

Inaktivierung des Antibiotikums



inaktiviertes Antibiotikum

β – Laktamasen

mit immer breiterem Spektrum

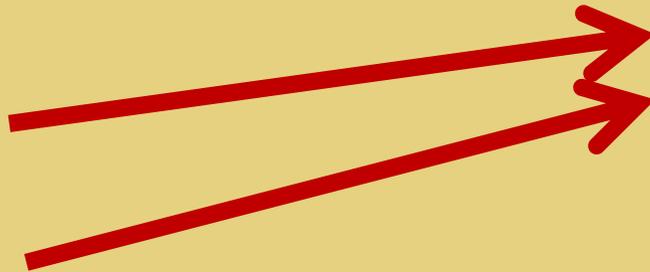


Schmalspektrum

Breitspektrum

TEM

SHV



ESBL

AmpC

Carbapenemasen

TEM
SHV
1965 ff

TEM - ESBL
SHV - ESBL
1980 ff

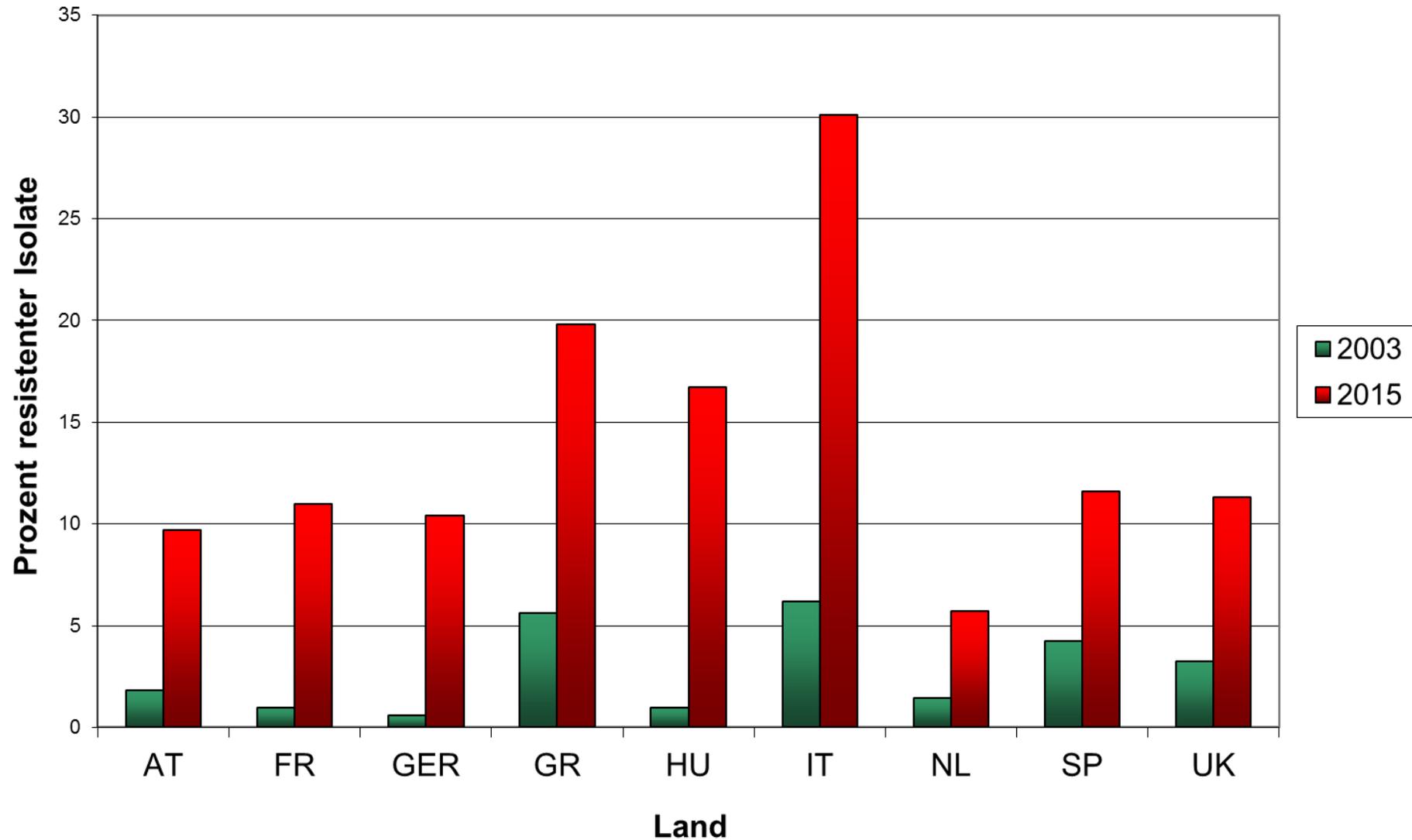
CTX-M ESBL
2000 ff

Carbapenemasen



Drittgenerations-Cephalosporine

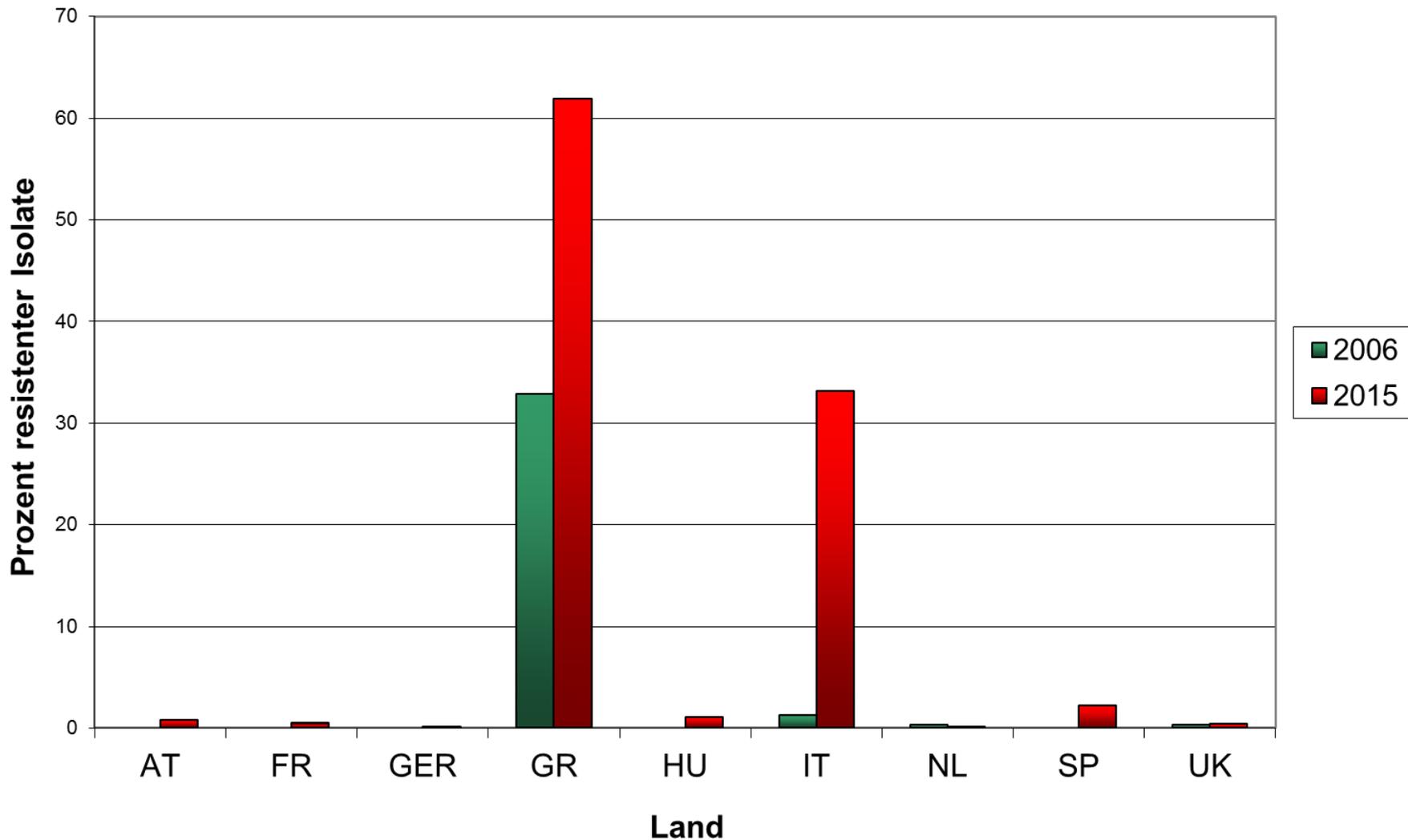
zunehmende Resistenz von invasiven *E. coli*



