



*division of hygiene  
and medical microbiology*

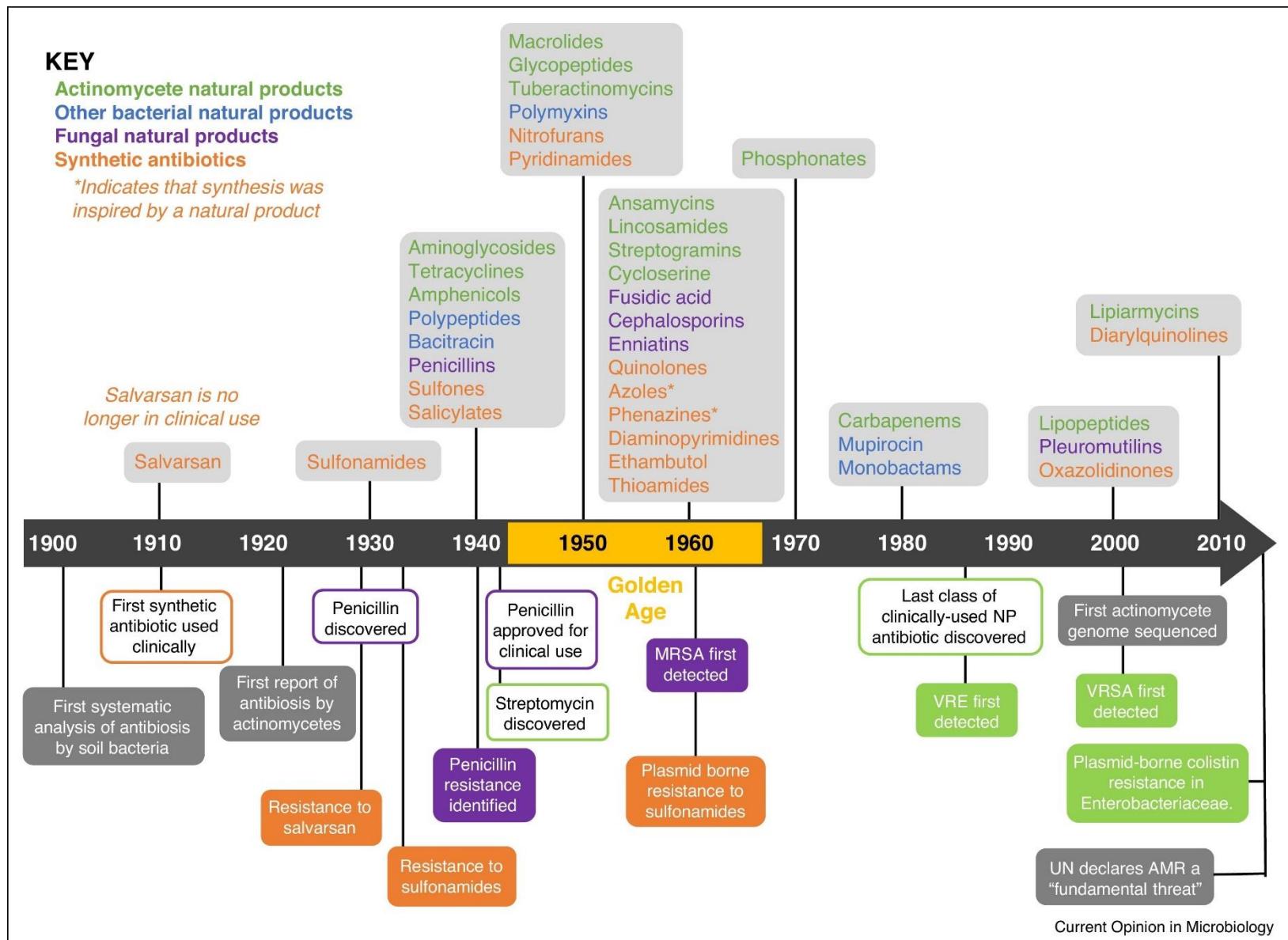
# Aktuelle Resistenzlage in Tirol

**Dr. med. univ. Miriam Alisa Govrins**

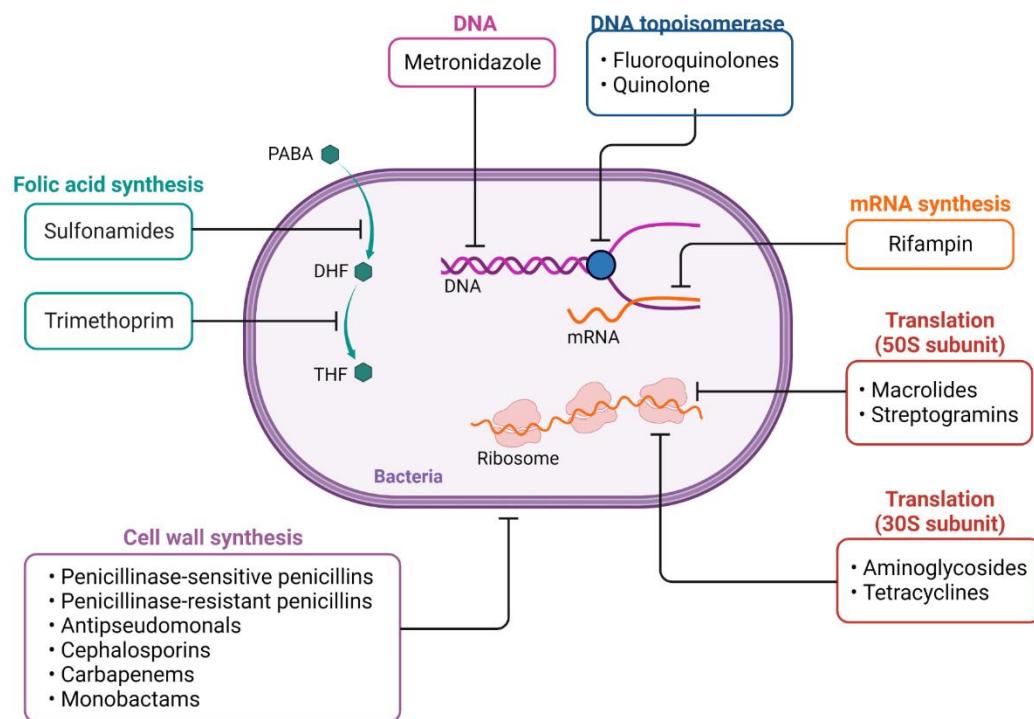
**Medizinische Universität Innsbruck**

**Institut für Hygiene und Medizinische Mikrobiologie**

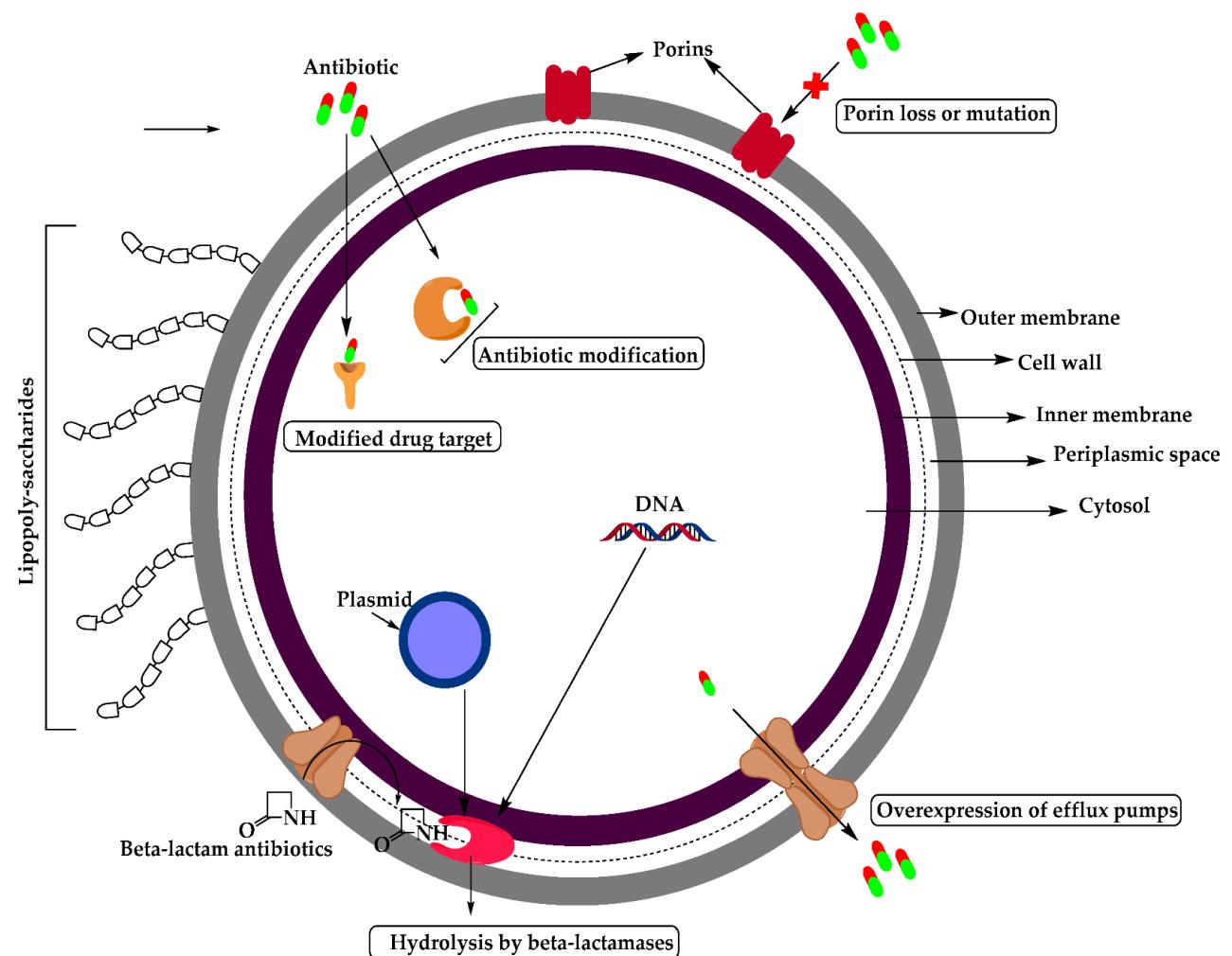
# Geschichte der Antibiotika



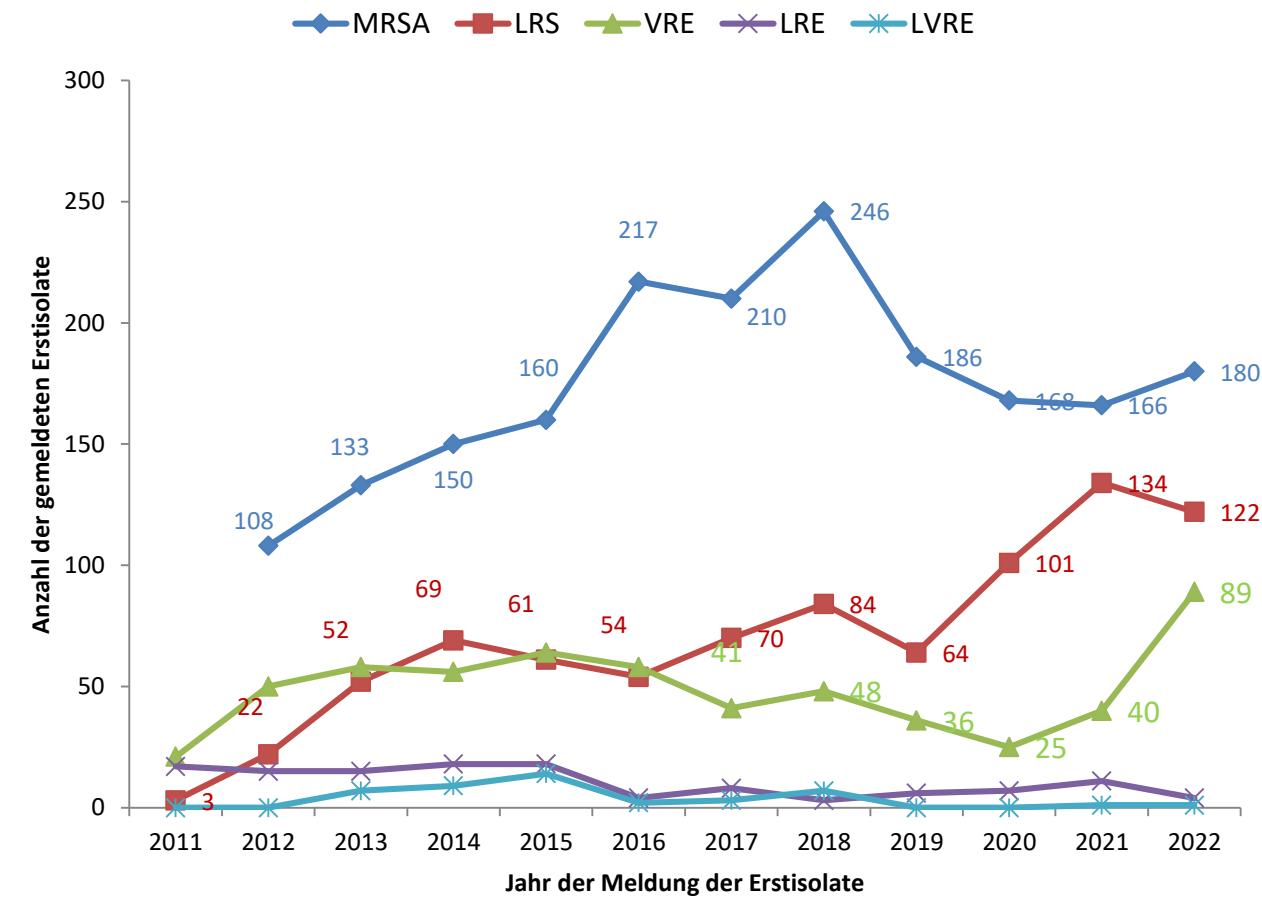
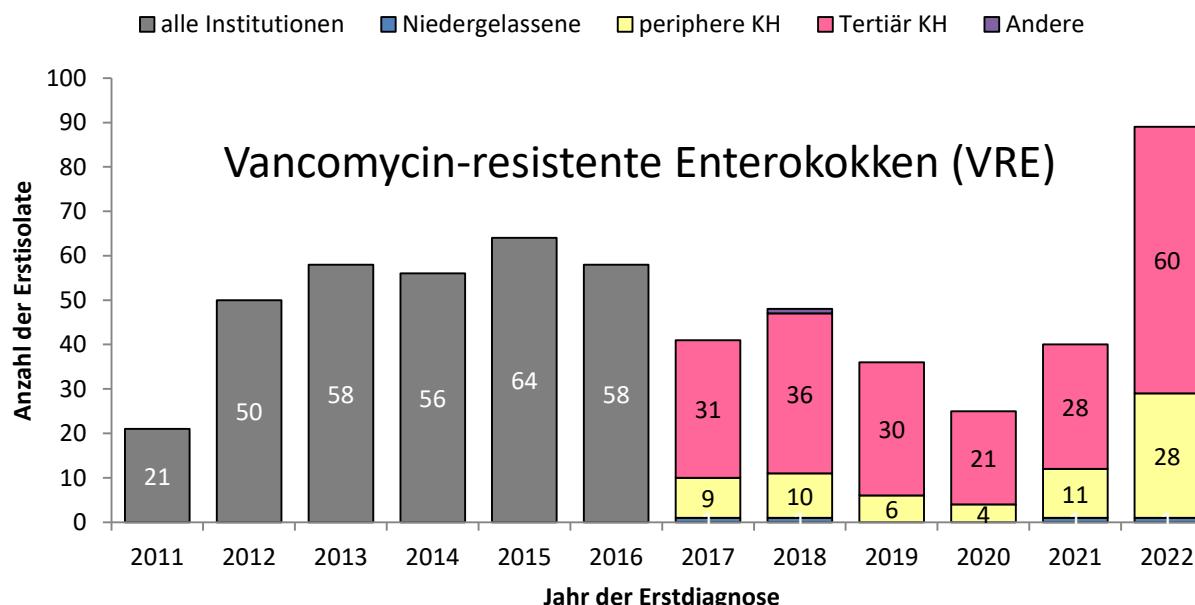
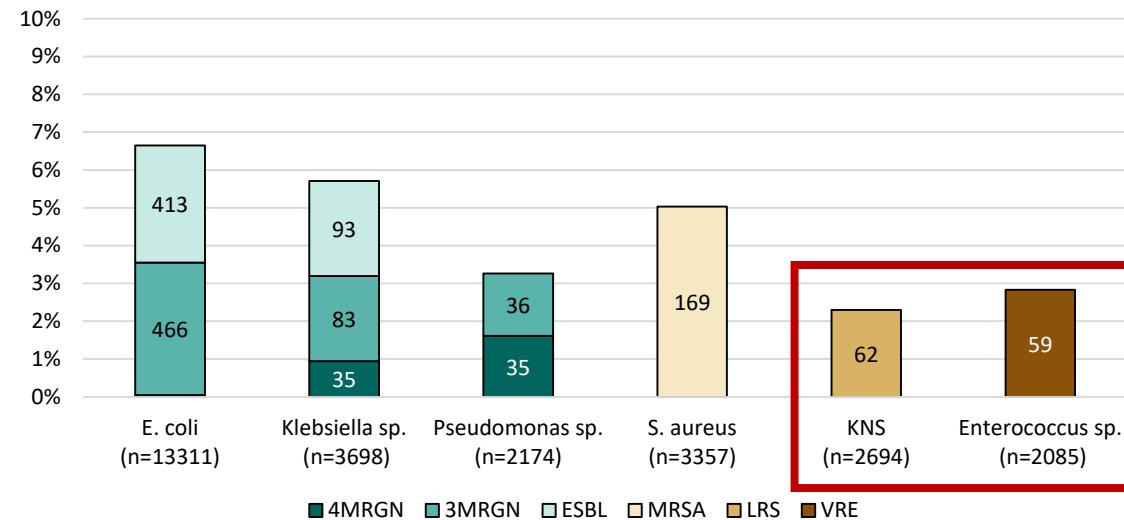
# Wirkmechanismen



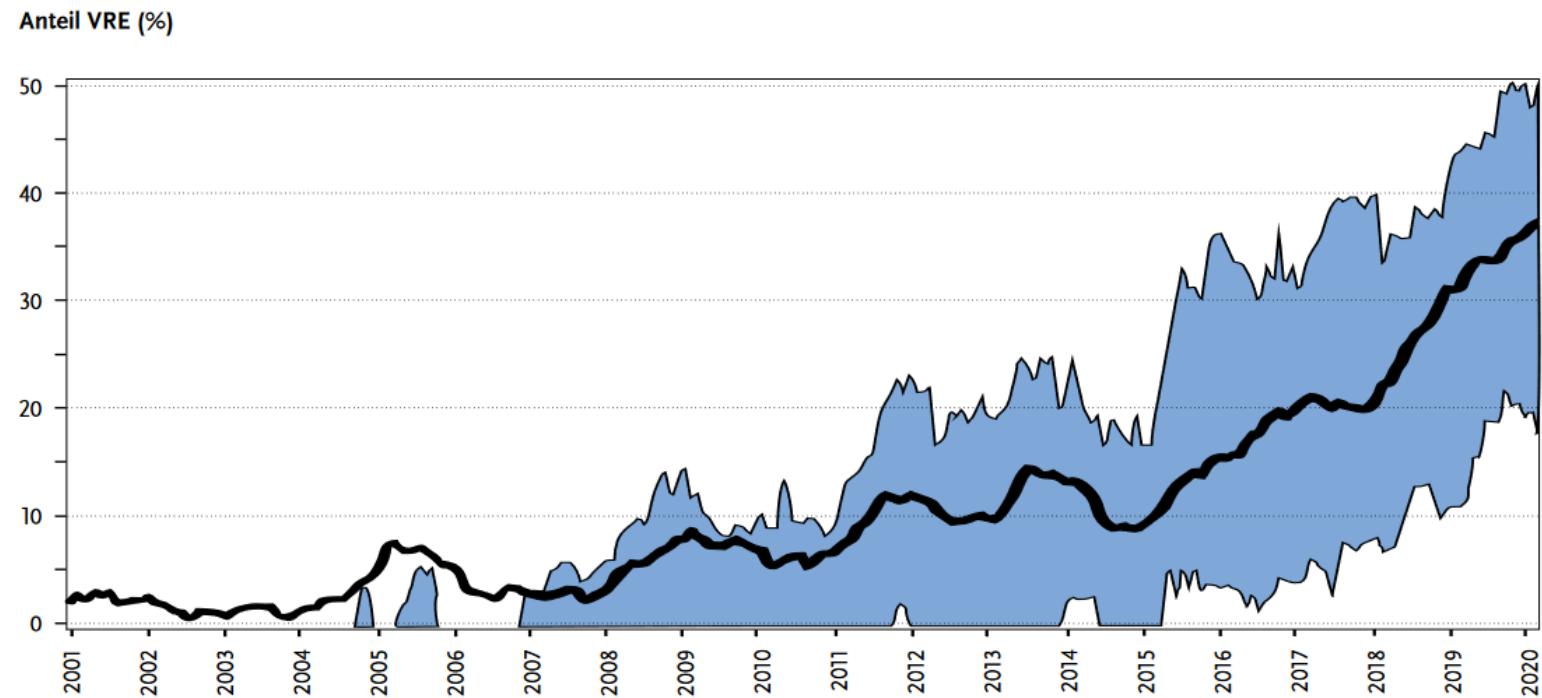
