



Nationales Referenzzentrum für  
gramnegative Krankenhauserreger

RUB

# Aktuelle Entwicklungen bei multiresistenten gramnegativen Erregern

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Nationales Referenzzentrum für gramnegative Krankenhauserreger  
Ruhr-Universität Bochum

## Problem:

### MRSA/VRE

- 1 Erreger
- 1 Resistenzmechanismus

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### MRGN

*Pseudomonas aeruginosa*      *Klebsiella pneumoniae*  
*Klebsiella aerogenes*      *Escherichia coli*  
*Acinetobacter baumannii*      *Enterobacter cloacae*  
*Proteus mirabilis*      *Serratia marcescens*

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### Vielzahl von Resistenzmechanismen

ESBL      AmpC  
Porinverlust      Carbapenemasen  
MCR      Exporterpumpen

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## Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

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Identification of a novel plasmid-mediated colistin-resistance gene, *mcr-2*, in *Escherichia coli*, Belgium, June 2016

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### Novel plasmid-mediated colistin resistance *mcr-4* gene in *Salmonella* and *Escherichia coli*, Italy 2013, Spain and Belgium, 2015 to 2016

A Carattoli<sup>1</sup>, L Villa<sup>1</sup>, C Feudi<sup>1,2</sup>, L Curcio<sup>3</sup>, S Orsini<sup>3</sup>, A Luppi<sup>4</sup>, G Pezzotti<sup>3</sup>, CF Magistrati<sup>3</sup>

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Journal of Antimicrobial Chemotherapy  
Hangqi Shen,<sup>a</sup>

Primary Medicine,  
University, Zhejiang  
, Institute of

*J Antimicrob Chemother* 2017; **72**: 3317–3324  
doi:10.1093/jac/dkx327 Advance Access publication 18 September 2017

Novel plasmid-mediated colistin resistance in *Salmonella* and *Escherichia coli*, Italy Belgium, 2015 to 2016

## Identification of a novel transposon-associated phosphoethanolamine transferase gene, *mcr-5*, conferring colistin resistance in *d*-tartrate fermenting *Salmonella enterica* subsp. *enterica* serovar Paratyphi B

Maria Borowiak<sup>1</sup>, Jennie Fischer<sup>1</sup>, Jens A. Hammerl<sup>1</sup>, Rene S. Hendriksen<sup>2</sup>, Istvan Szabo<sup>1</sup> and Burkhard Malorny<sup>1\*</sup>

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Identification of colistin resistance in *Escherichia coli* in 2016

bereits seit den 80er Jahren ist *mcr* zu finden

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# MCR in Deutschland

seit Ende 2015: 936 colistinresistente Isolate



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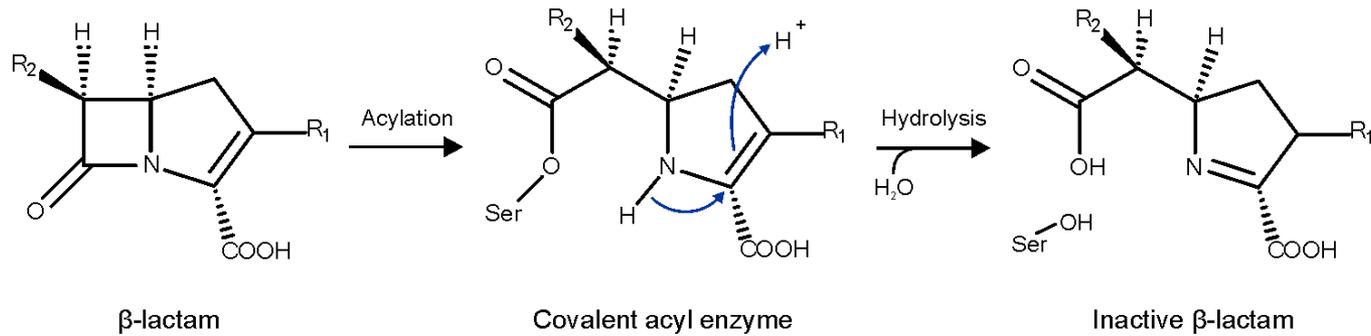
zum Vergleich: colistinresistente Tiermastisolate bis  
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→ plasmidkodierte Colistinresistenz in der  
Humanmedizin in Deutschland noch sehr selten

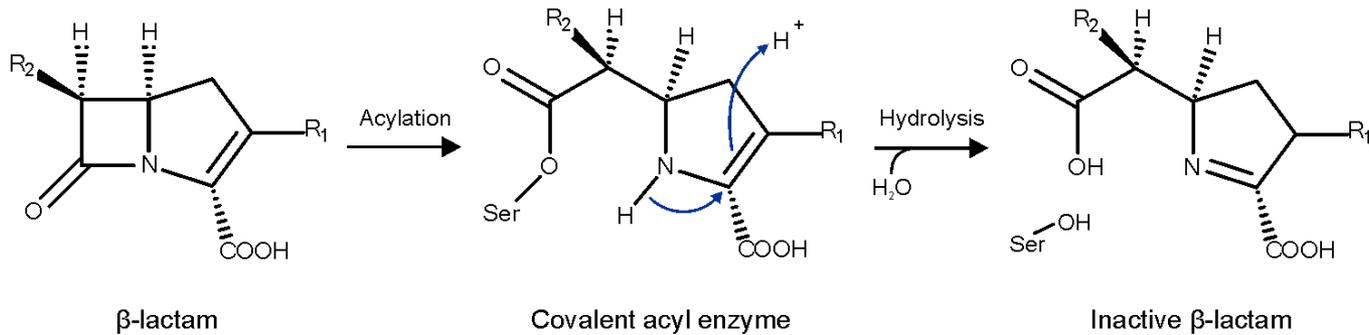
# Carbapenemasen



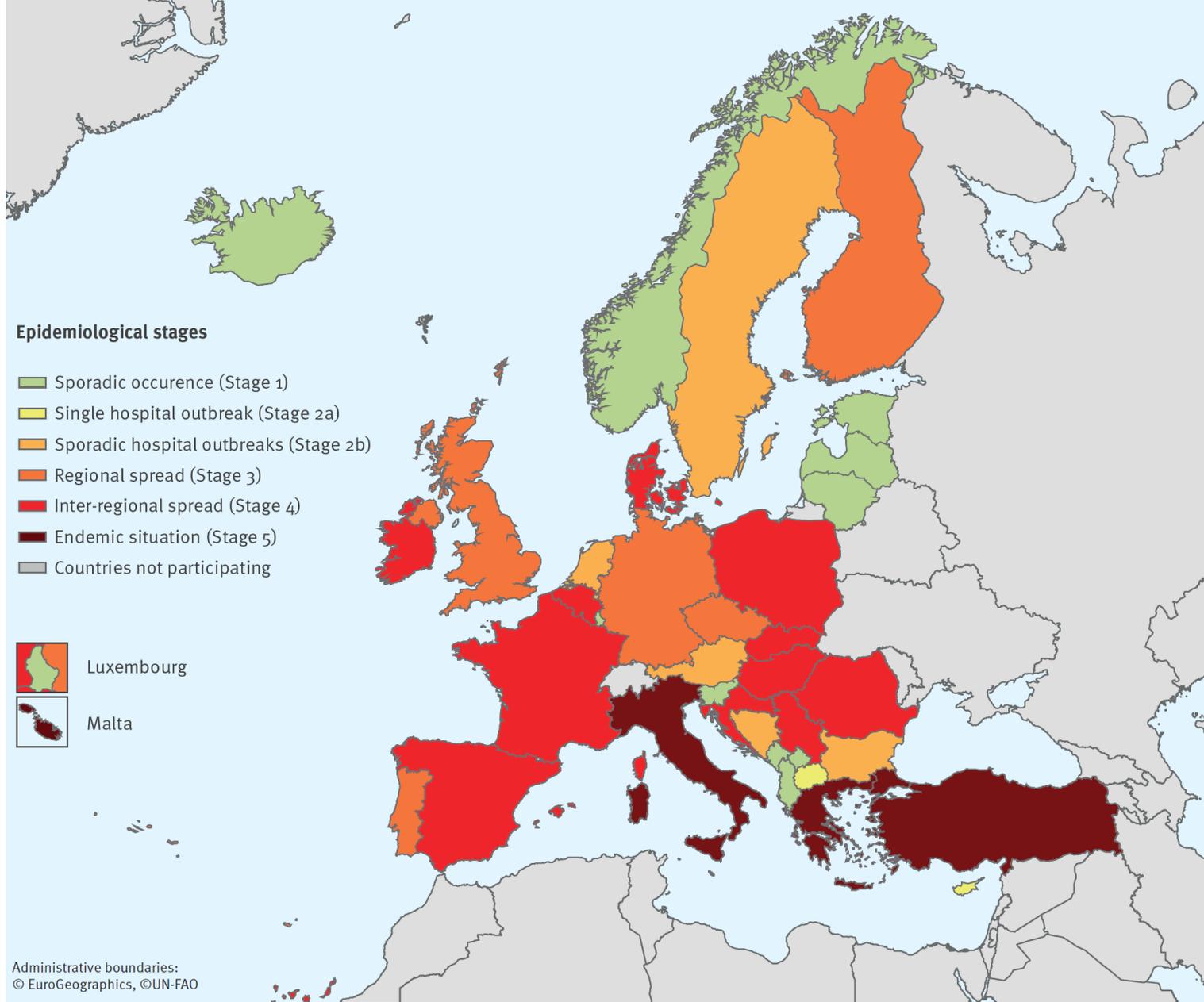
# Carbapenemasen



# Carbapenemasen



- **Betalaktame werden irreversibel inaktiviert**
- **drastische Limitation der Therapieoptionen**
- **Der mit Abstand wichtigste Resistenzmechanismus bei Gram-negativen Bakterien mit klinischer Relevanz**



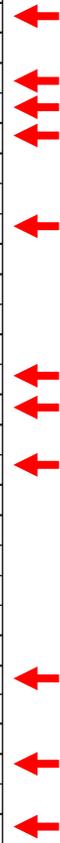
Brolund *et al.*, Euro Surveill. 2019;24(9)

Country	Epidemiological stage for the spread of carbapenemase-producing Enterobacteriaceae				Change in epidemiological stage 2015–18
	2010 [11]	2013 [9]	2014–15 [8]	2018	
Albania	NA	2a	1	1	→
Austria	0	2b	2b	2b	→
Belgium	2b	3	4	4	→
Bosnia and Herzegovina <sup>a</sup>	1	1	0	2b	↑
Bulgaria	0	2a	2a	2b	→
Croatia	1	3	3	4	↑
Cyprus	2a	2a	1	2a	↑
Czech Republic	1	2b	2b	3	↑
Denmark	1	2a	4	4	→
Estonia	0	2a	1	1	→
Finland	1	2a	2a	3	↑
France	3	3	4	4	→
Germany	3	3	3	3	→
Greece	5	5	5	5	→
Hungary	3	4	4	4	→
Iceland	0	0	0	1	↑
Ireland	1	4	3	4	↑
Italy	4	5	5	5	→
Kosovo <sup>b</sup>	NA	2b	0	1	↑
Latvia	1	1	1	1	→
Lithuania	1	1	1	1	→
Luxembourg	NA	1	1	1	→
Malta	1	5	5	5	→
Montenegro	NA	0	1	1	→
The Netherlands	2a	2b	2a	2b	→
North Macedonia	NA	0	1	2a	↑
Norway	2a	2a	1	1	→
Poland	4	3	4	4	→
Portugal	1	1	2b	3	↑
Romania	1	1	4	4	→
Serbia	1	1	2b	4	↑
Slovak Republic	NA	2a	4	4	→
Slovenia	0	1	2a	1	↓
Spain	2b	3	4	4	→
Sweden	2a	2b	2a	2b	→
Turkey	NA	2a	5	5	→
United Kingdom <sup>c</sup>	2b	3	3	3	→

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### Epidemiological stages

- **Stage 0:** no case reported
- **Stage 1:** sporadic occurrence (epidemiologically unrelated single cases)
- **Stage 2a:** single hospital outbreak (two or more epidemiologically associated cases with indistinguishable geno- or phenotype in a single institution)
- **Stage 2b:** sporadic hospital outbreaks (unrelated hospital outbreaks with epidemiologically unrelated introduction or different strains, no autochthonous inter-institutional transmission reported)
- **Stage 3:** regional spread (more than one epidemiologically related hospital outbreak confined to hospitals that are part of the same region or health district, indicating regional autochthonous inter-institutional transmission)
- **Stage 4:** inter-regional spread (multiple epidemiologically related outbreaks occurring in different health districts, indicating inter-regional autochthonous inter-institutional transmission)
- **Stage 5:** endemic situation (most hospitals in a country are repeatedly seeing cases admitted from autochthonous sources)

Sweden	2a	2b	2a	2b	→
Turkey	NA	2a	5	5	→
United Kingdom <sup>c</sup>	2b	3	3	3	→

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# Wichtig:

- fast immer freiwillige Teilnahme an Surveillancesystemen!
- wahres Ausmaß möglicherweise unterschätzt!