(Humandaten aus EARS-Net)

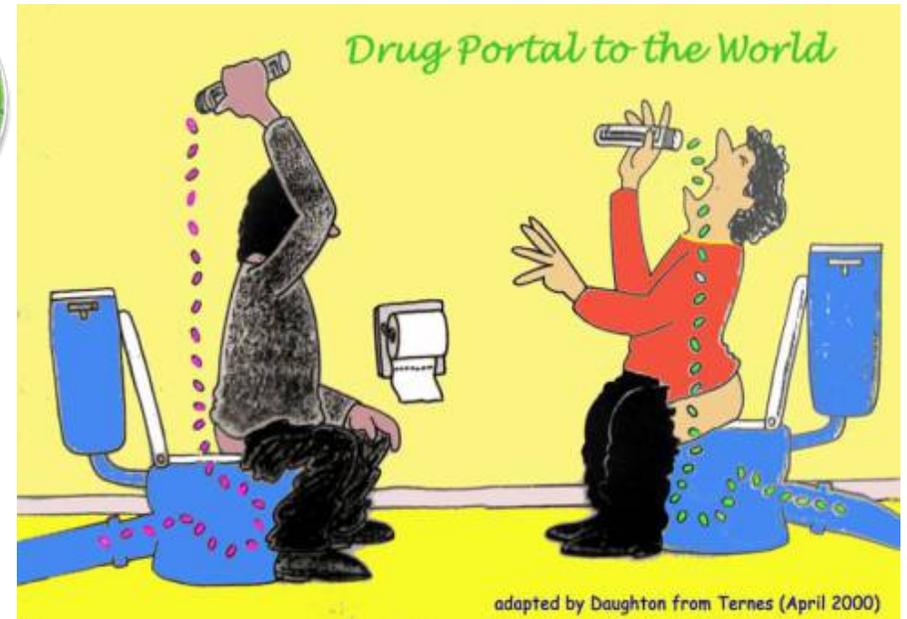
Carbapeneme

zunehmende Resistenz