# Resistenzmechanismen



# Multiresistenzen 2022

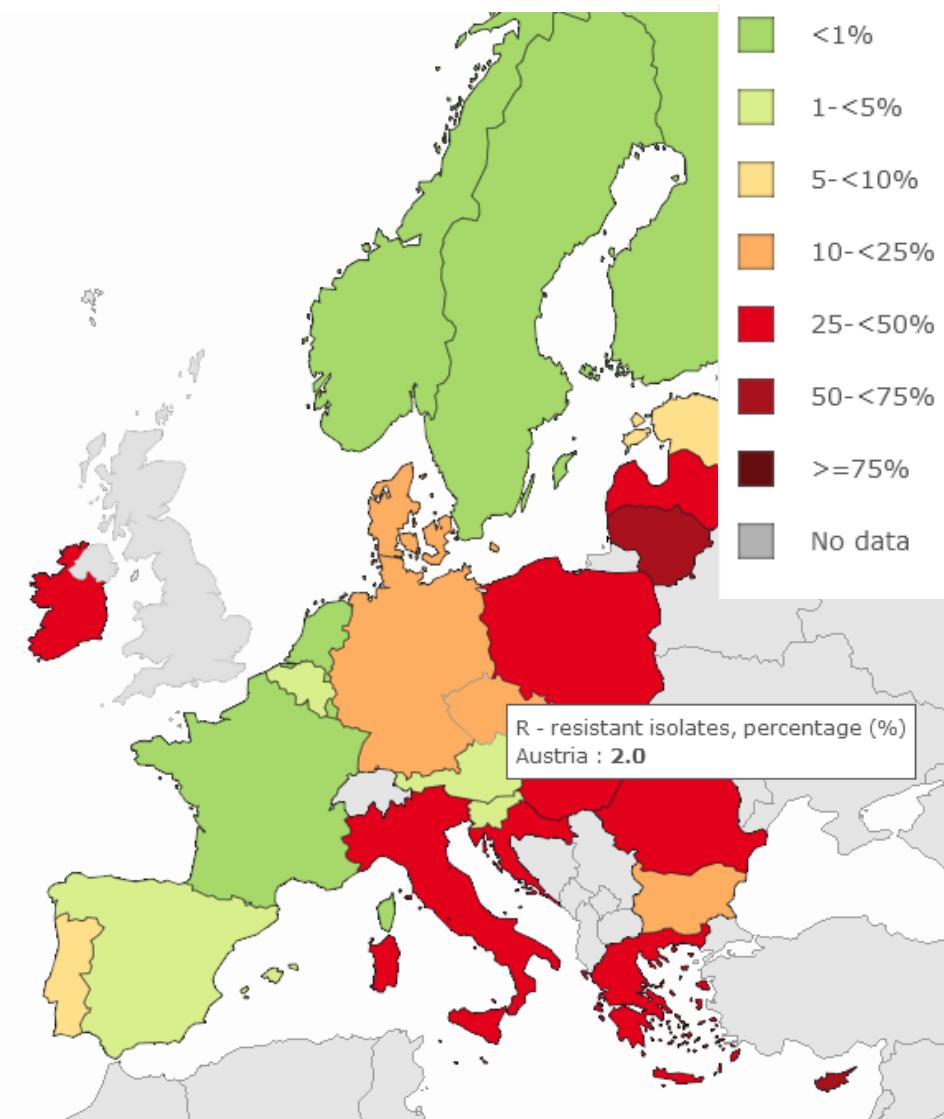


# Vancomycin-resistente Enterokokken



**Abb. 2 |** Vancomycin-Resistenzraten von *E. faecium* aus Intensivstationen deutscher Krankenhäuser im Rahmen des SARI-Projekts in den Jahren 2001–2020. Auf der X-Achse ist der Anteil von VRE pro 100 *E. faecium*-Isolaten in Prozent dargestellt. Die schwarze Linie stellt den Mittelwert dar. Die obere und untere Begrenzung des blauen Bereichs stellt die 75 % bzw. die 25 % Perzentile dar. Grafik modifiziert nach <https://eu-burden.info/sari/auswertung/pages/vre.php>.