# Situation in Deutschland



verschiedene Surveillance-Systeme:

- ARS (freiwillige Teilnahme)
- Labormeldepflicht carbapenemresistenter *Enterobacterales* & *Acinetobacter baumannii*
- NRZ für gramnegative Krankenhauserreger (freiwillige Einsendungen)

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EuSCAPE-Studie 2012: 0,047 Fälle/1000 Aufnahmen



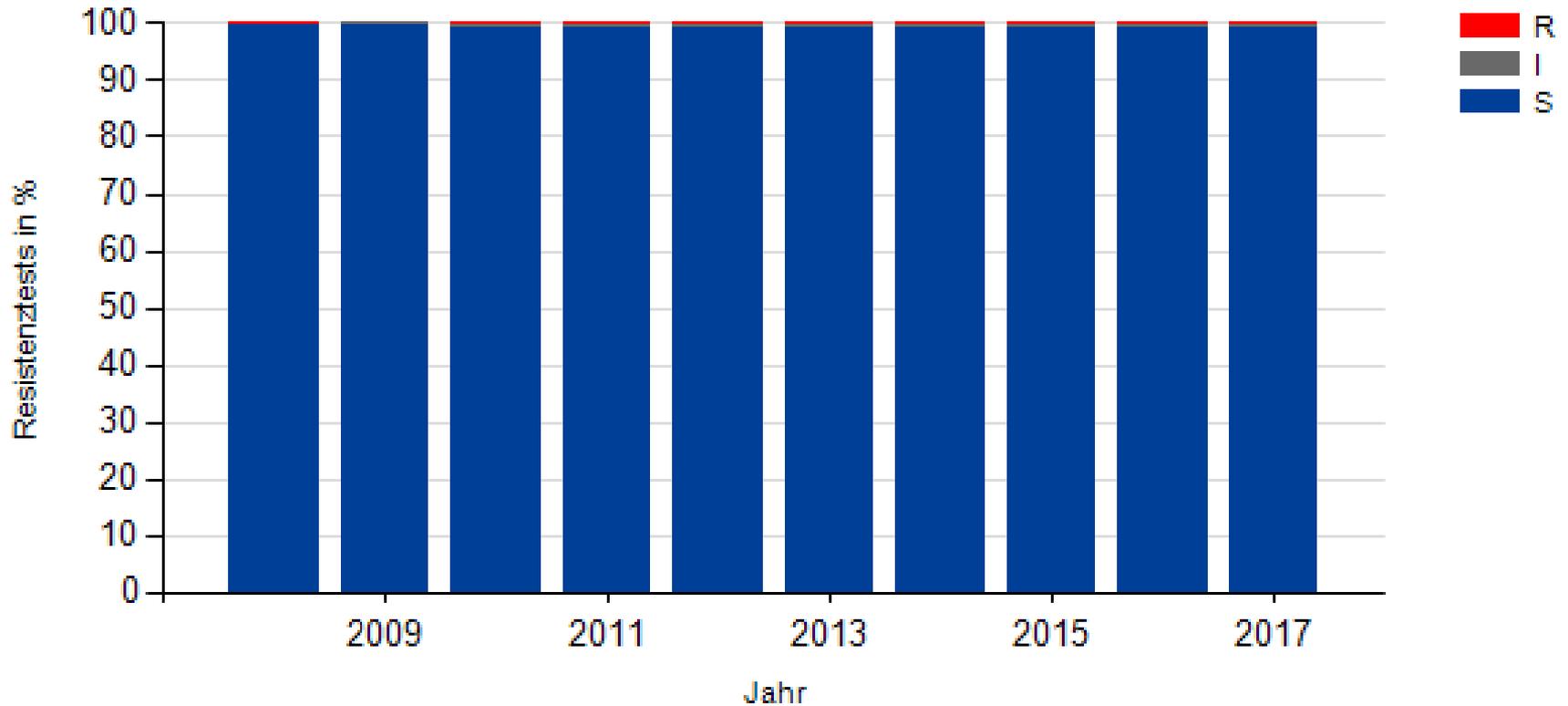
# Meldepflicht

*Acinetobacter* 2017: 786 Fälle

*Enterobacterales* 2017: 3.577 Fälle

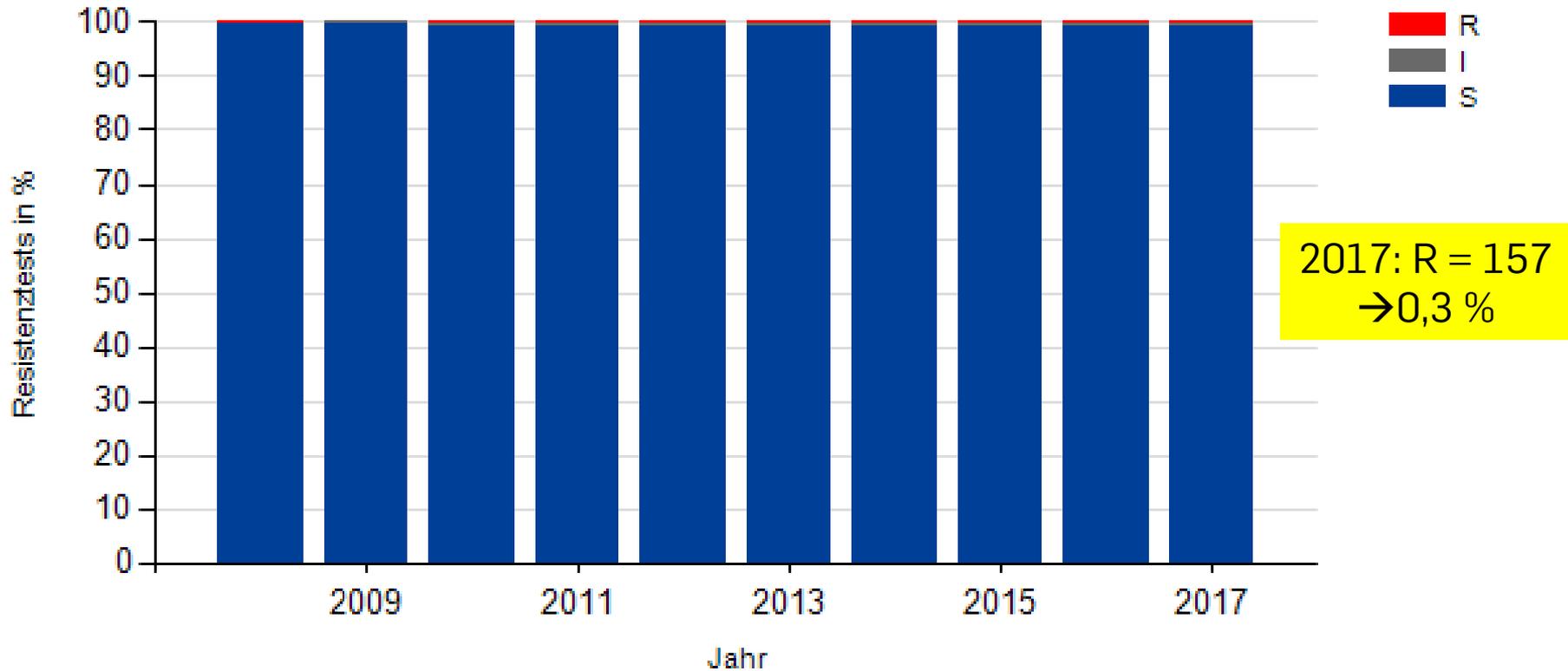
## Meropenem bei *K. pneumoniae* (2017: n = 50.473)