von invasiven *K. pneumoniae*



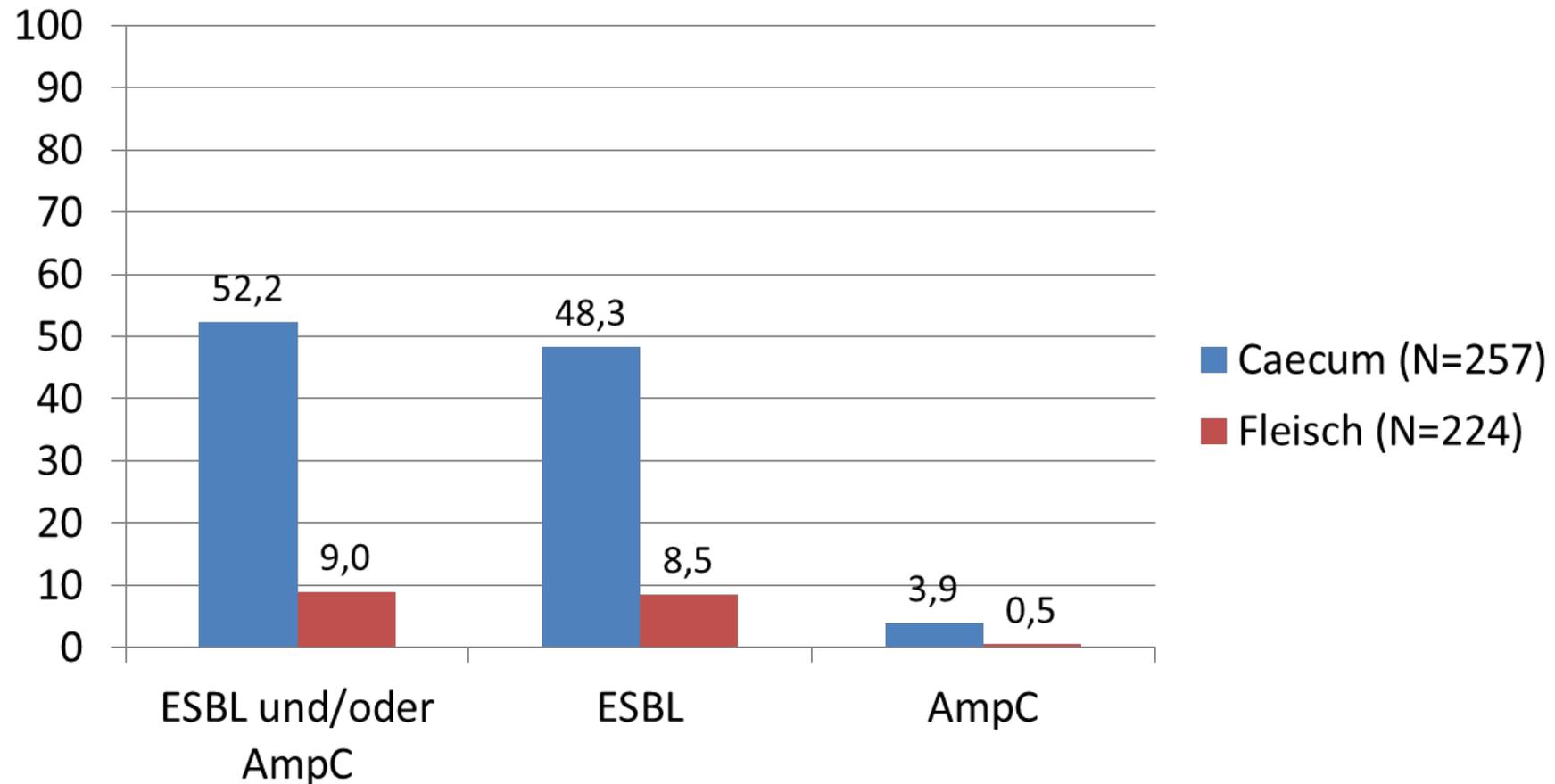
(Humandaten aus EARS-Net)