Deutschland



# VRE Österreichweit 2020 (Blutkulturisolate)

Tabelle 33: Enterokokken –Vancomycin-resistant nach Bundesland 2020 (Teil 1)

	B		K		NÖ		OÖ		S	
	n	%R	n	%R	n	%R	n	%R	n	%R
<i>E. faecalis</i>	17	0,0	57	0,0	91	0,0	205	0,0	58	0,0
<i>E. faecium</i>	22	0,0	39	2,6	46	2,2	87	1,1	28	10,7

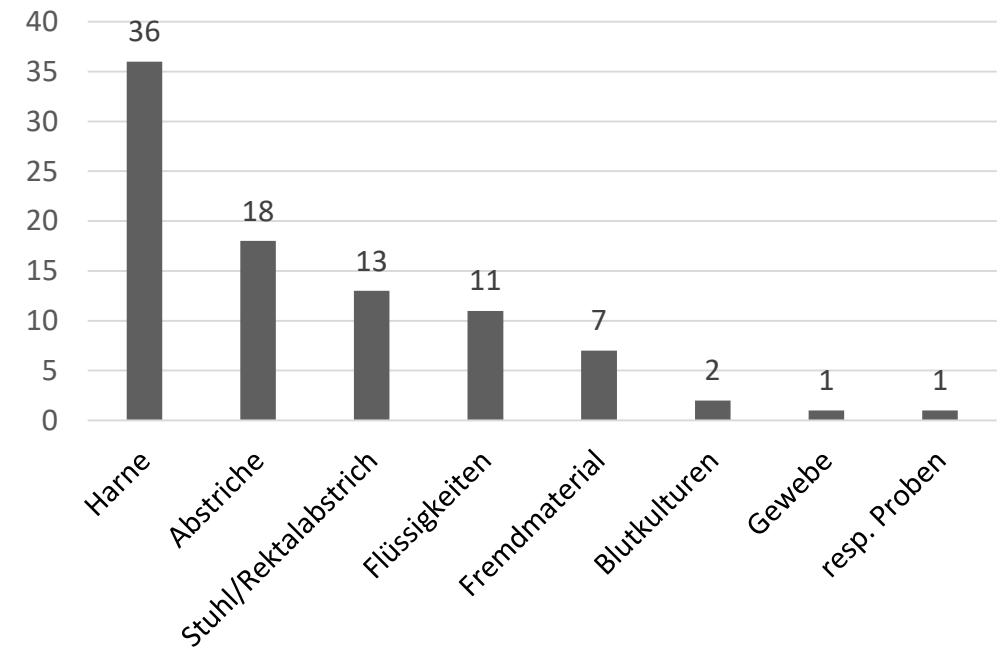
Tabelle 34: Enterokokken –Vancomycin-resistant nach Bundesland 2020 (Teil 2)

	ST		T		V		W	
	n	%R	n	%R	n	%R	n	%R
<i>E. faecalis</i>	131	0,8	180	0,0	33	3,0	317	0,0
<i>E. faecium</i>	82	6,1	120	11,7	16	0,0	228	5,3

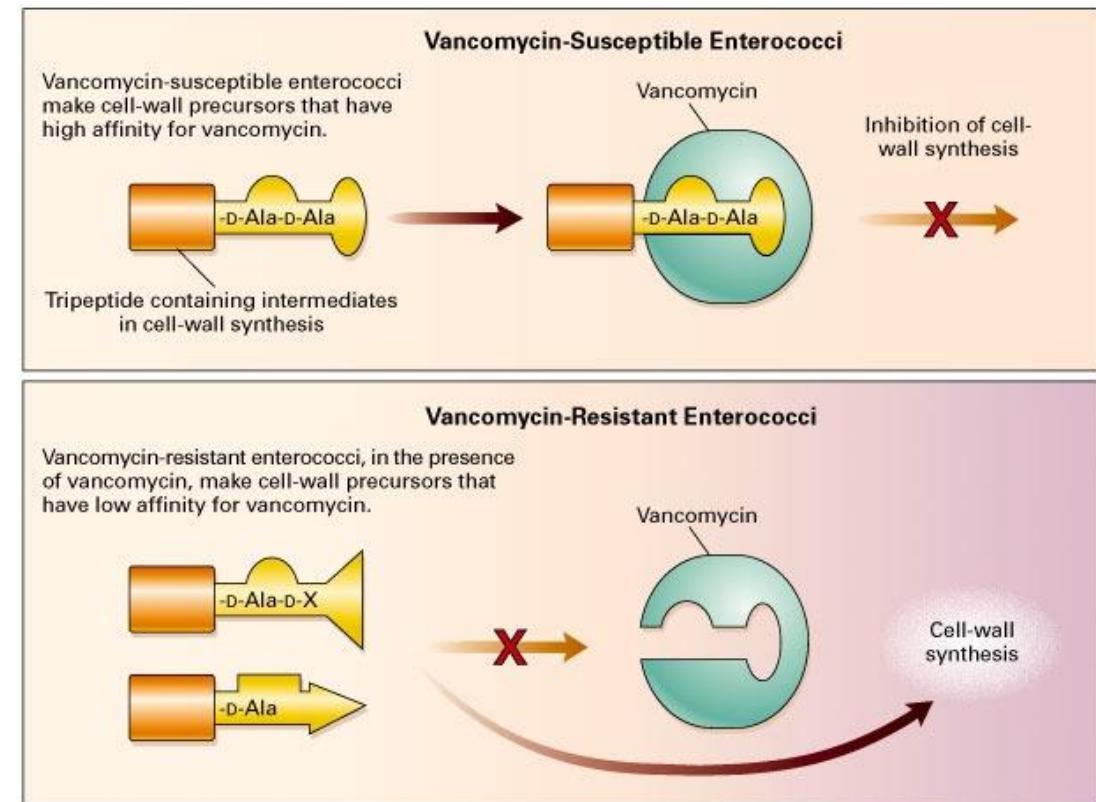
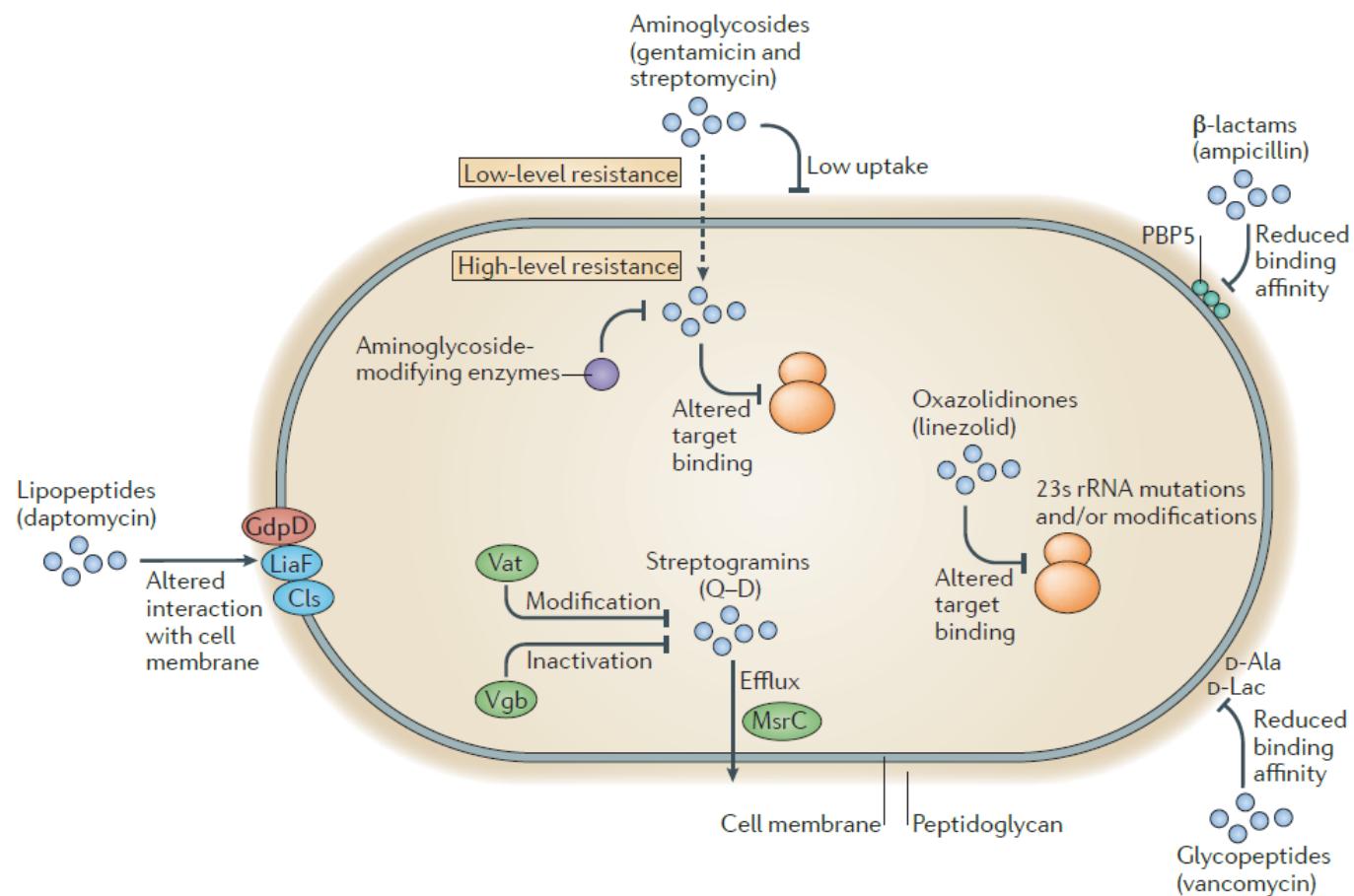
→ 2022 in Blutkulturisolaten 10,9% der *E. faecium* VRE (n=6/55)