### Prozentuale Verteilung der Resistenztestergebnisse nach Jahr

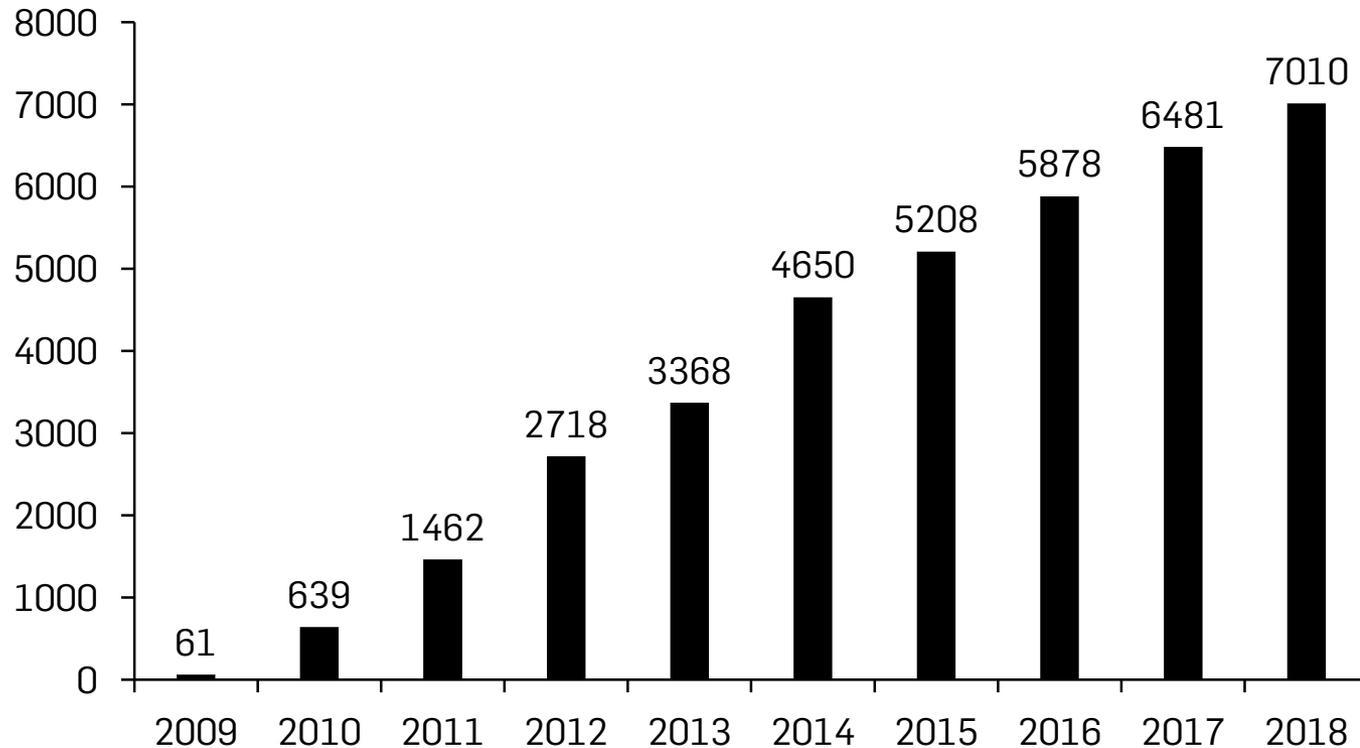


## Meropenem bei *K. pneumoniae* (2017: n = 50.473)

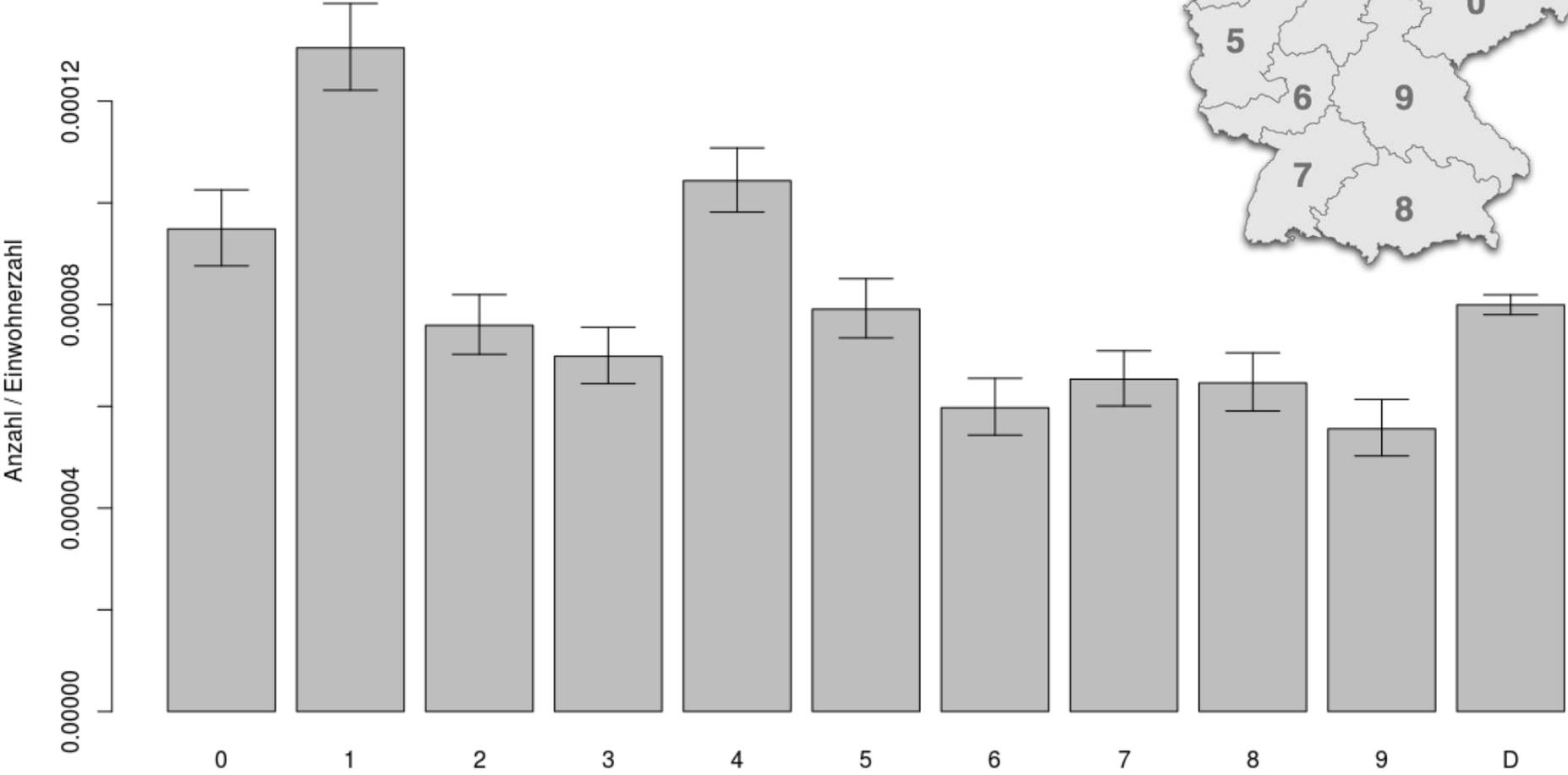
### Prozentuale Verteilung der Resistenztestergebnisse nach Jahr