Resistenz - (re)cycling



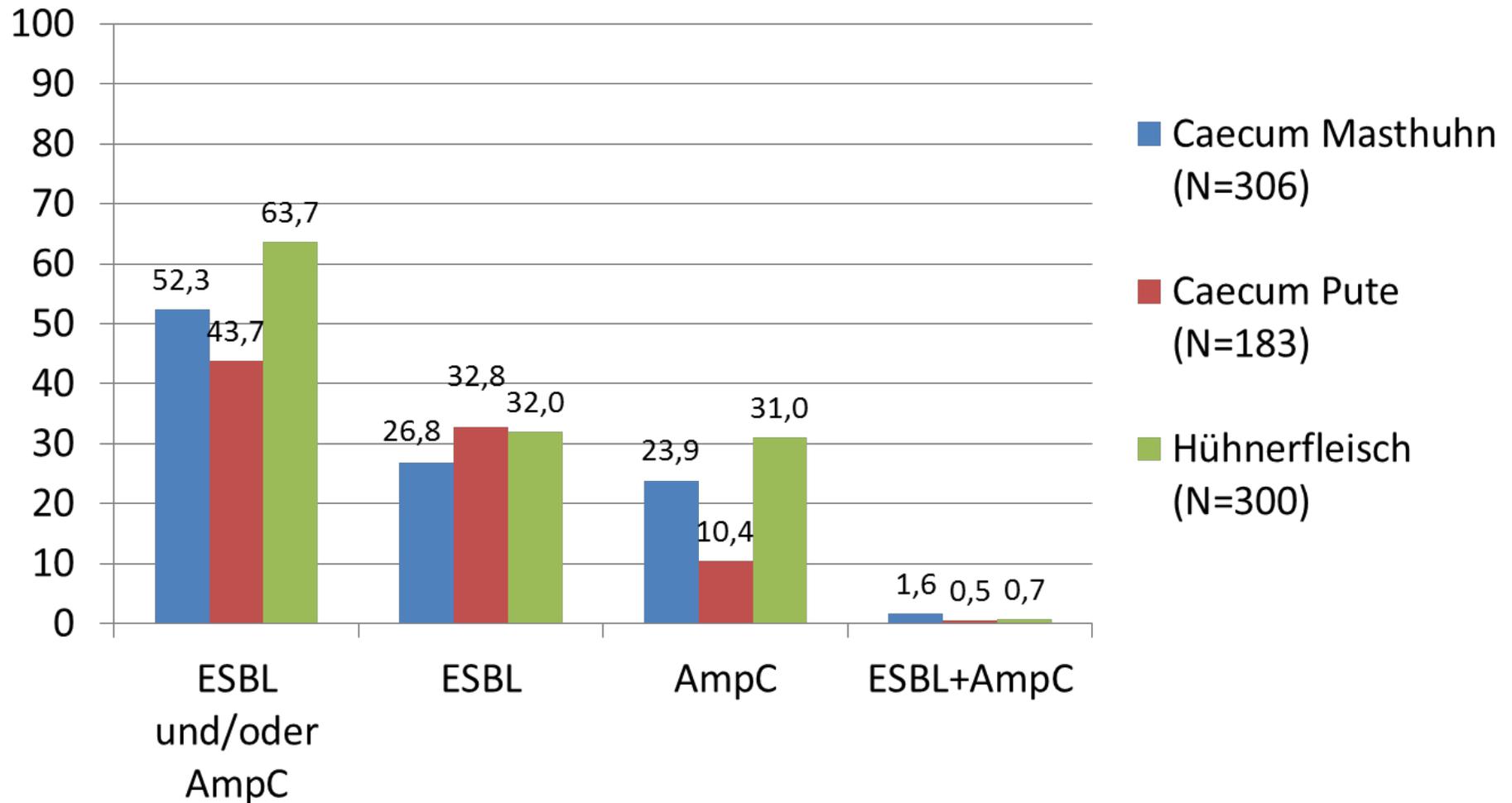
Resistenzmonitoring

Anteil (%) ESBL- bzw. AmpC-bildende *E. coli*, Schwein, 2015 Österreich



Resistenzmonitoring

Anteil (%) ESBL- bzw. AmpC-bildende *E. coli*, 2016 Österreich



- kein Nachweis von Carbapenemase-bildenden *E. coli*

Antibiotikaresistenz

als Reiseandenken....



TABLE 3. Travel destinations of travelers who were negative for ESBL-producing strains before the trip and rate of fecal colonization with ESBL-producing *E. coli* strains upon return^a

Continent or region	No. of travelers	No. (%) of travelers positive for ESBL-producing isolates
Africa	25	1 (4)
Asia (India excluded)	31	10 (32)
Central America	6	0 (0)
India	8	7 (88)
Middle East	14	4 (29)
North America	2	0 (0)
South America	1	0 (0)
Southern Europe	16	2 (13)

^a The rate of acquisition of ESBL-producing strains was highest for travelers visiting India ($P < 0.001$). Three participants visited more than one continent, and therefore, the sum of travelers in this table exceeds the actual number of 100.