Tirol:  
→ 20% auf ICUs

Materialien: nicht nur Screeningproben

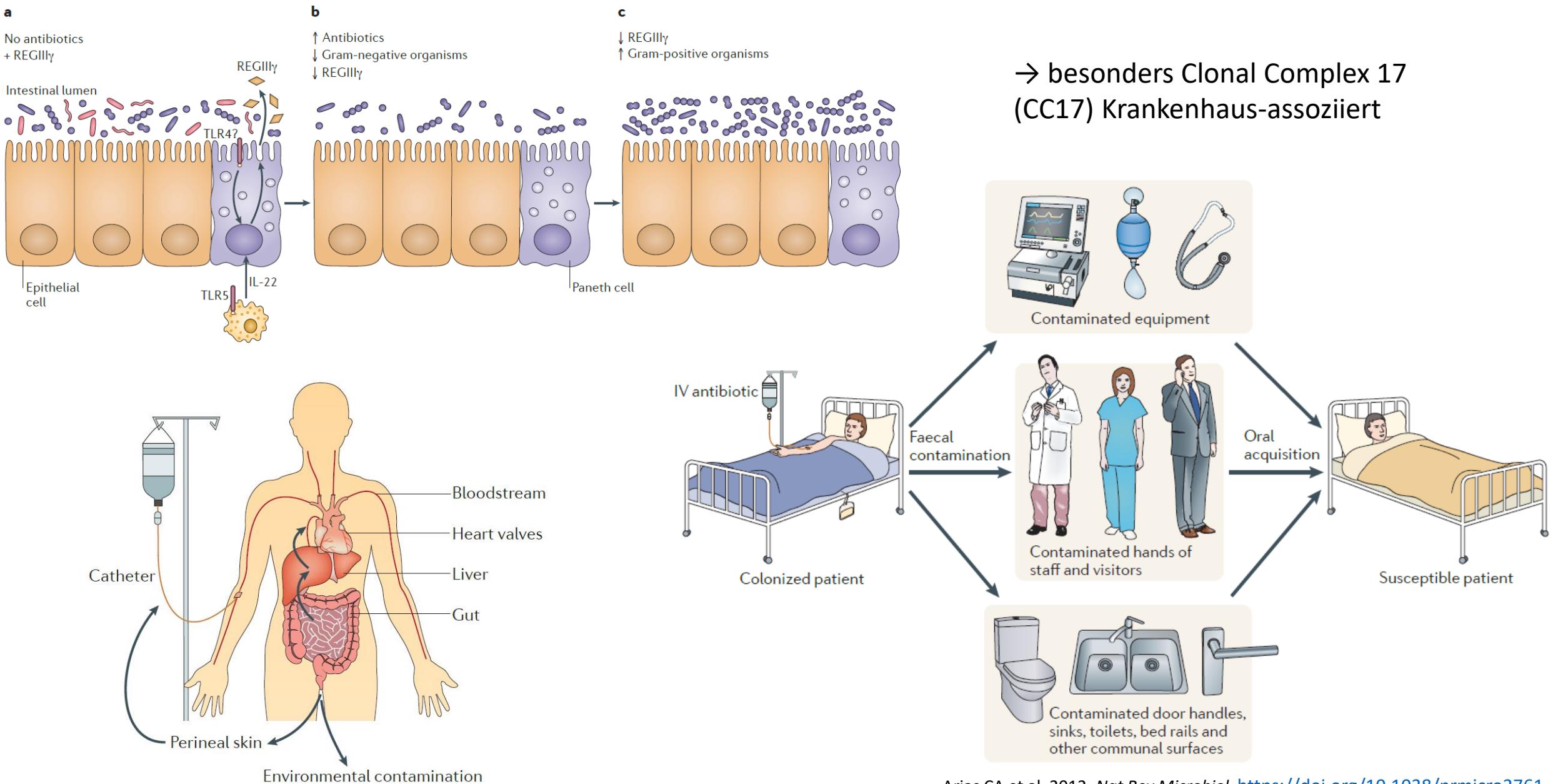


# Mechanismen von Glykopeptid-Resistenz

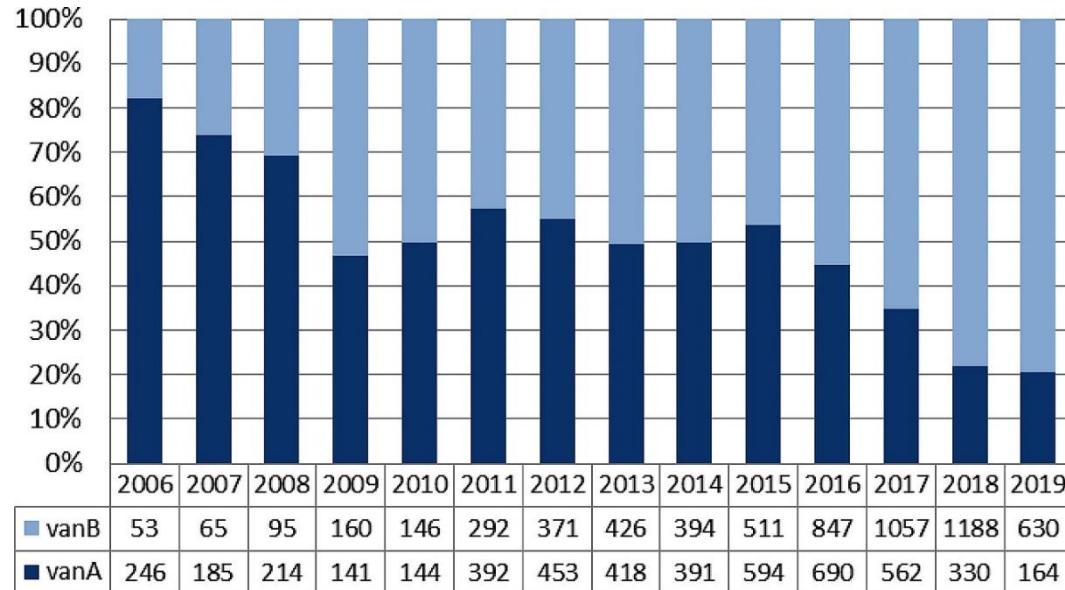


→ vanA: resistant auf Vancomycin und Teicoplanin  
 → vanB: resistant auf Vancomycin, sensibel auf Teicoplanin

# Vancomycin-resistente Enterokokken



# Vancomycin-resistente Enterokokken in Deutschland



→ vanA: resistent auf Vancomycin und Teicoplanin

→ vanB: resistent auf Vancomycin, sensibel auf Teicoplanin

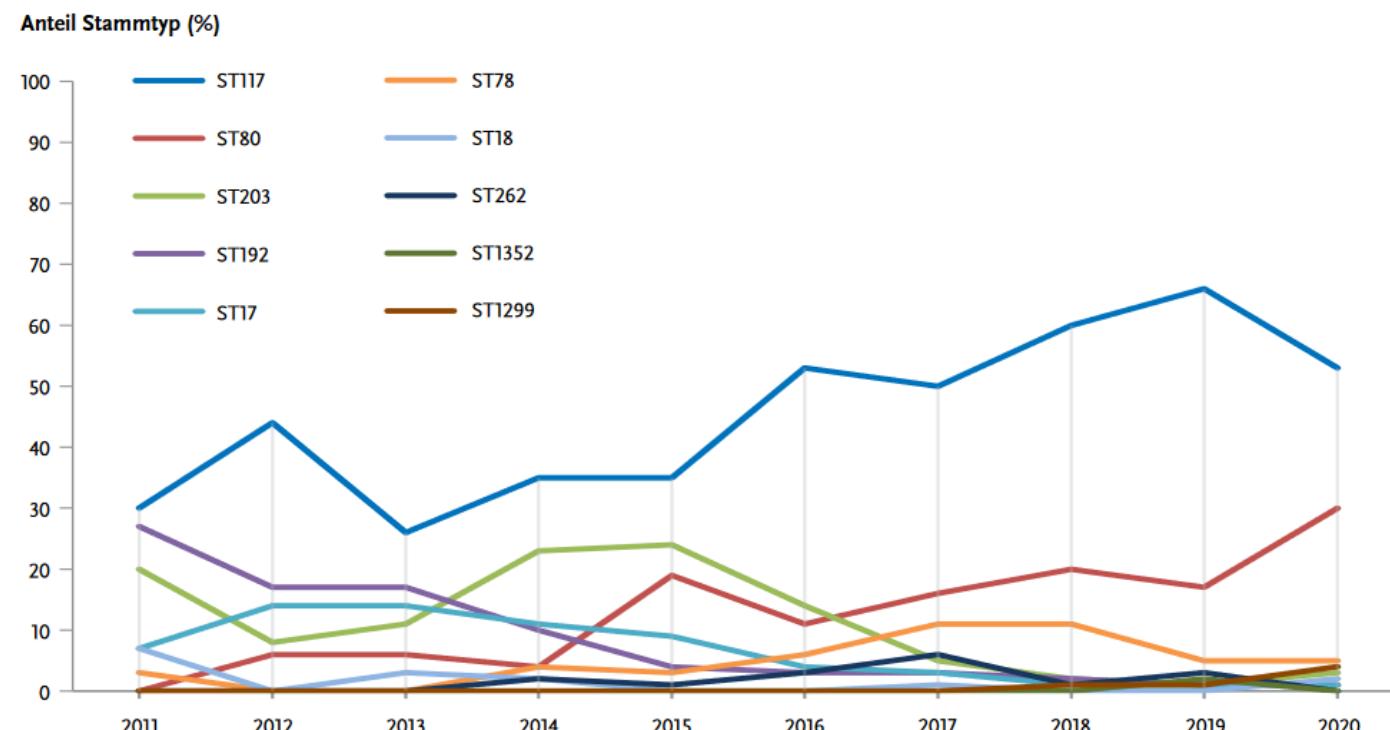
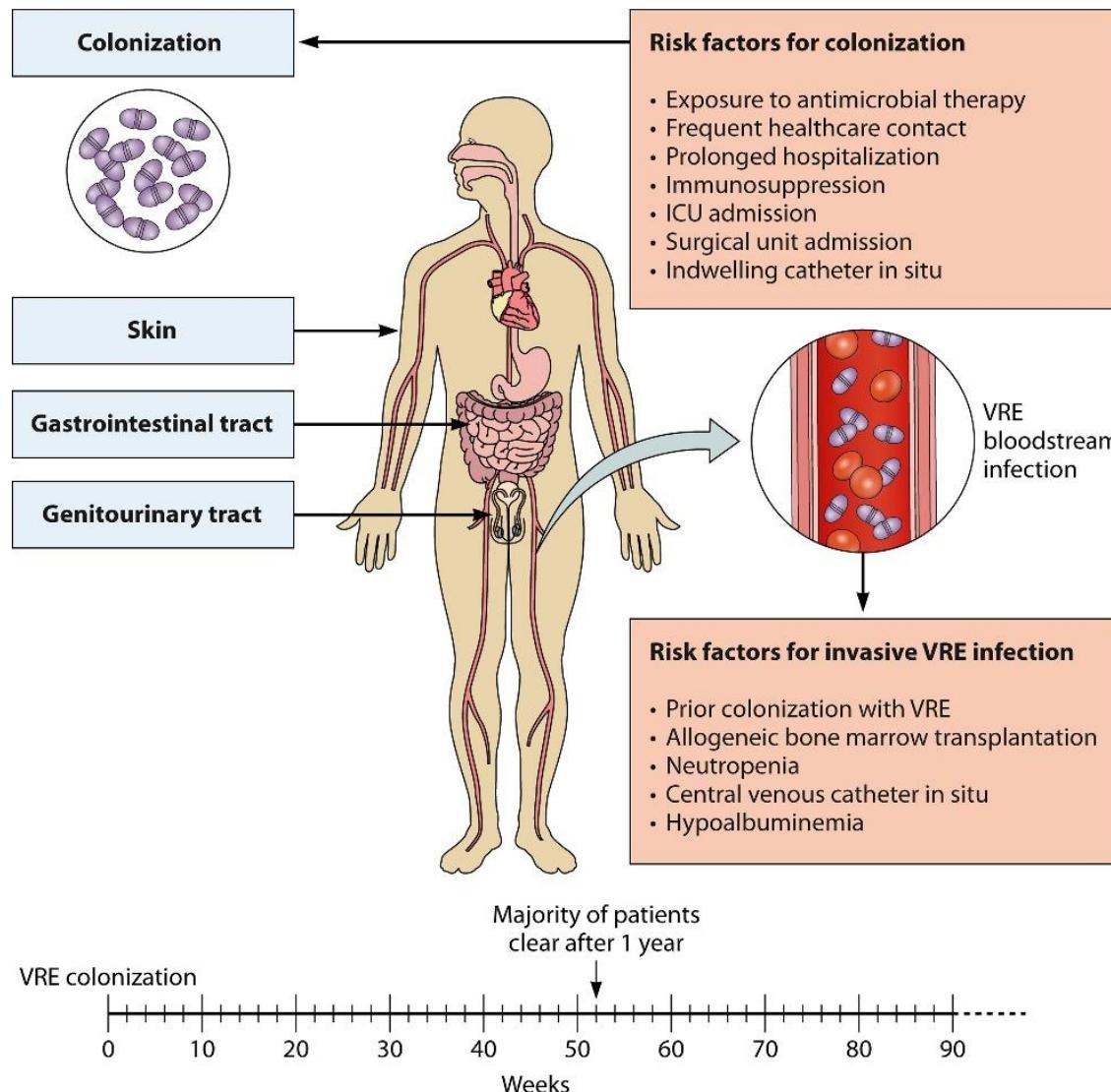


Abb. 4 | Prozentualer Anteil der häufigsten Stammtypen nach MLST bei invasiven *E. faecium*-Isolaten von 2011–2020 (Daten des NRZ). Farbig markierte Linien beschreiben die Verteilung der entsprechenden Sequenztypen (ST) über die Zeit.