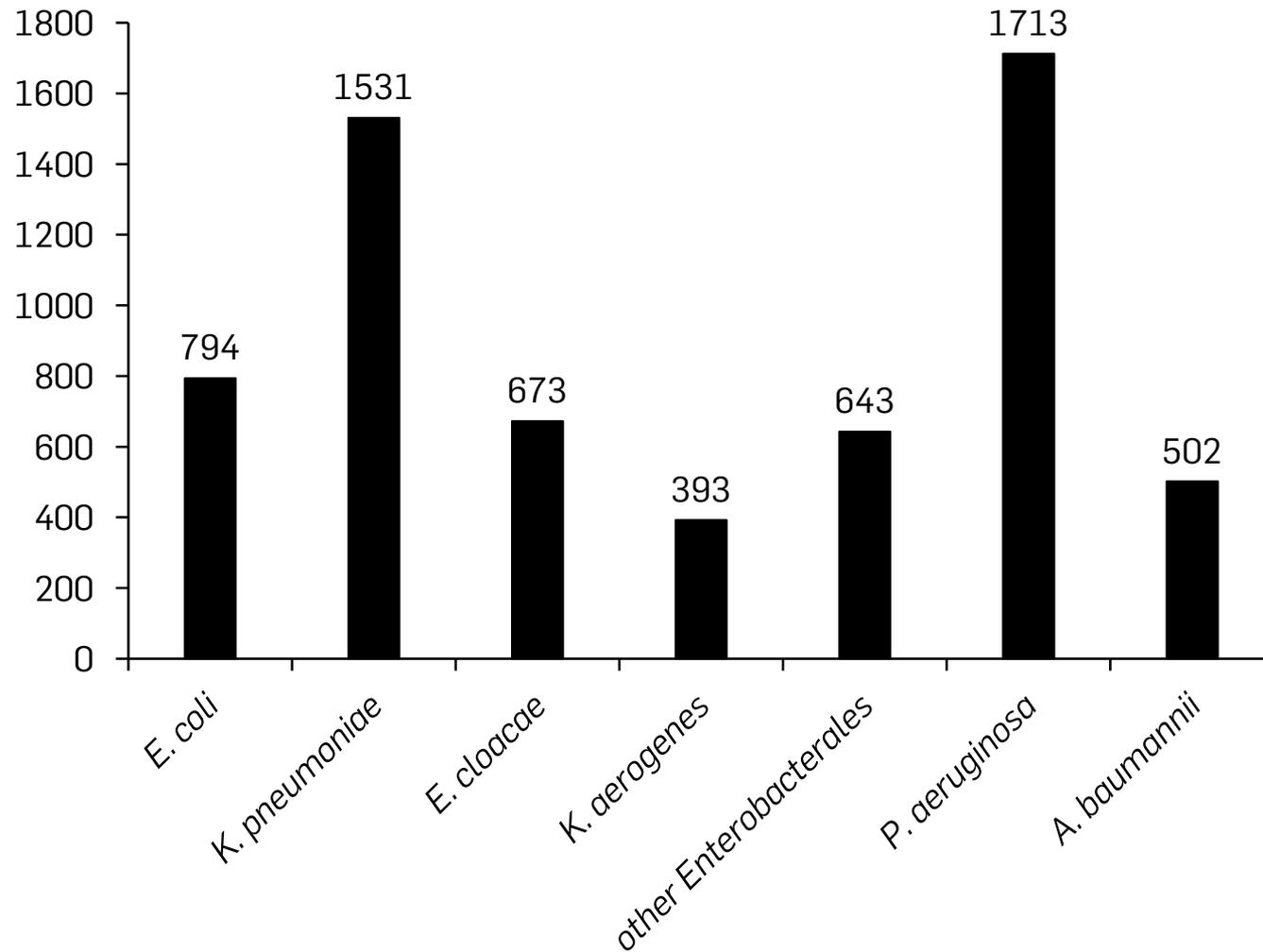
# Einsendungen an das NRZ 2018



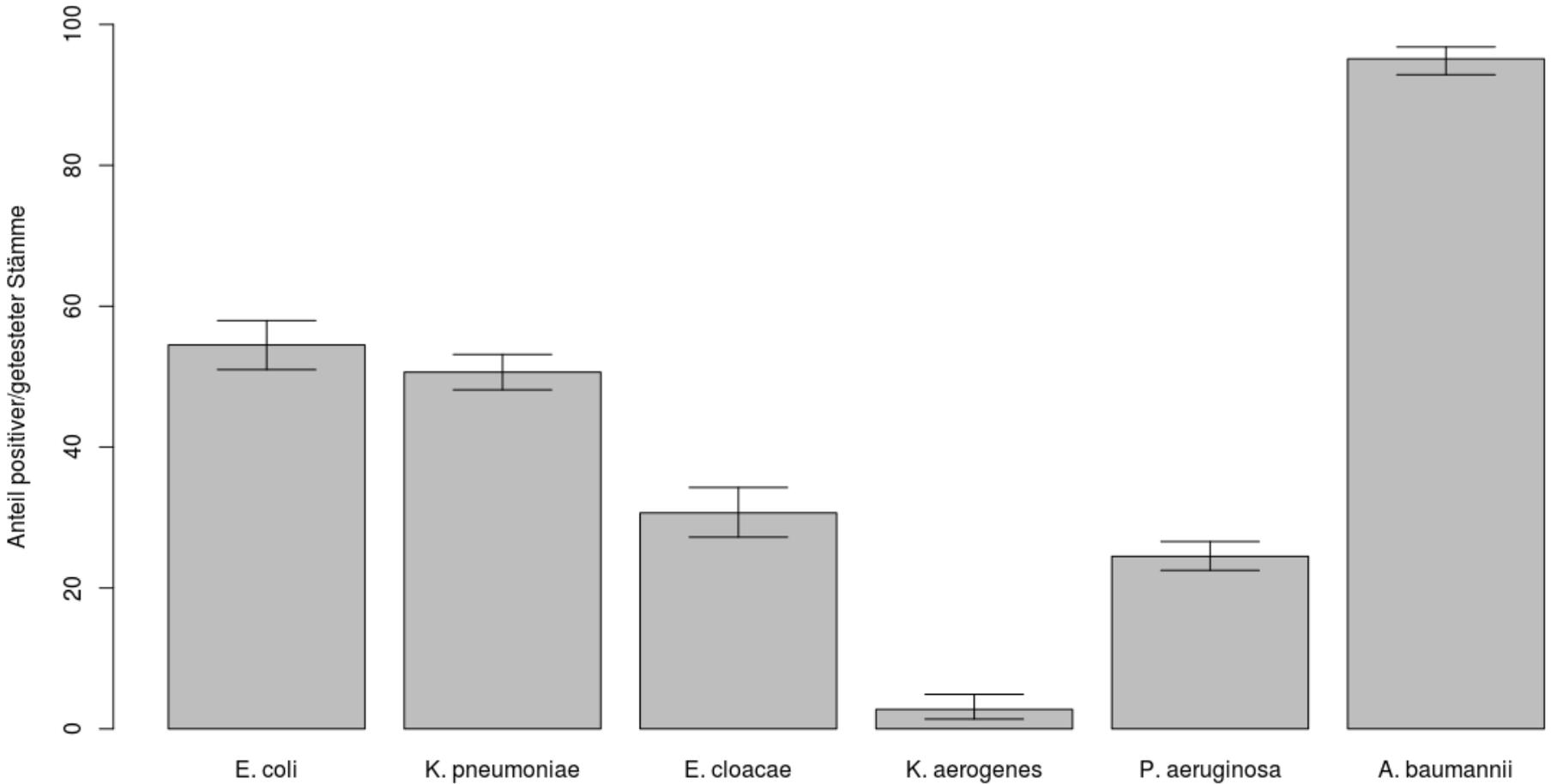
# Einsendungen an das NRZ 2018



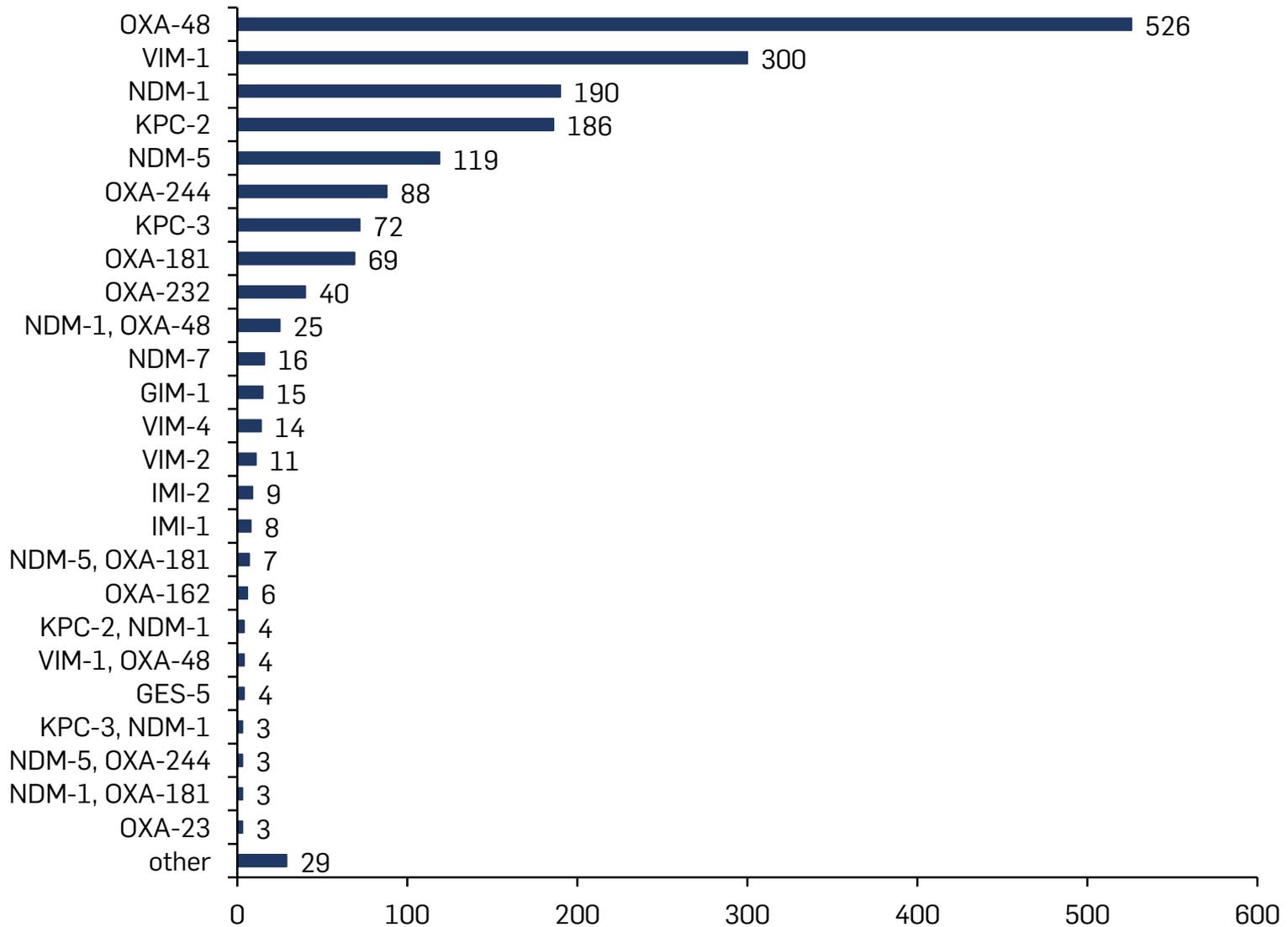
# Speziesverteilung 2018



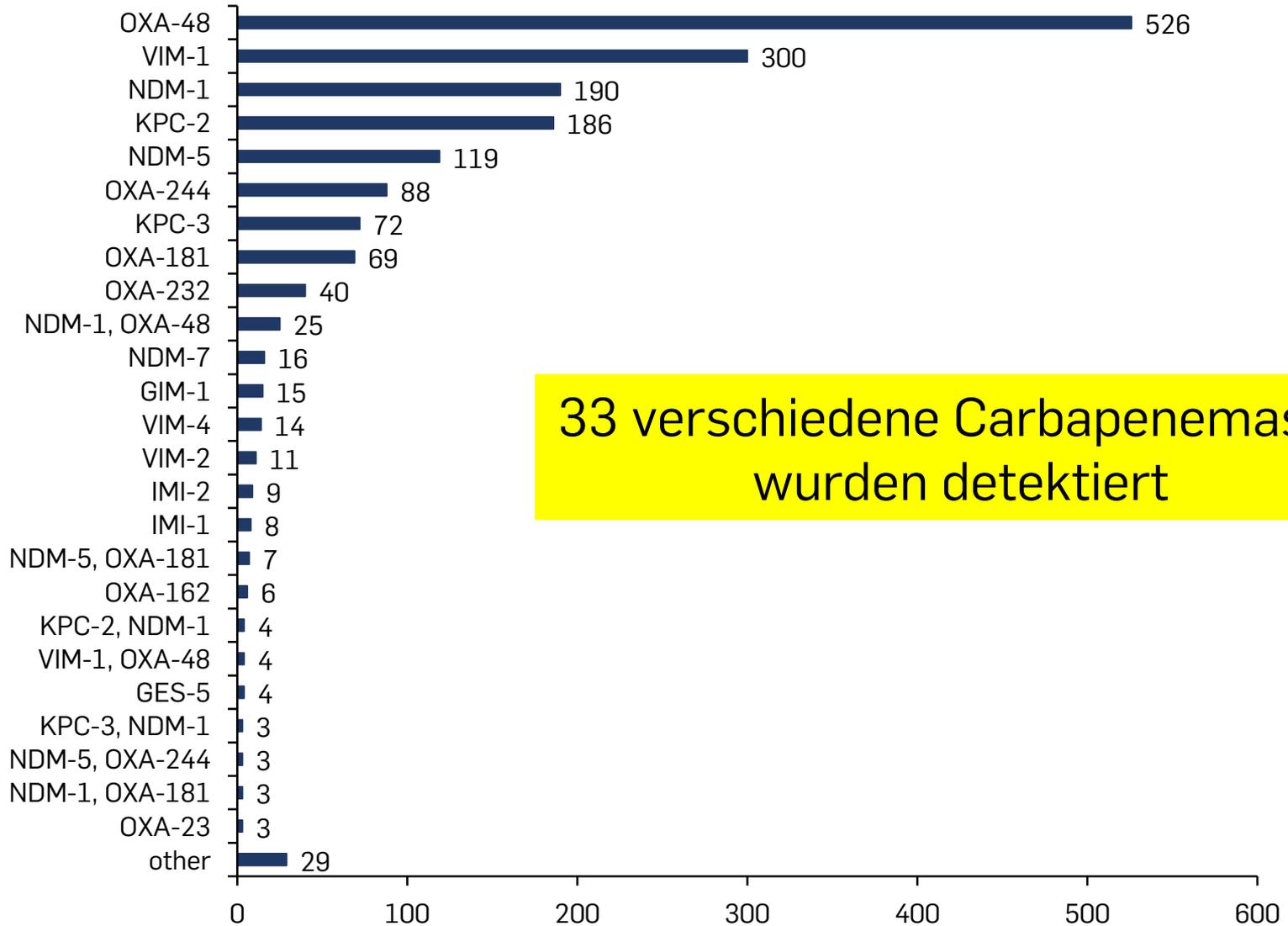