Tängden et al. Antimicrob Agents Chemother. 2010;54(9):3564-8



Antibiotika-Einsatz bei Nutztieren



Anstieg von 63.151 Tonnen (2010) auf 105.596 Tonnen (2030) weltweit prognostiziert (+67%)

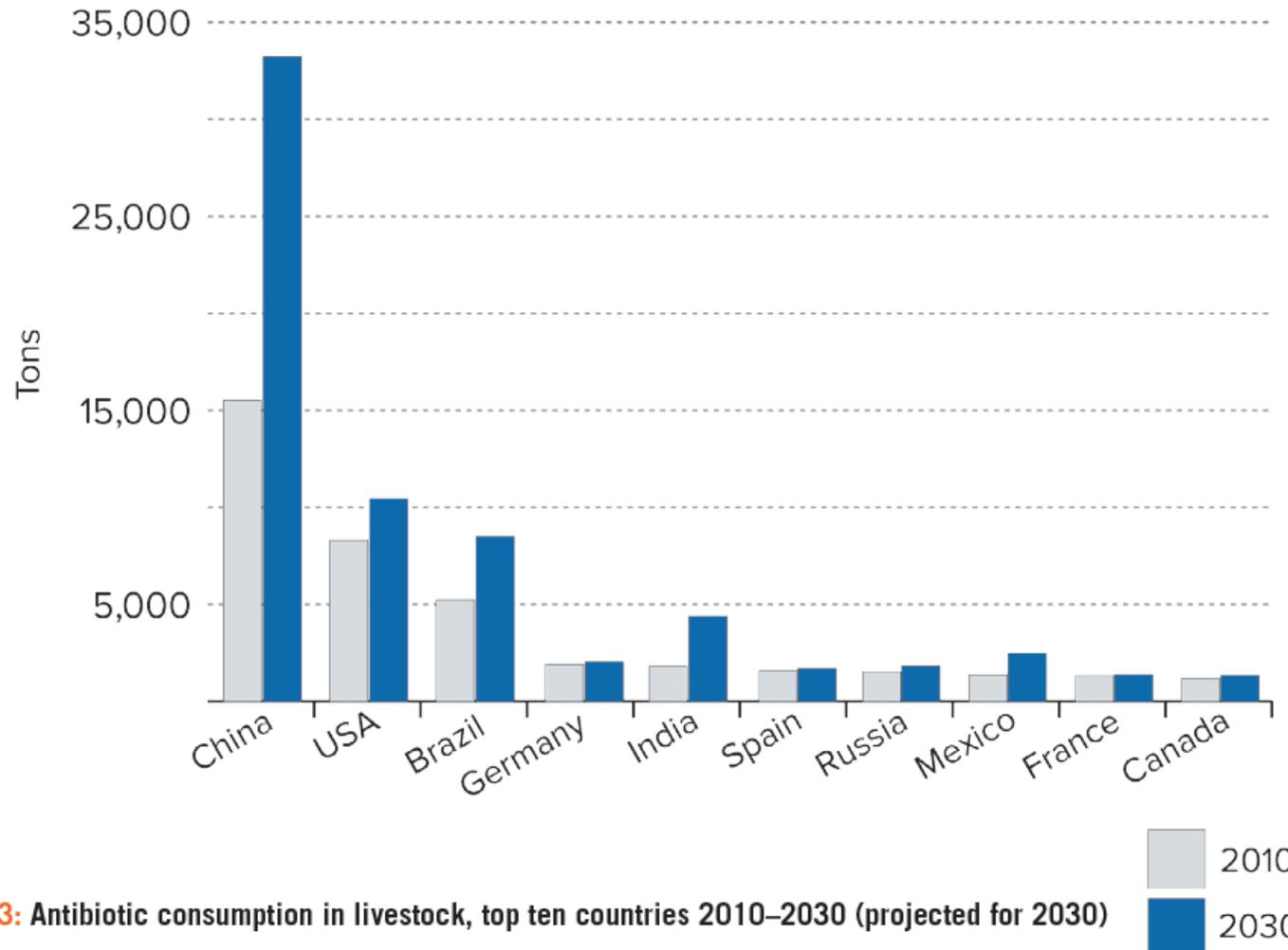


FIGURE ES-3: Antibiotic consumption in livestock, top ten countries 2010–2030 (projected for 2030)