→ in Tirol 2022 81,6% resistent auf Teicoplanin (vanA), 2021 weniger als die Hälfte

# Vancomycin-resistente Enterokokken – Eradikation & Therapie?



## Kultureller Erregernachweis:

VRE

gezüchtet

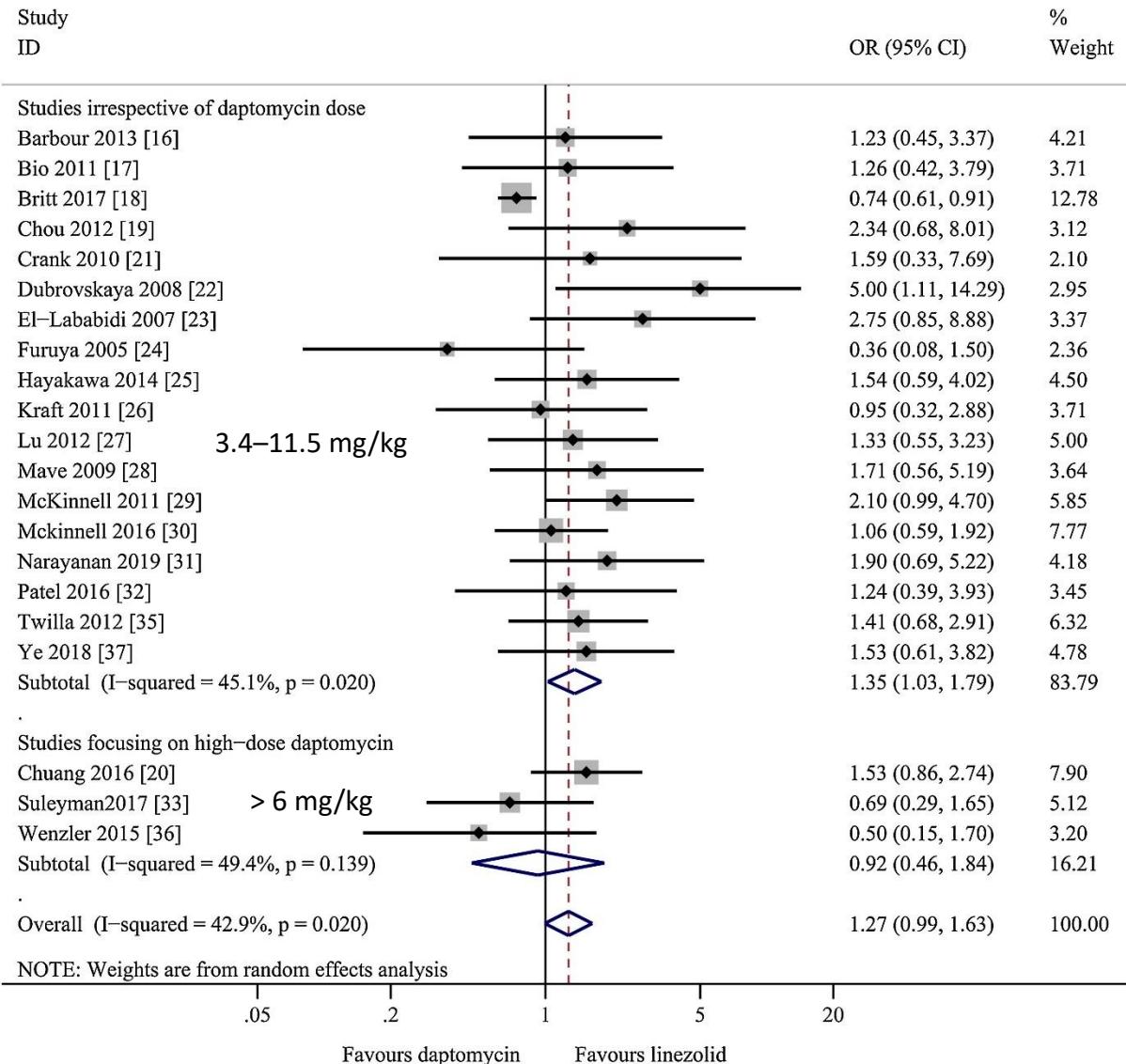
**Enterococcus faecium**

1.

Vancomycin-resistenter Enterococcus (VRE).  
Daptomycin: Kein Grenzwert zur Kategorisierung der Empfindlichkeit verfügbar, die MHK beträgt 4 mg/l.

Antibiotikum/Antimykotikum	1.
Aminopenicillin	R
Amoxicillin + Clavulansäure	R
Imipenem	R
Linezolid	S
Piperacillin-Tazobactam	R
Teicoplanin	R
Tigecyclin	S
Vancomycin	R

# Vancomycin-resistente Enterokokken – Therapie?



→ in älteren Studien: Mortalität niedriger bei Dosierungen > 10 mg/kg

## Kultureller Erregernachweis:

VRE

gezüchtet

### **Enterococcus faecium**

1. Vancomycin-resistenter Enterococcus (VRE).

Daptomycin: Kein Grenzwert zur Kategorisierung der Empfindlichkeit verfügbar, die MHK beträgt 4 mg/l.

Antibiotikum/Antimykotikum	1.
Aminopenicillin	R
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Imipenem	R
Linezolid	S
Piperacillin-Tazobactam	R
Teicoplanin	R
Tigecyclin	S
Vancomycin	R

Miscellaneous agents	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Daptomycin <sup>1</sup>	IE	IE			IE	IE	

# Vancomycin-resistente Enterokokken – Daptomycin

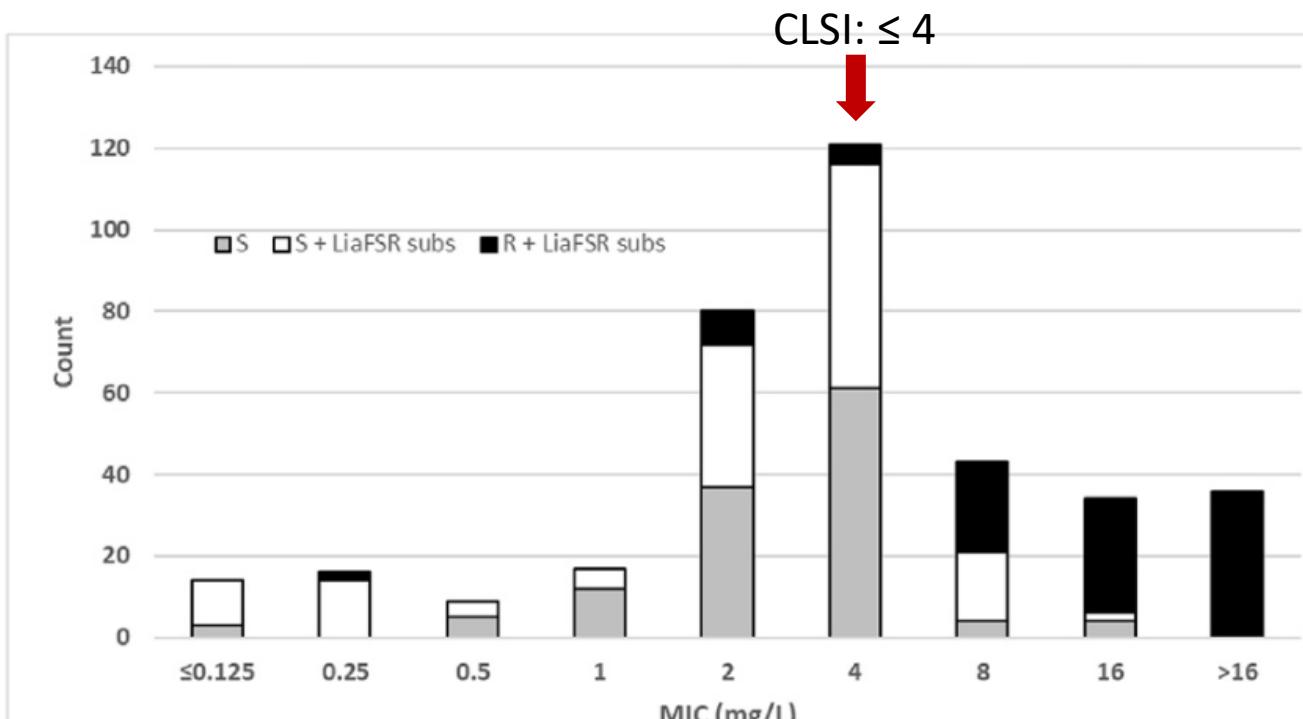
## Kultureller Erregernachweis:

VRE gezüchtet

1. **Enterococcus faecium**

Vancomycin-resistenter Enterococcus (VRE).

Daptomycin: Kein Grenzwert zur Kategorisierung der Empfindlichkeit verfügbar, die MHK beträgt 4 mg/l.



Miscellaneous agents	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Daptomycin <sup>1</sup>	IE	IE			IE	IE	

- ❖ PK/PD Modellierungen sprechen gegen Daptomycin bei MHK  $\geq 4$
  - ❖ EMA Zulassung unterhalb der benötigten Dosierung
  - ❖ Intra-assay Variation
  - ❖ Wildtyp-Population gespalten