# Carbapenemaseanteile 2018



# Carbapenemasen bei *Enterobacterales* 2018

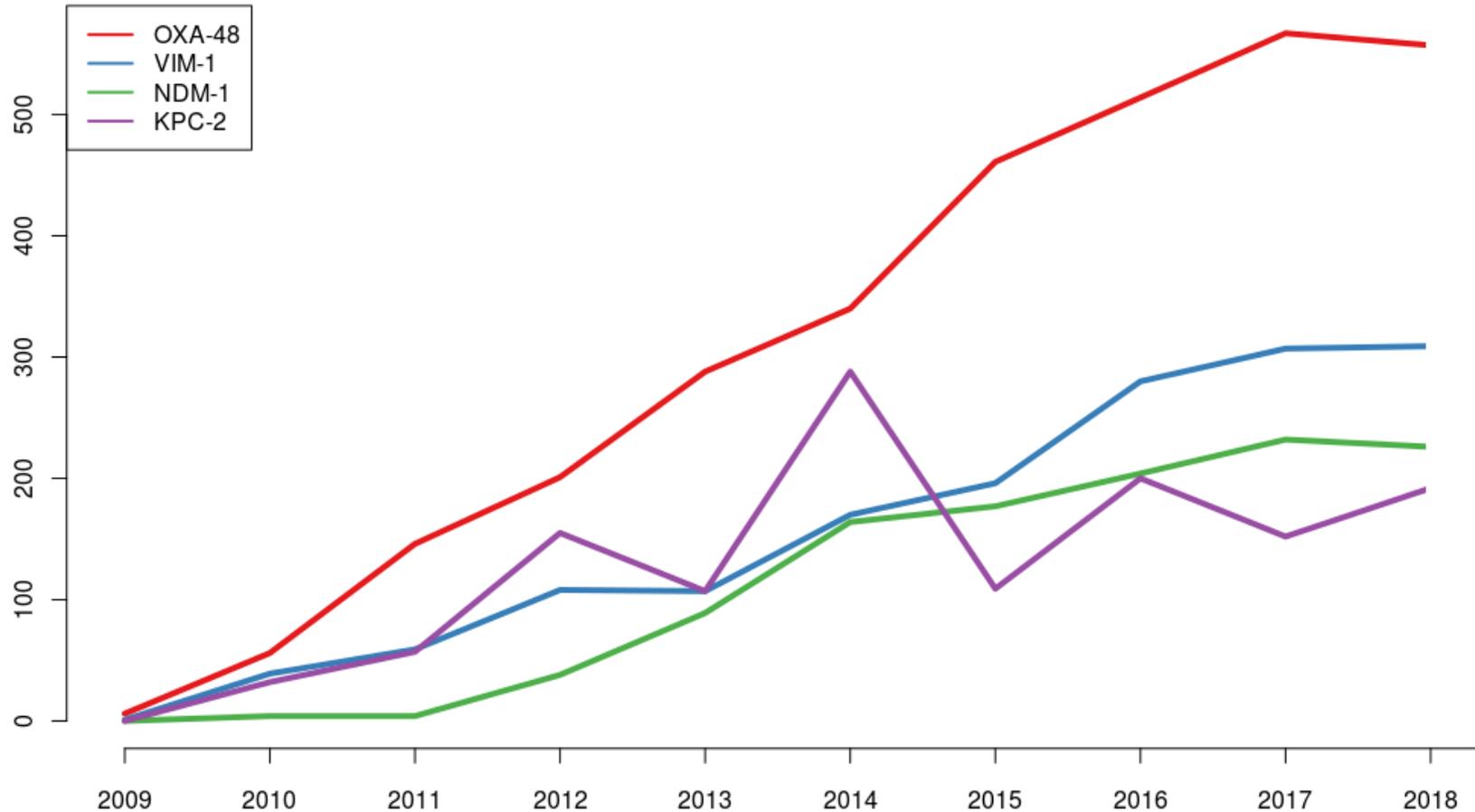


# Carbapenemasen bei *Enterobacterales* 2018

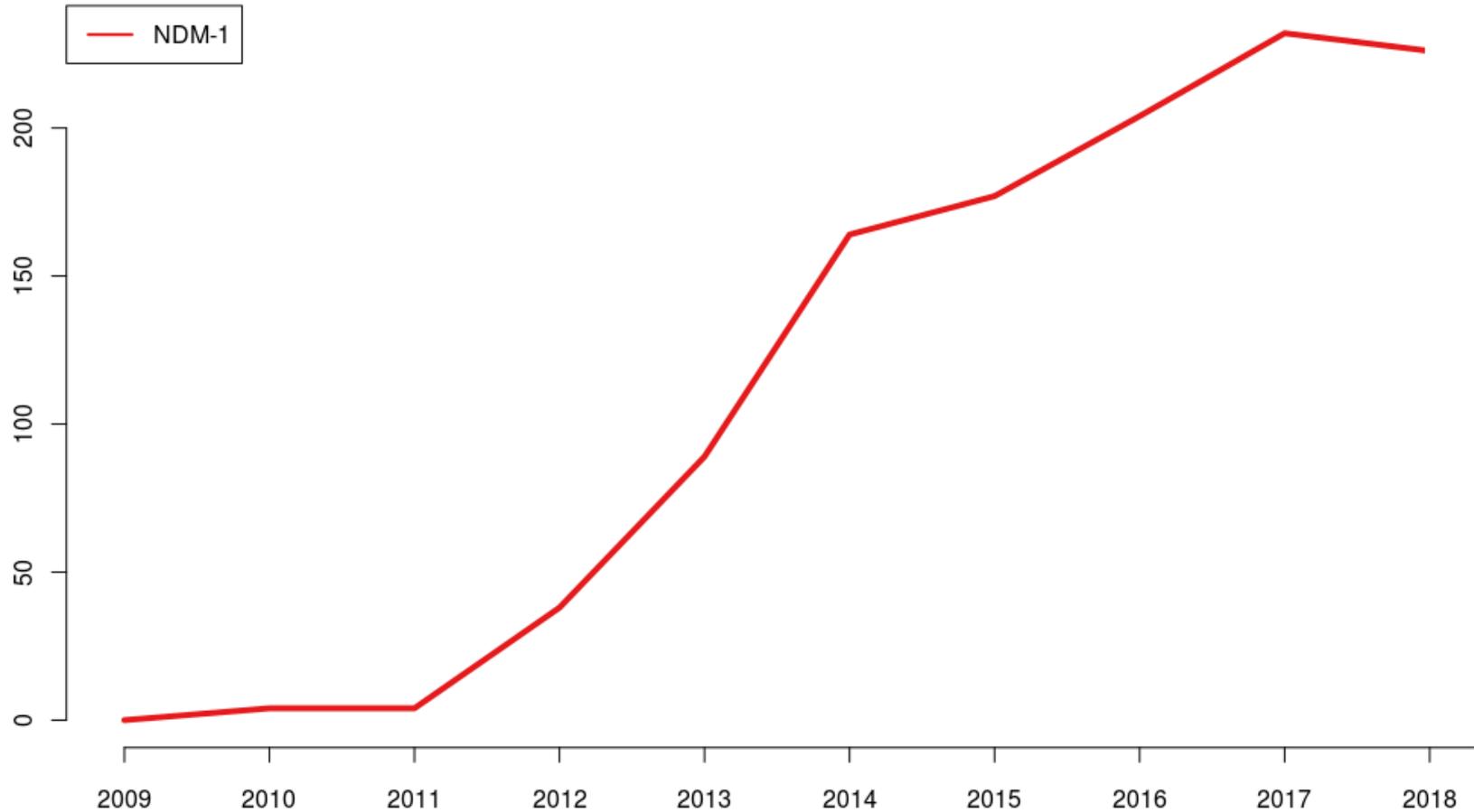


33 verschiedene Carbapenemasen  
wurden detektiert

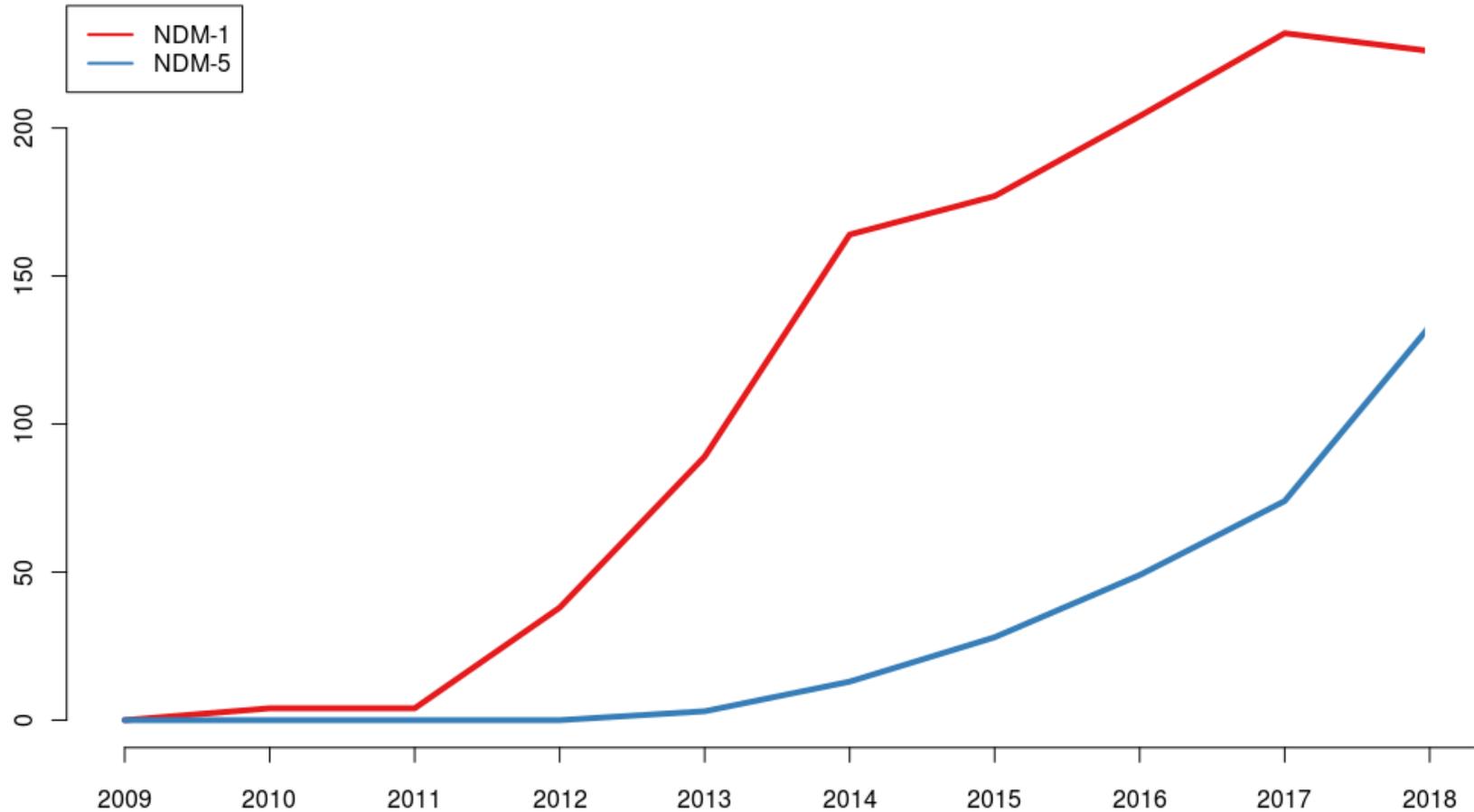