Source: Van Boeckel et al. 2015

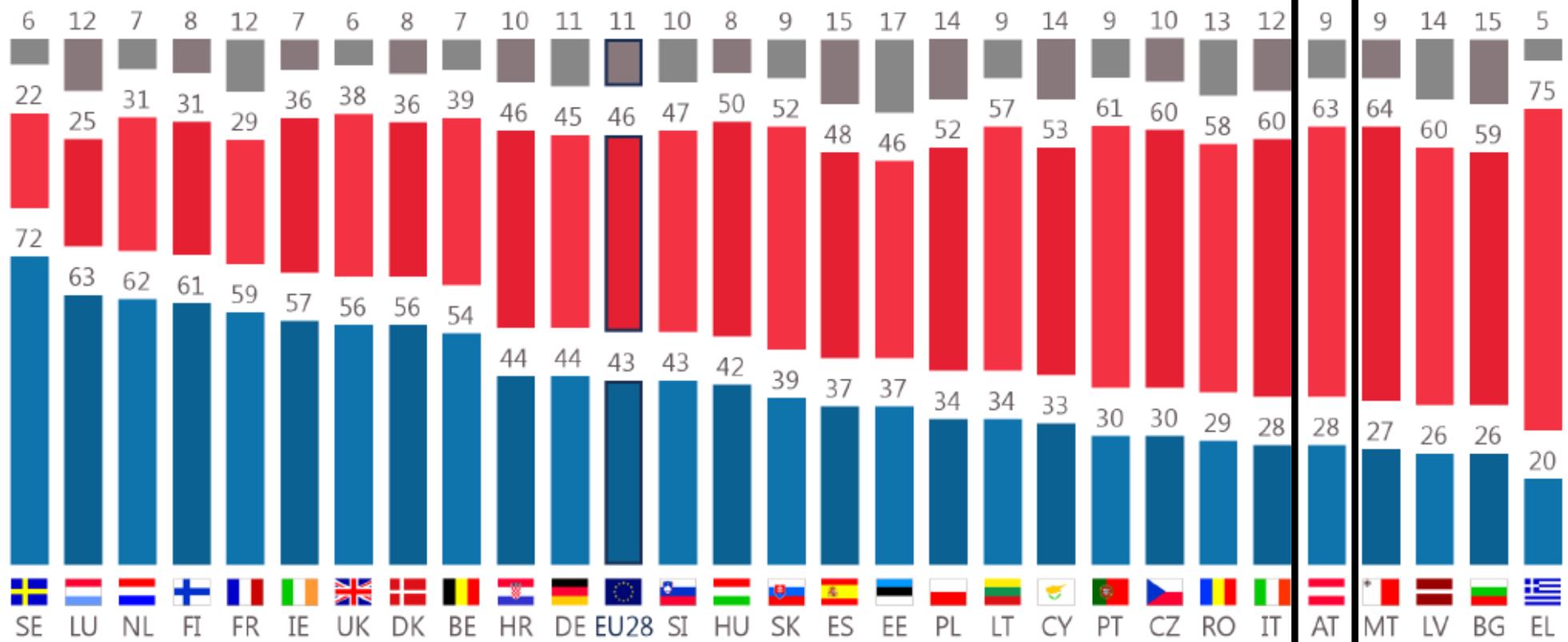
Wissen ist mangelhaft

Special Eurobarometer 445



QB4.1 For each of the following statements, please tell me whether you think it is true or false.

Antibiotics kill viruses (%)



■ Correct answer
 ■ Incorrect answer
 ■ Don't know

Correct Answer=False

2016.4325
 Special Eurobarometer 445 - April 2016
 "Antimicrobial Resistance"
 Report
 EN

EW-04-16-436-EN-N
 978-92-79-58818-1
 doi:10.2875/760366

Danke für Ihre Aufmerksamkeit



**„Suggested remedy for the common cold:
A good gulp of whiskey at bedtime – it’s
not very scientific, but it helps.“**

Alexander Fleming