# Linezolid- und Vancomycin-resistente Enterokokken

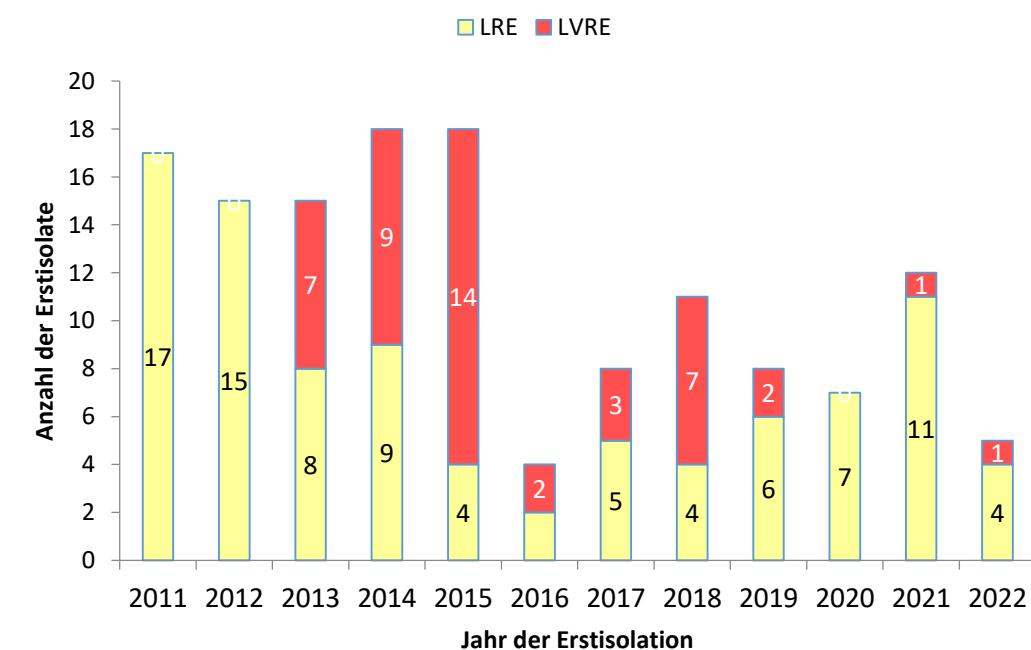
## Deutschland

Antibiotikum <sup>b)</sup>	2016	2017	2018	2019	2020
	(n=871)	(n=1091)	(n=1210)	(n=632)	(n=423)
Ampicillin	100,0	100,0	99,8	99,4	99,3
Gentamicin	15,3	6,9	6,8	6,5	4,7
Streptomycin	33,9	26,4	13,4	4,0	7,8
Vancomycin <sup>c)</sup>	99,4	98,6	99,5	98,6	96,4
Teicoplanin <sup>c)</sup>	4,7	3,8	2,6	0,5	0,7
Daptomycin	0,9	1,2	0,6	0,3	0,2
Erythromycin	97,1	97,7	97,5	94,0	96,0
Ciprofloxacin <sup>d)</sup>	100,0	100,0	99,8	99,5	99,8
Linezolid	5,1	5,2	6,9	18,2	25,1
Tetracyclin	14,0	14,0	5,3	3,5	5,7
Tigecyclin	0,9	2,7	0,3	0,8	1,4
Rifampicin	91,5	86,8	91,7	47,6	62,2

Tab. 5 | Resistzenzen (%) der 2016–2020 an das NRZ eingesandten *vanB*-positiven *E. faecium*-Isolate<sup>a)</sup>

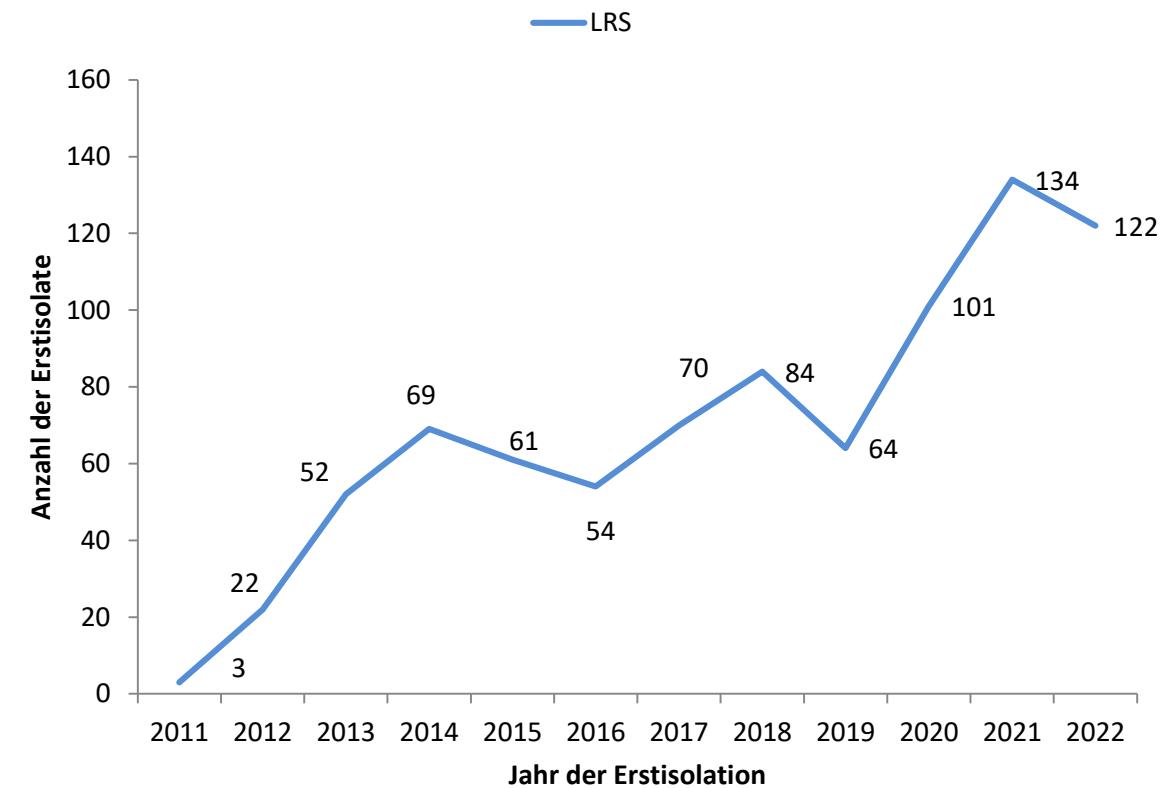
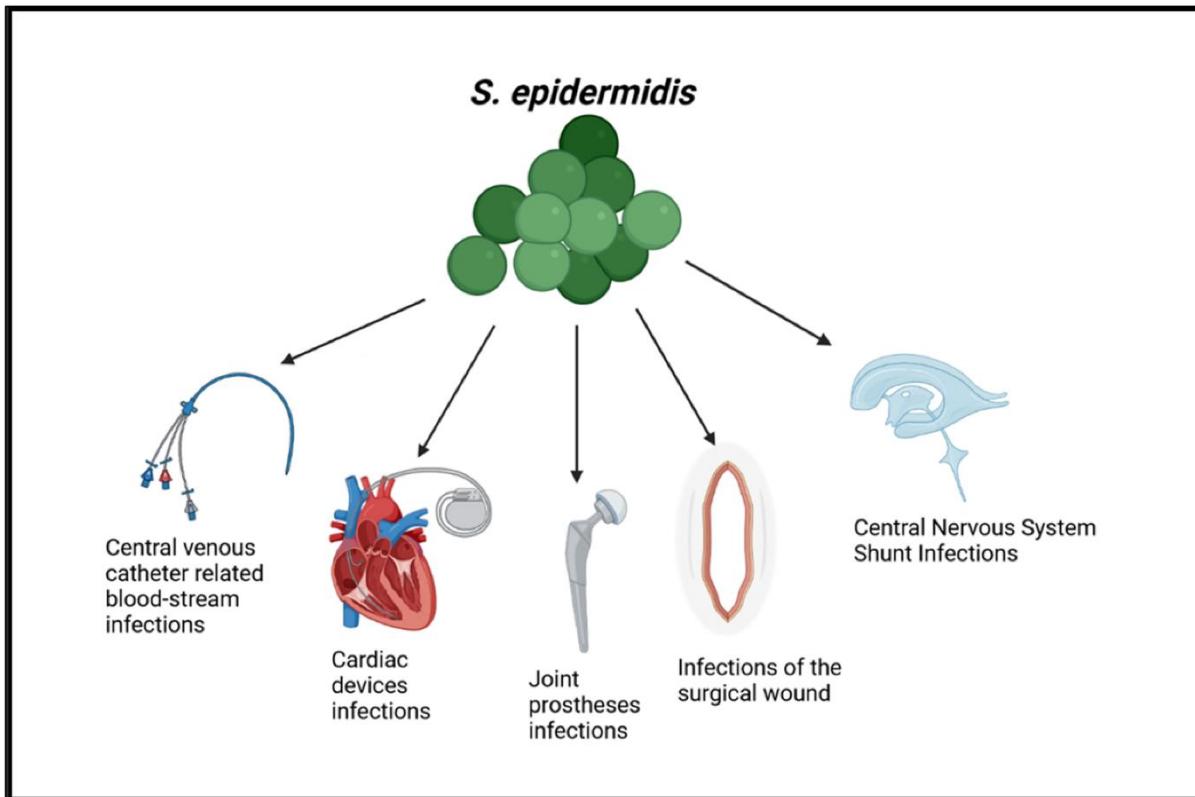
<sup>a)</sup> Es sind alle *vanB*-positiven *E. faecium*-Isolate aufgeführt, unabhängig von ihrem VRE-Phänotyp; <sup>b)</sup> Alle Angaben entsprechend klinischer Grenzwerte bzw. ECOFF nach EUCAST v6.0 bis v10.; bei STR und GEN sind *high-level* Resistzenzen angegeben; <sup>c)</sup> Einzelne Isolate besitzen *vanB* und *vanA* (2020: n=3; hier nicht eingeschlossen); sehr selten sind VanB-Isolate TEI-r (2019: n=3; 2020: n=6) bzw. VAN-s (2019: n=8; 2020: n=14); <sup>d)</sup> CIP Hochresistenz MHK >16 mg/L.

## Tirol



→ keine Zunahme von Linezolid- und Vancomycin-resistenten Enterokokken

# Linezolidresistente Staphylokokken



- ❖ 52% in Fremdgewebe (z.B. Katheterspitzen)
- ❖ 22% in Blutkulturen
- ❖ 15% in Abstrichen