# Carbapenemasen bei *Enterobacterales*



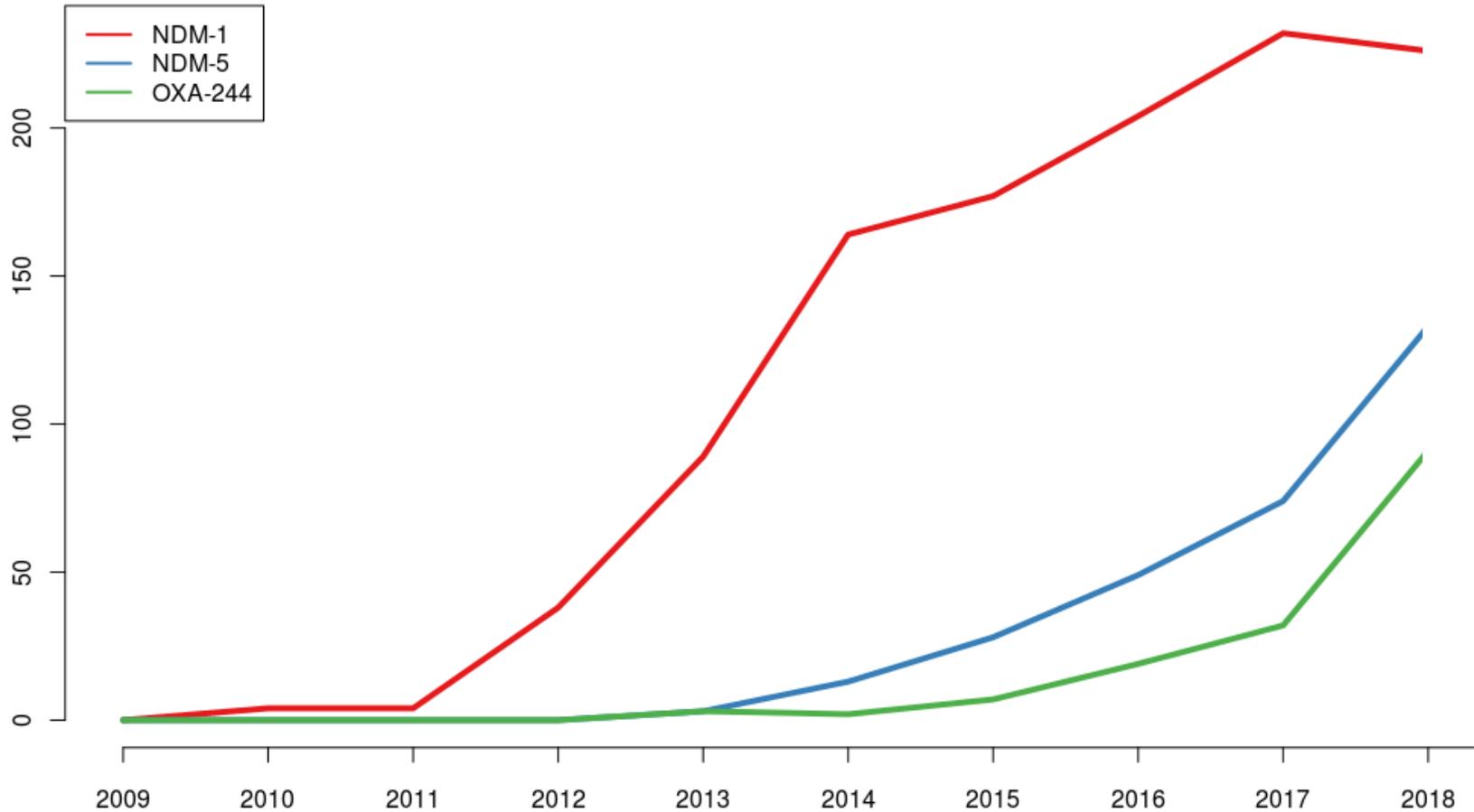
# Neue Entwicklungen



# NDM-5



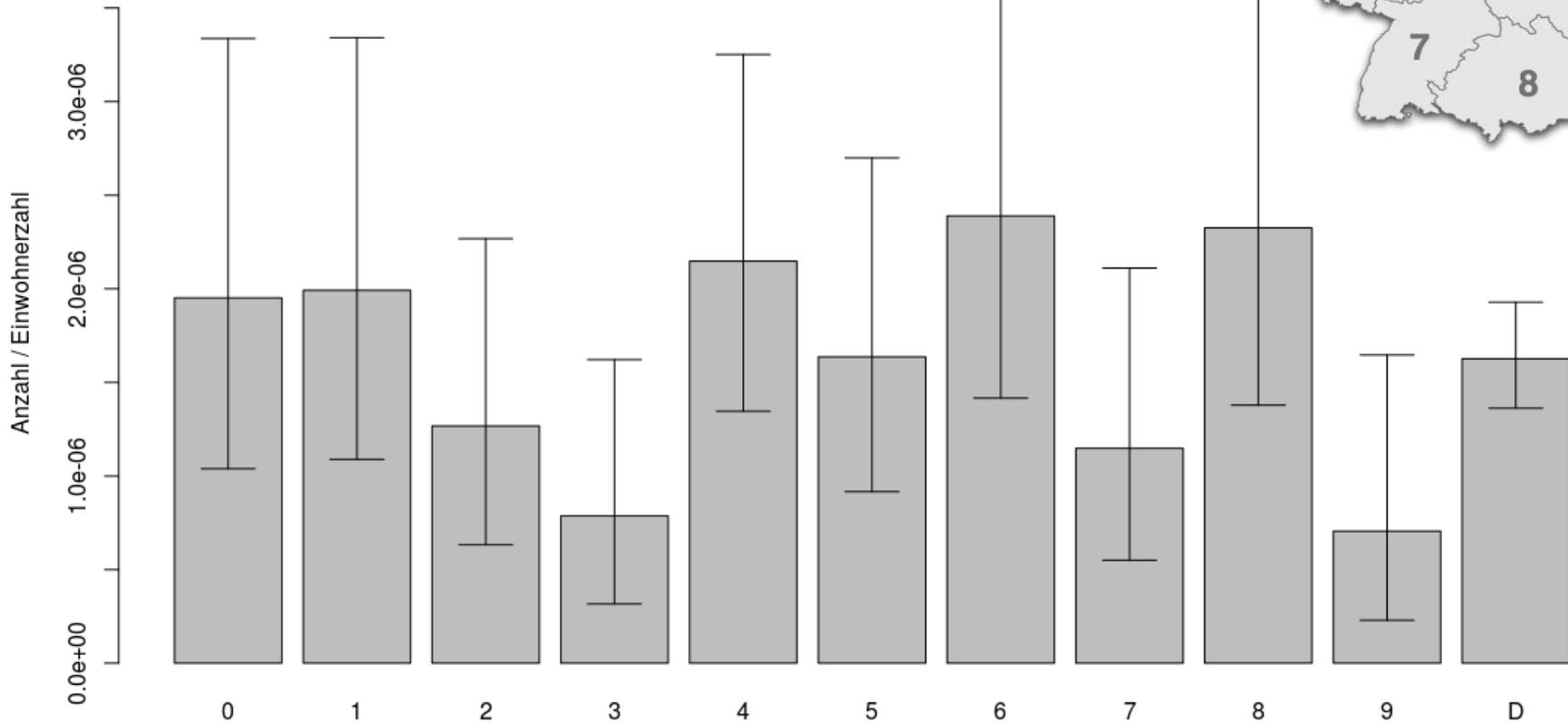
# OXA-244



# NDM-5



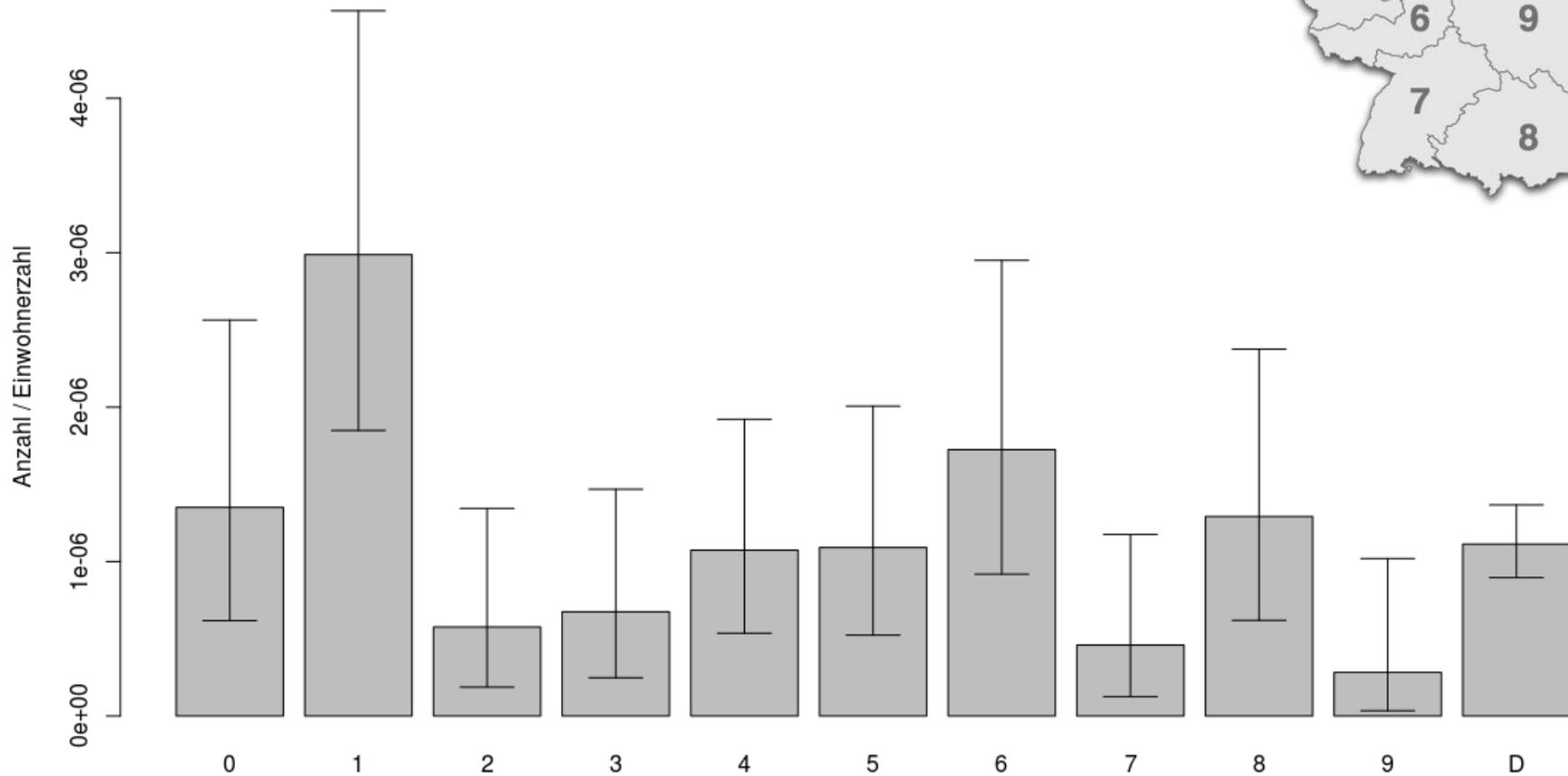
Anteil NDM-5 bezogen auf Einwohner  
nach PLZ-Bereichen  
Zeitraum: 01.01.2018 - 31.12.2018



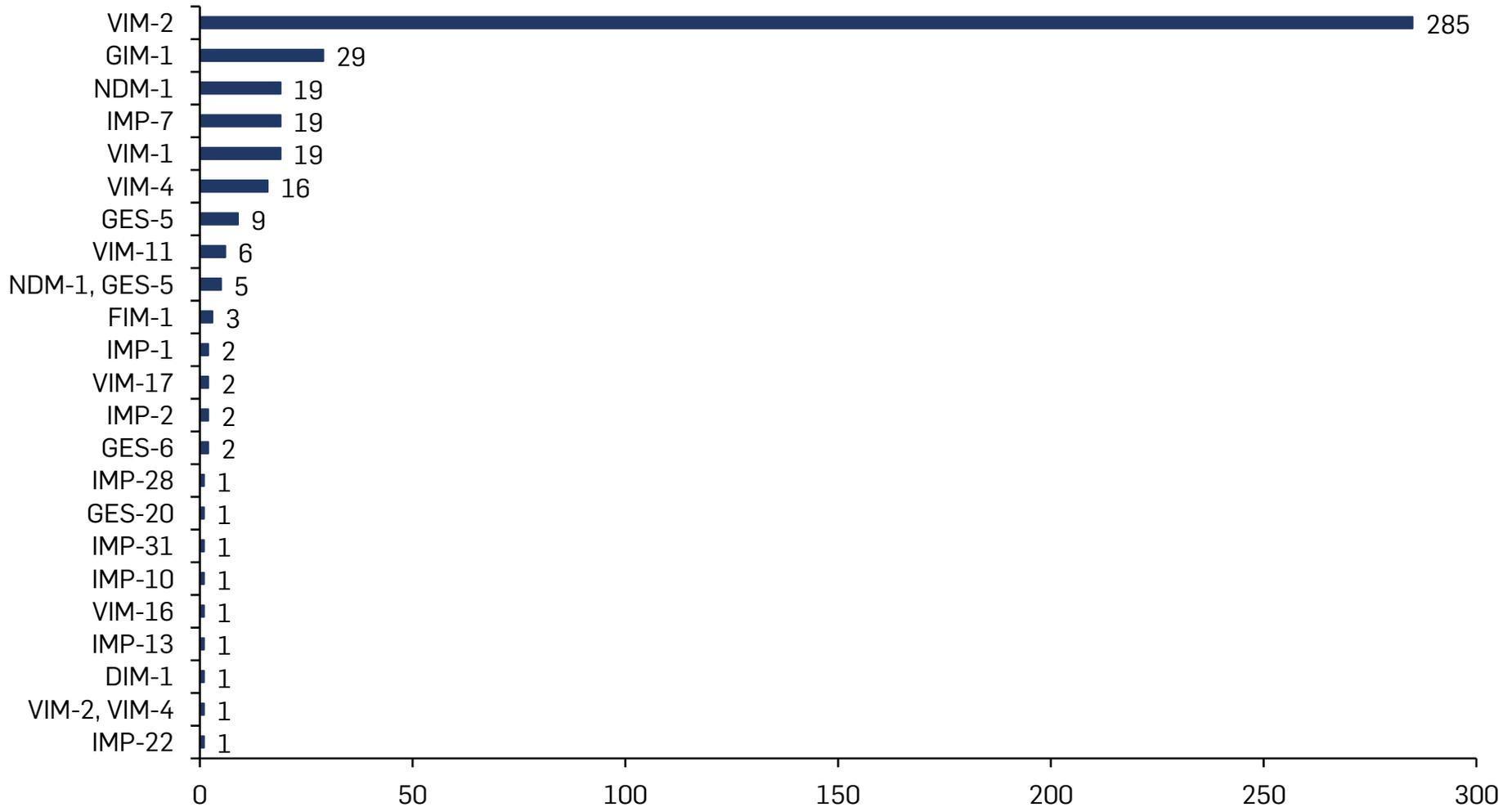
# OXA-244



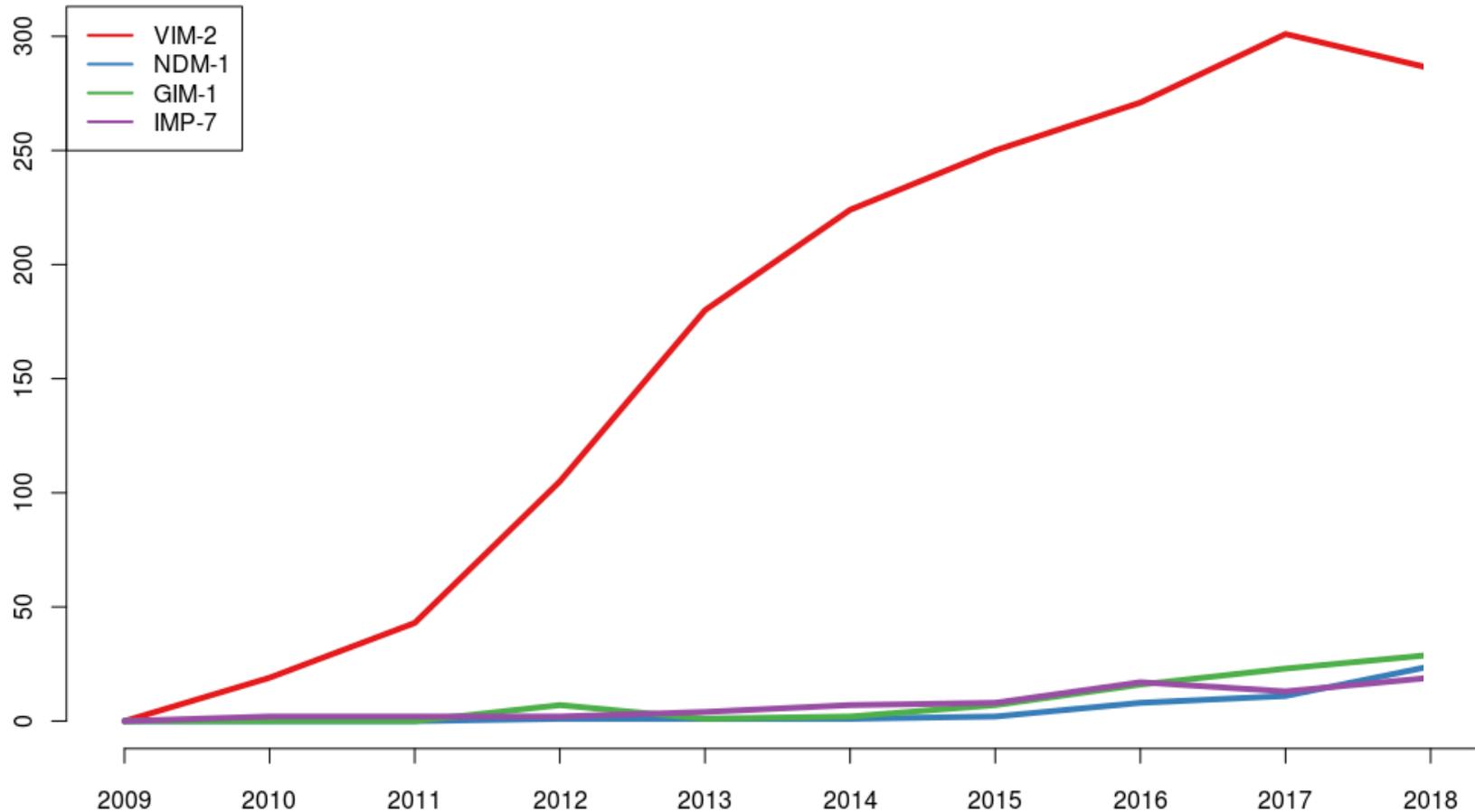
Anteil OXA-244 bezogen auf Einwohner  
nach PLZ-Bereichen  
Zeitraum: 01.01.2018 - 31.12.2018



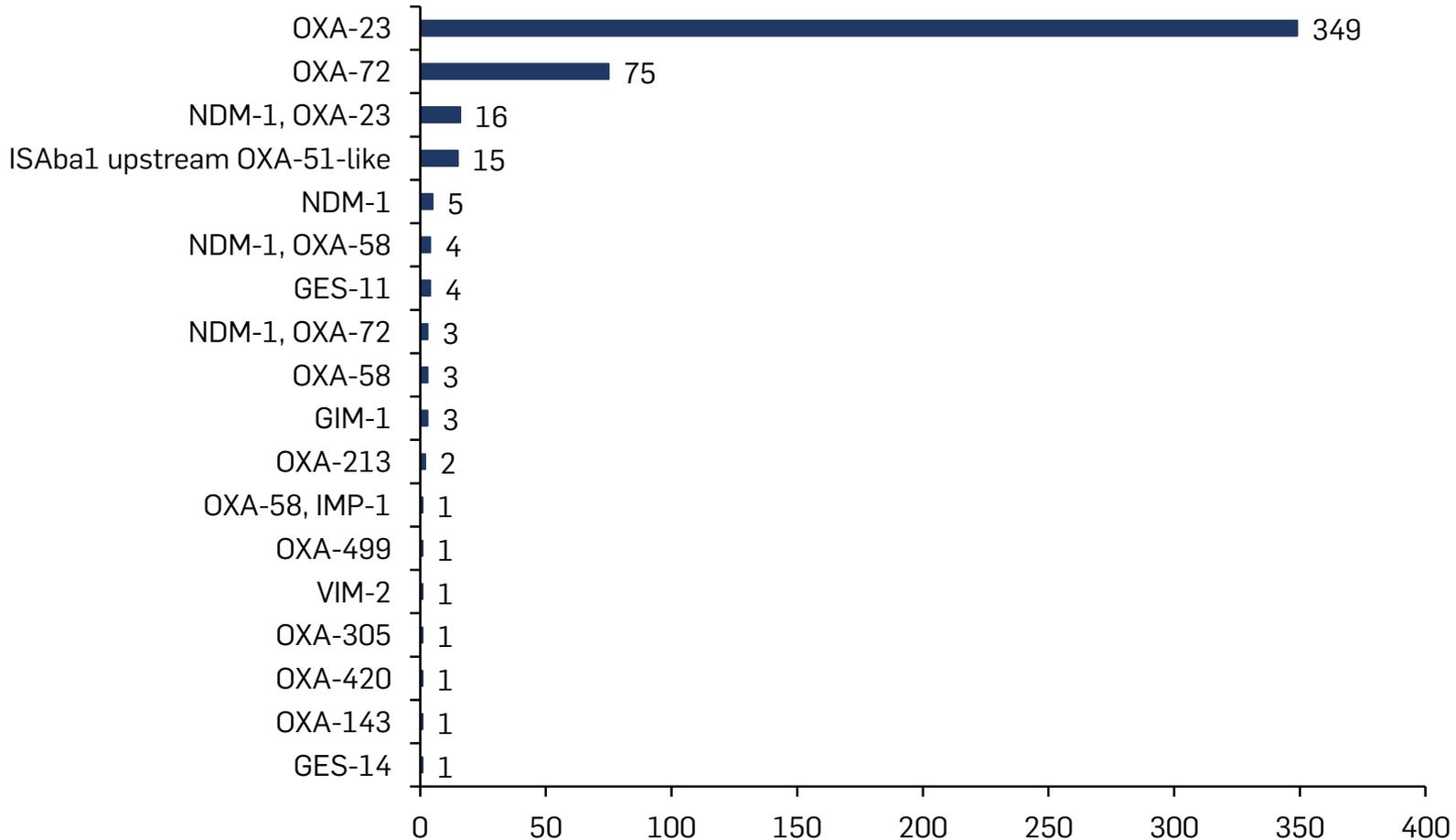
# Carbapenemasen bei *P. aeruginosa* 2018