# Antibiotikaverbrauch

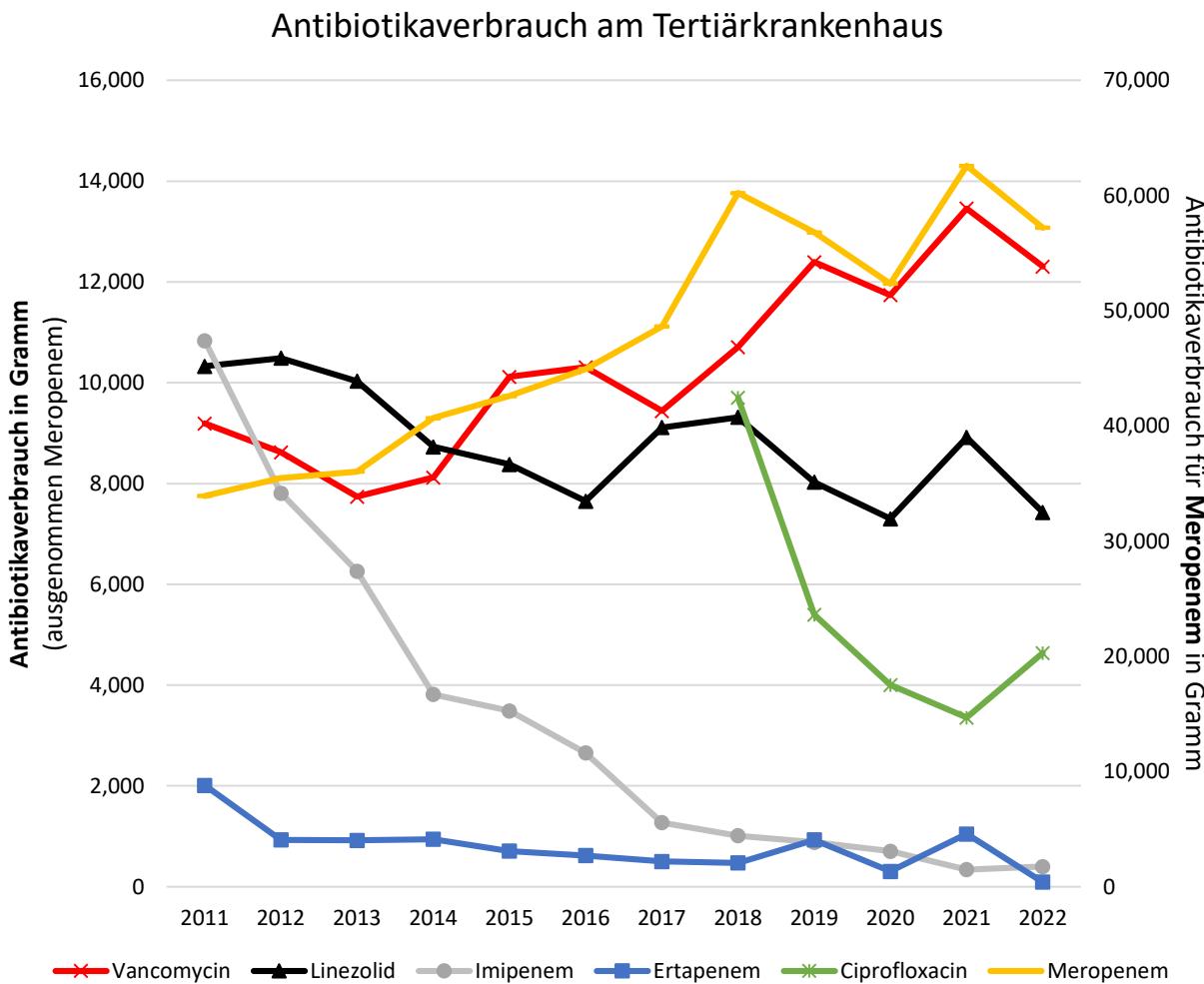
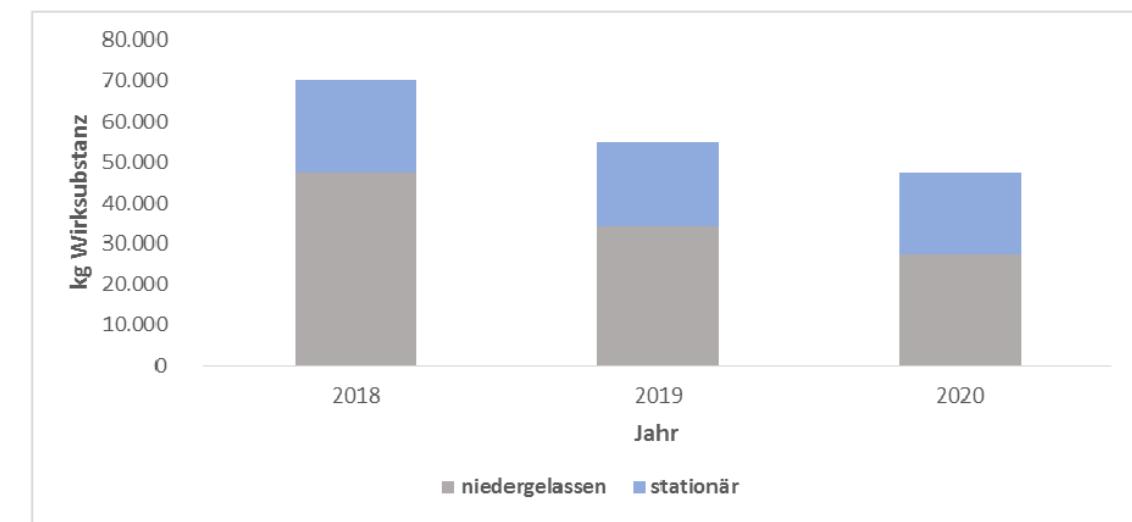
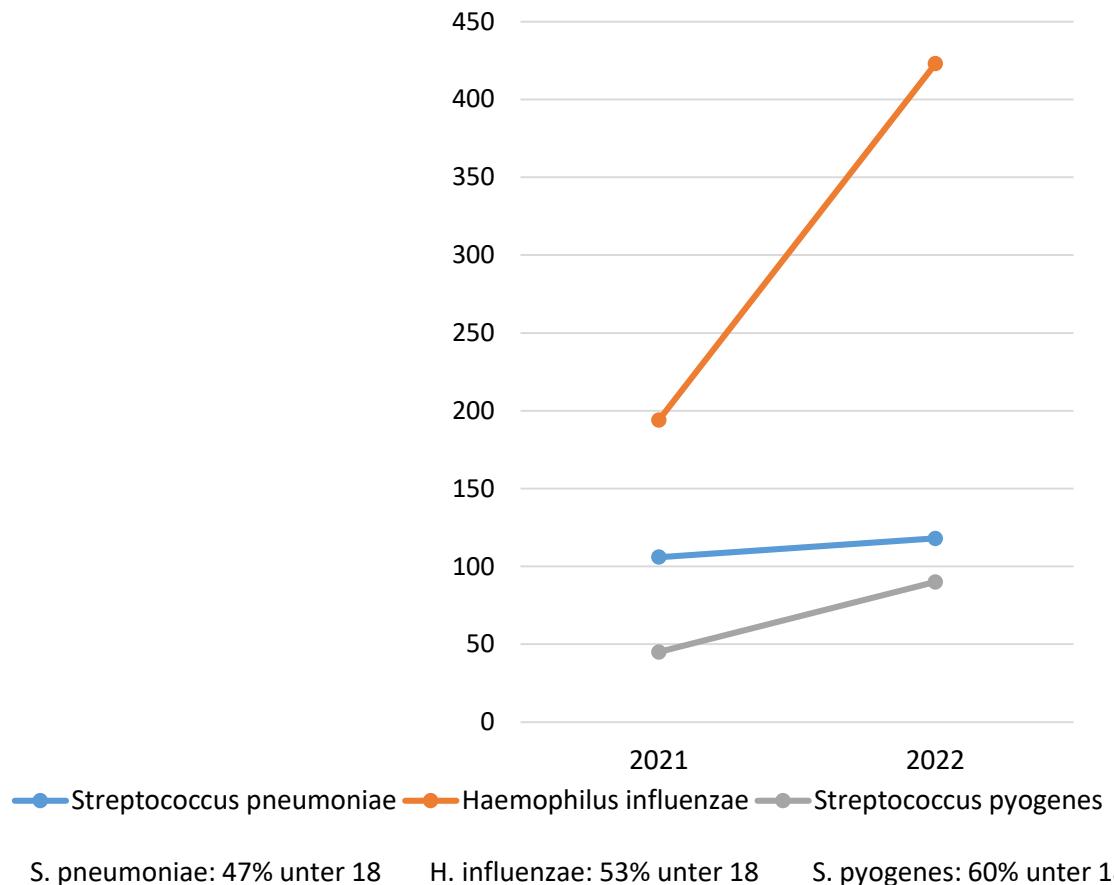


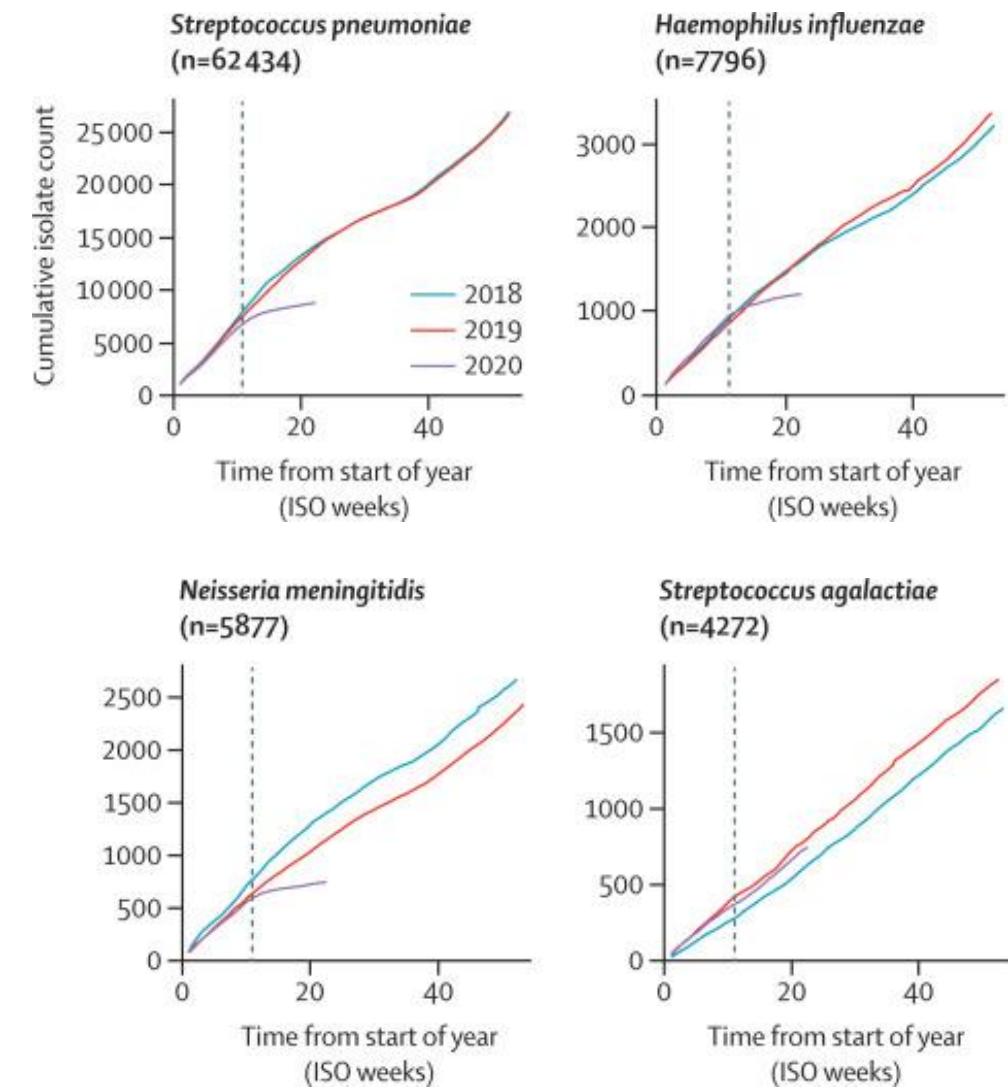
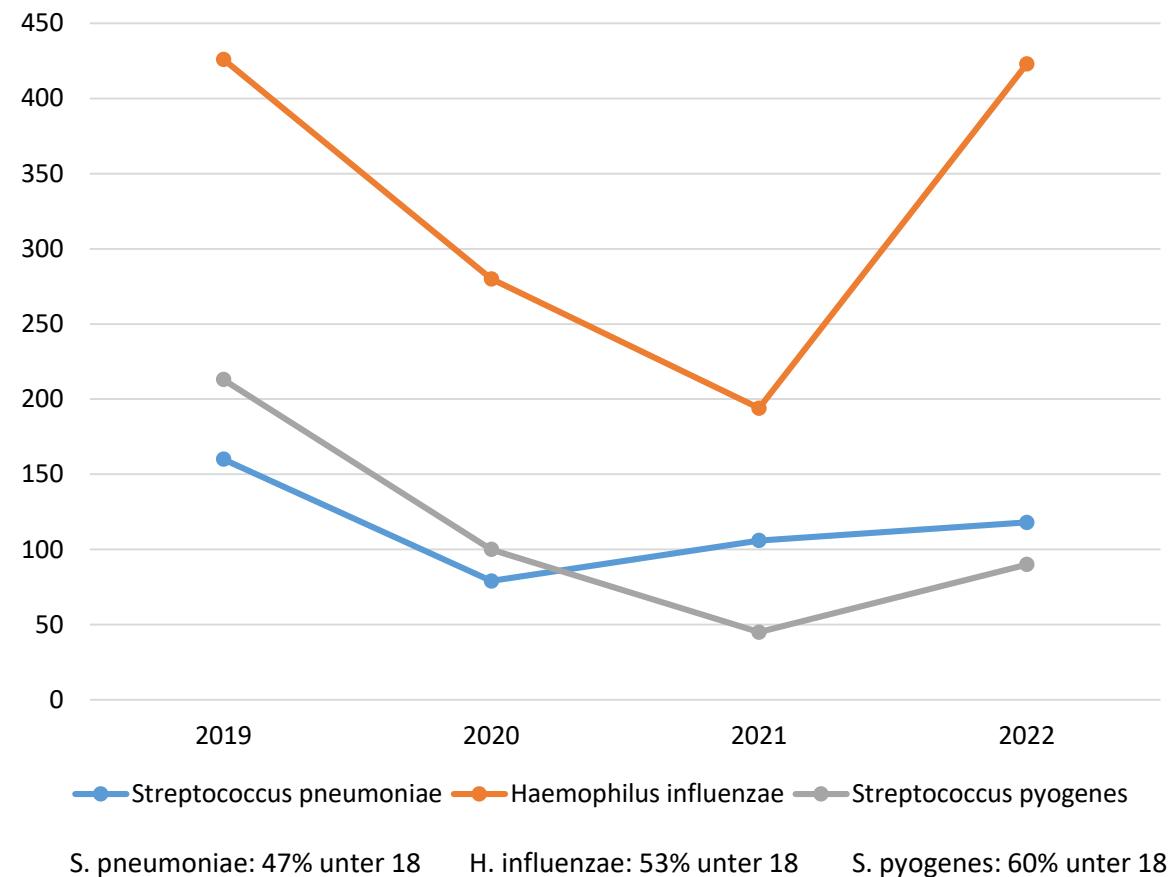
Abbildung 166: Gesamtverbrauch Antibiotika in Österreich nach niedergelassenem Bereich versus stationärem Bereich in kg Wirksubstanz 2018-2020