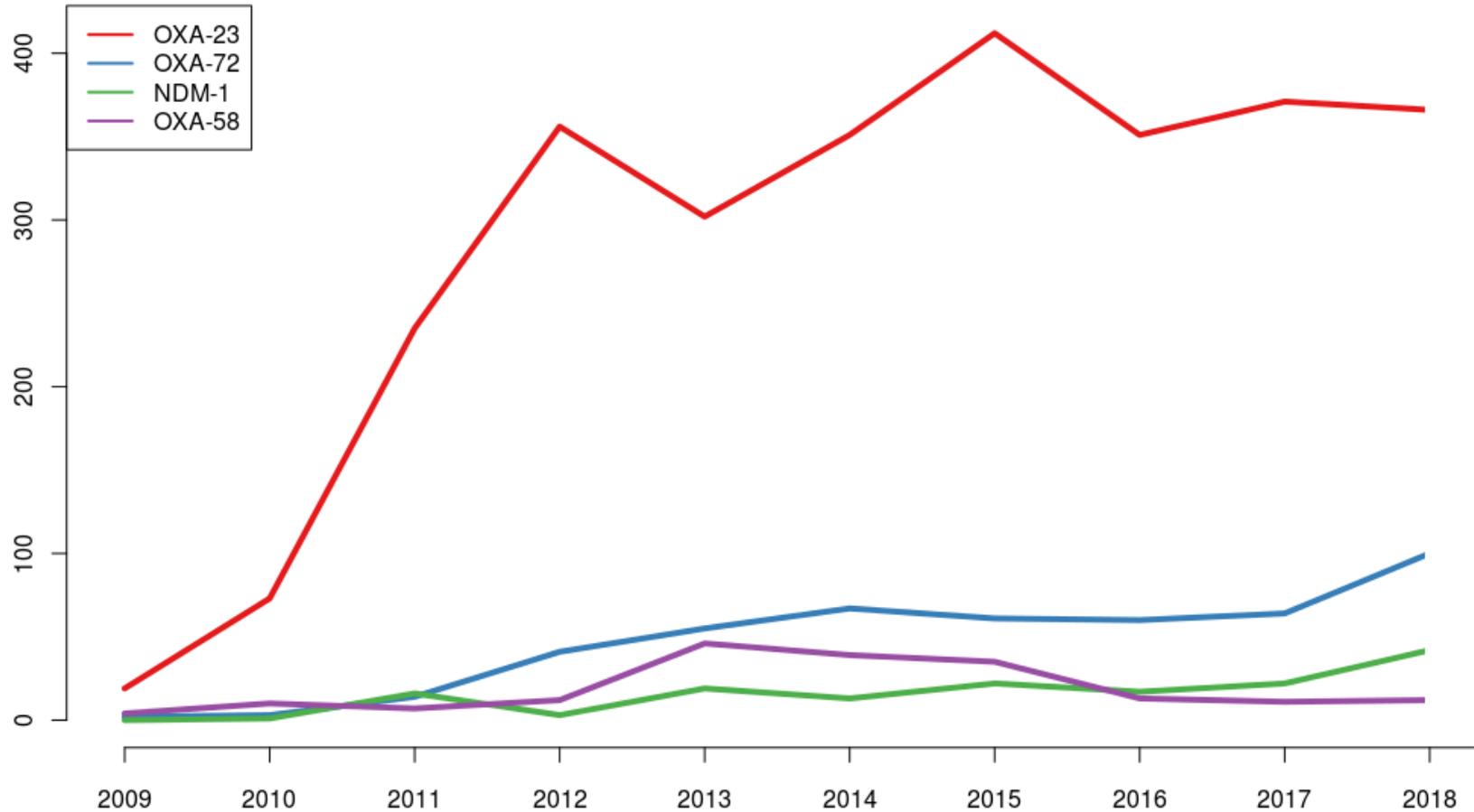
# Carbapenemasen bei *P. aeruginosa*



# Carbapenemasen bei *A. baumannii* 2018

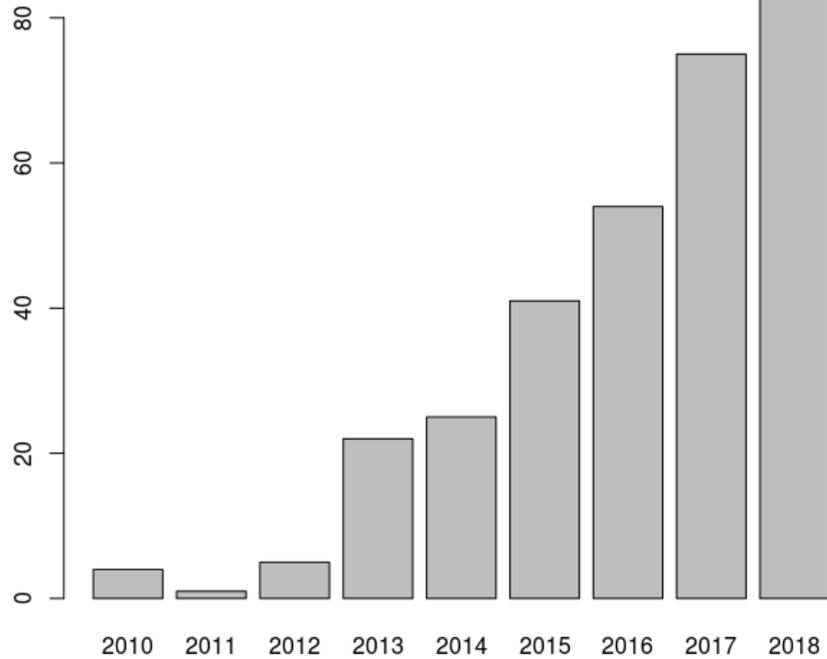


# *A. baumannii*



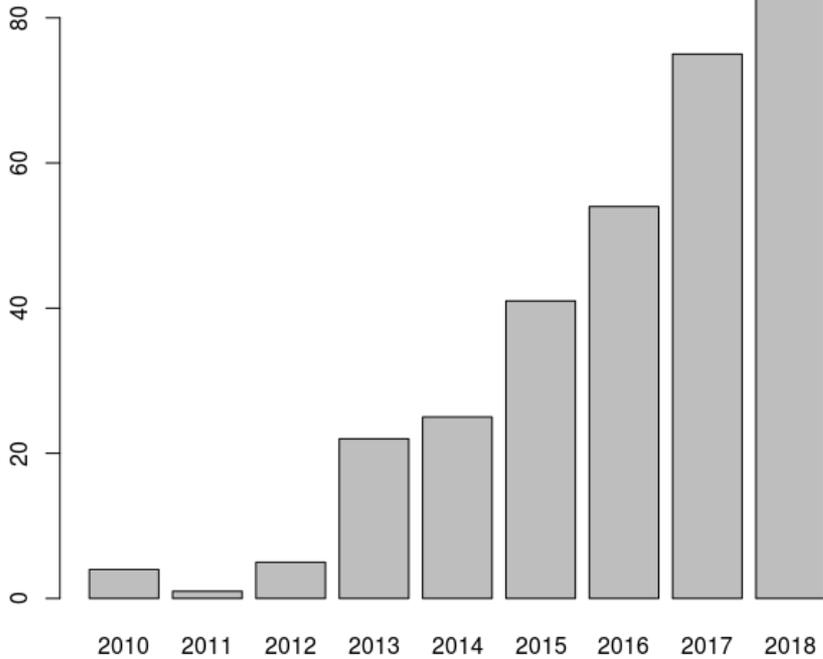
# Doppelcarbapenemasen

Gesamt

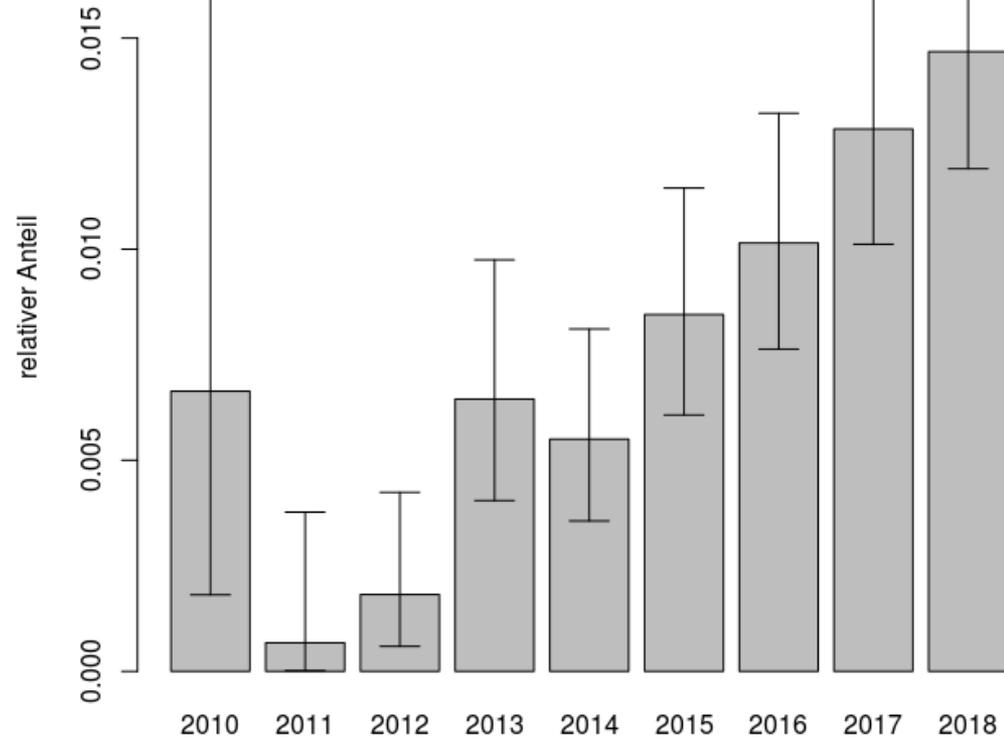


# Doppelcarbapenemasen

## Gesamt

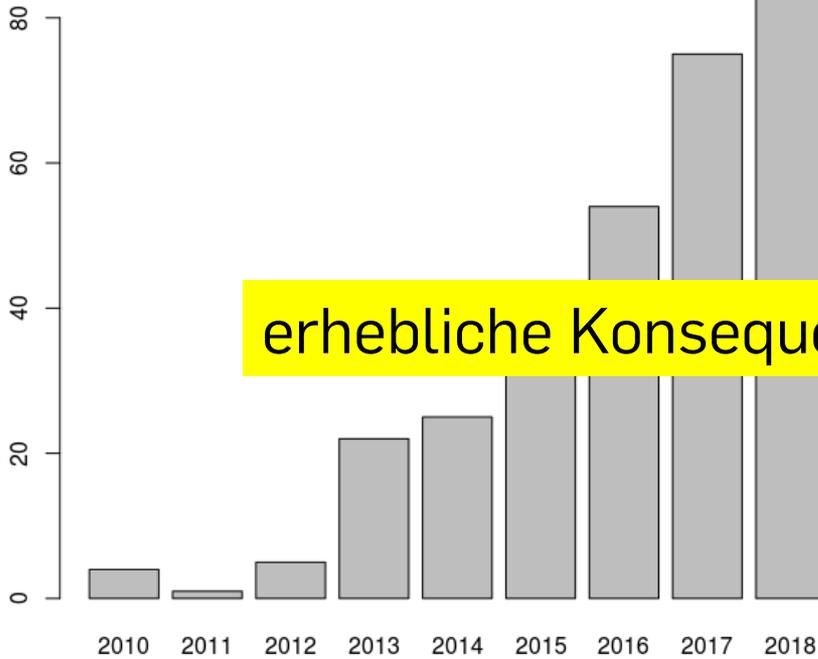


## Relativer Anteil

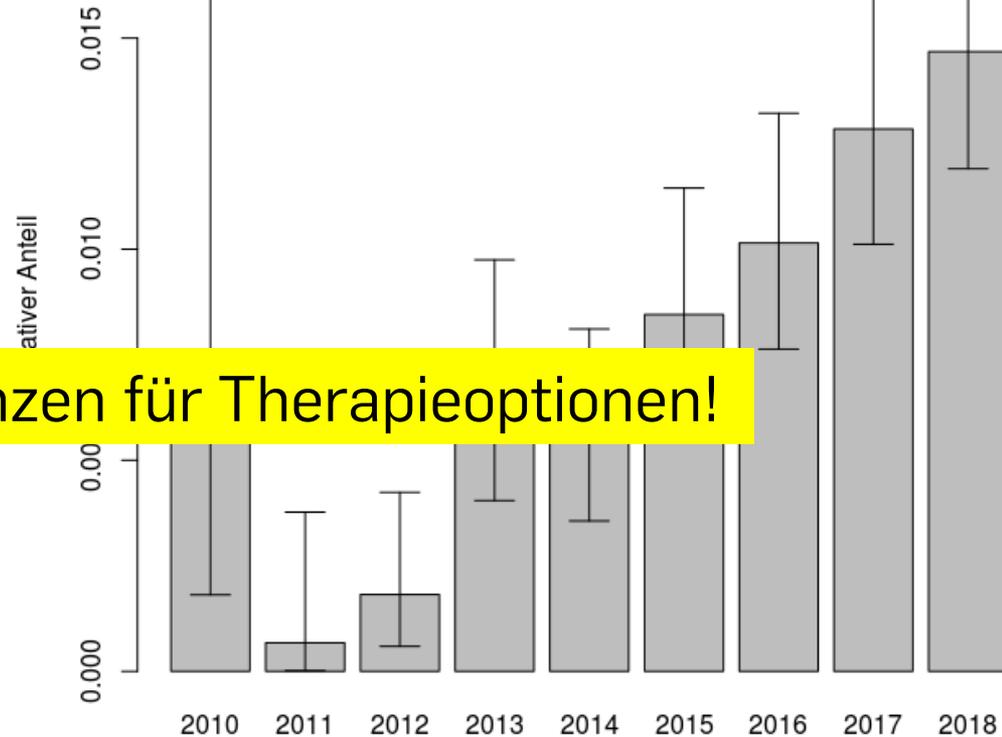


# Doppelcarbapenemase

Gesamt



Relativer Anteil



erhebliche Konsequenzen für Therapieoptionen!

# Wie geht es weiter?

2019: EURGen-Net-Studie zur Prävalenz von carbapenem- und/oder colistinresistenten *Enterobacterales* (EuSCAPE-Nachfolgestudie)

# Zum Schluss...

## Neudefinition von I durch EUCAST



# Was I bislang bedeutete...

1. Antimikrobielle Aktivität gegenüber Mikroorganismus mit unklarem therapeutischen Effekt
2. „Pufferzone“ die verhindert, dass unkontrollierte technische Abweichungen zu wesentlichen Fehlern der Interpretation führen (very major error/major error).
3. Antimikrobielle Aktivität gegenüber Mikroorganismus bei hoher Dosis/erhöhter Exposition
4. Antimikrobielle Aktivität gegenüber Mikroorganismus bei Anreicherung am Infektionsort

# ...und was es nun bedeutet

- ~~1. Antimikrobielle Aktivität gegenüber Mikroorganismus mit unklarem  
therapeutischen Effekt~~
- ~~2. „Pufferzone“ die verhindert, dass unkontrollierte technische Abweichungen zu  
wesentlichen Fehlern der Interpretation führen (very major error/major error).~~
- ~~3. Antimikrobielle Aktivität gegenüber Mikroorganismus bei hoher Dosis/erhöhter  
Exposition~~
- ~~4. Antimikrobielle Aktivität gegenüber Mikroorganismus bei Anreicherung am  
Infektionsort~~

ab 01.01.2019:

**„I“ bedeutet ausschließlich „sensibel bei erhöhter Exposition [Dosis]“**  
(susceptible Increased exposure)

**→ „I“ ist „sensibel“ mit Hinweis auf hohe Dosierung**

# Zum Teil deutliche Konsequenzen

## *Pseudomonas aeruginosa*

	<b>bis 2018</b>	<b>ab 2020</b>	<b>Dosis</b>	<b>übergangsweise 2019</b>
Piperacillin-Tazobactam	S*	I	4 x 4,5g	S*
Ceftazidim	S*	I	3 x 2g	S*
Imipenem	S*	I	4 x 1g	S*
Meropenem	S	S		S
Ciprofloxacin	S*	I	3 x 400mg	S*
Aztreonam	I	I		S*

\* gilt nur bei hoher Dosis

# Zum Teil deutliche Konsequenzen

## *Pseudomonas aeruginosa*

	<b>bis 2018</b>	<b>ab 2020</b>	<b>Dosis</b>	<b>übergangsweise 2019</b>
Piperacillin-Tazobactam	S*	I	4 x 4,5g	S*
Ceftazidim	S*	I	3 x 2g	S*
Imipenem	S*	I	4 x 1g	S*
Meropenem	S	S		S
Ciprofloxacin	S*	I	3 x 400mg	S*
Aztreonam	I	I		S*

\* gilt nur bei hoher Dosis

Konsequenzen für MRGN-Klassifikation? I wie R?

# Konsequenzen für die MRGN-Klassifikation:

- Neudefinition der I-Kategorie durch EUCAST
- KRINKO: **I** wie **S** bewerten  
+ Fähigkeit, Carbapenemase zu detektieren
- weitere Neuerung:  
*P. aeruginosa* + Carbapenemase = 4MRGN

Vielen Dank an alle Einsender und für  
Ihre Aufmerksamkeit!