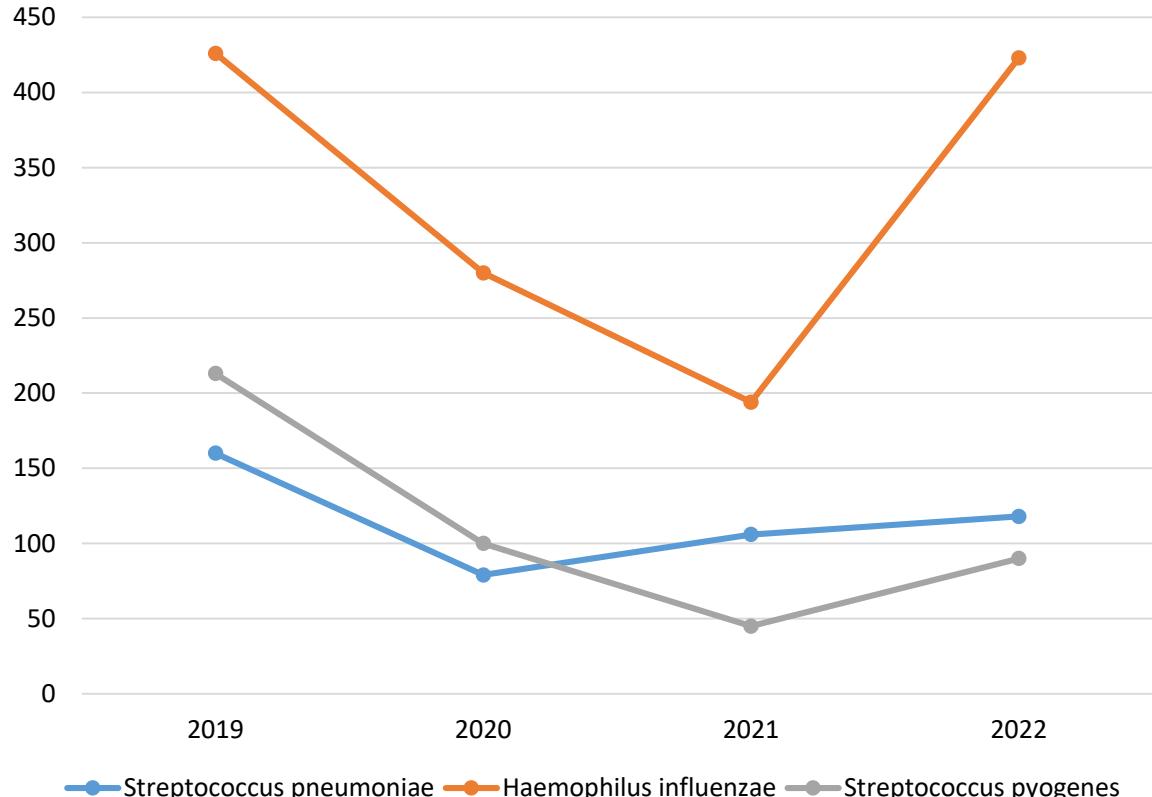
# Respiratorische Erreger – Veränderungen über die letzten Jahre



# Respiratorische Erreger – Veränderungen über die letzten Jahre



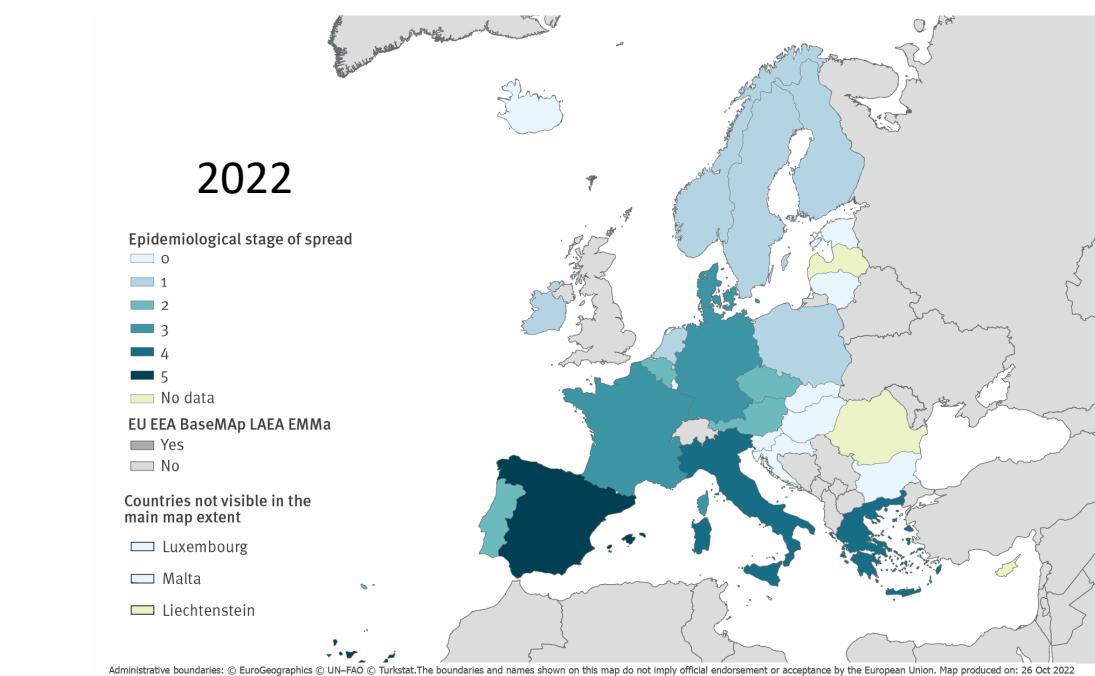
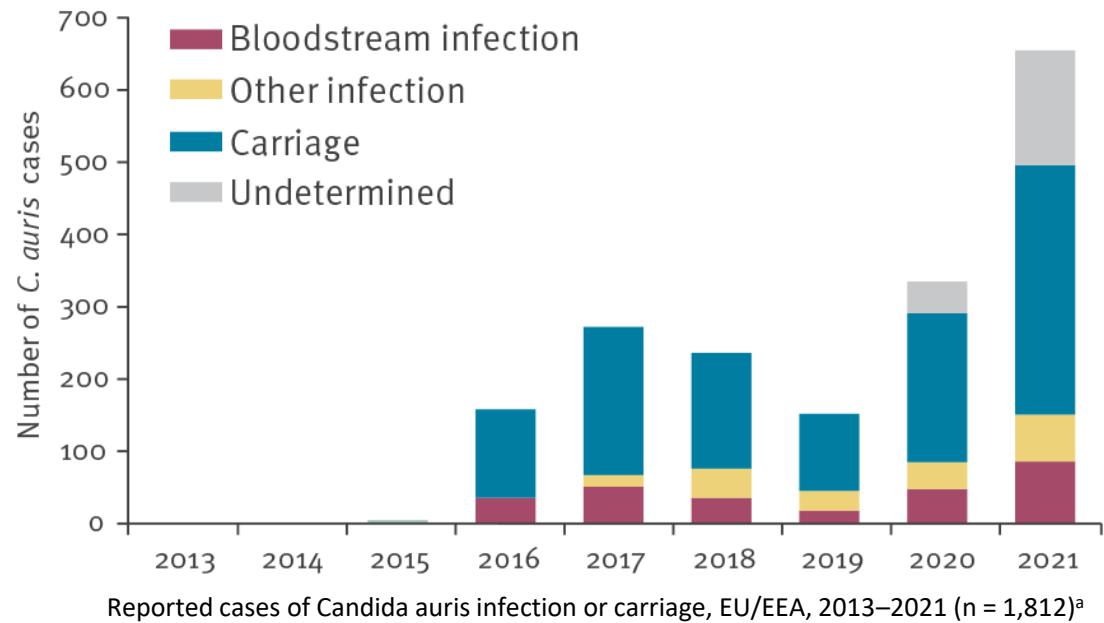
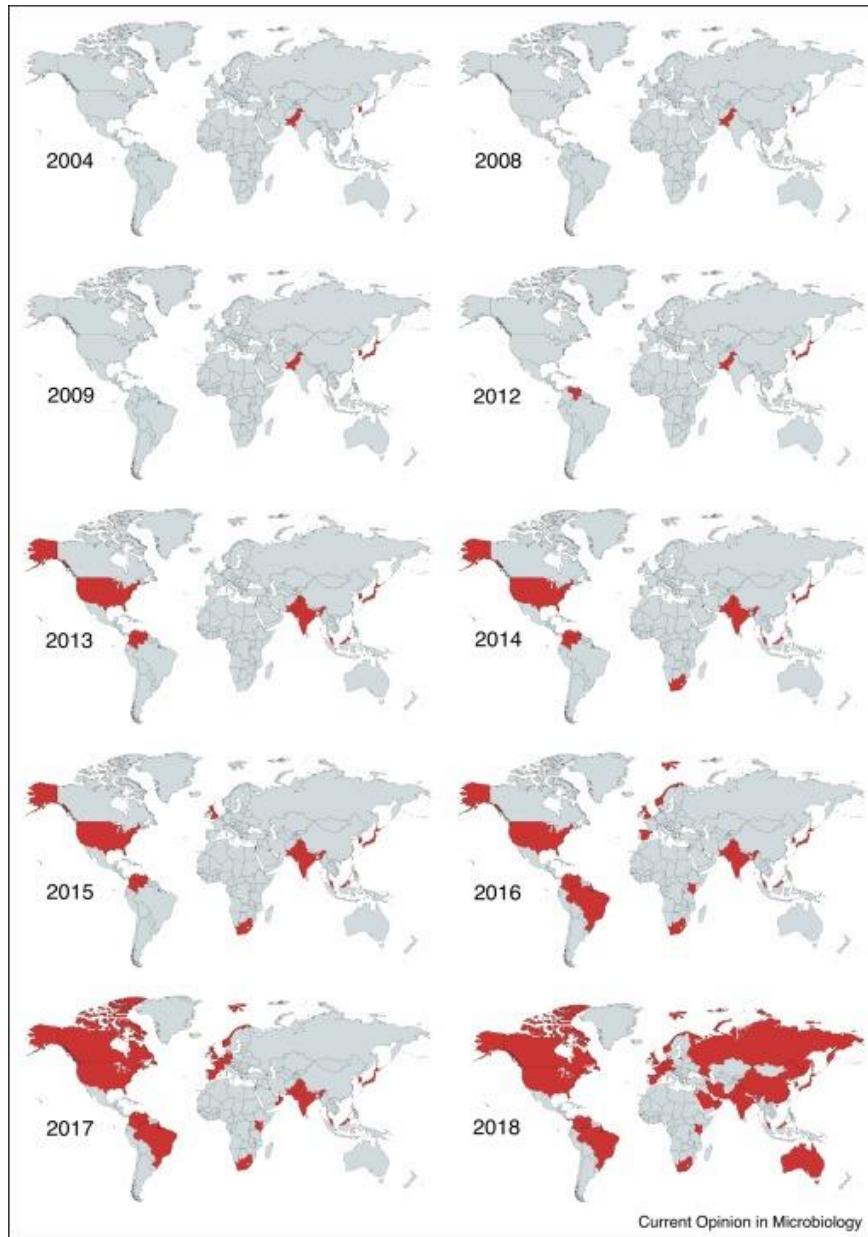
# Respiratorische Erreger – Veränderungen über die letzten Jahre



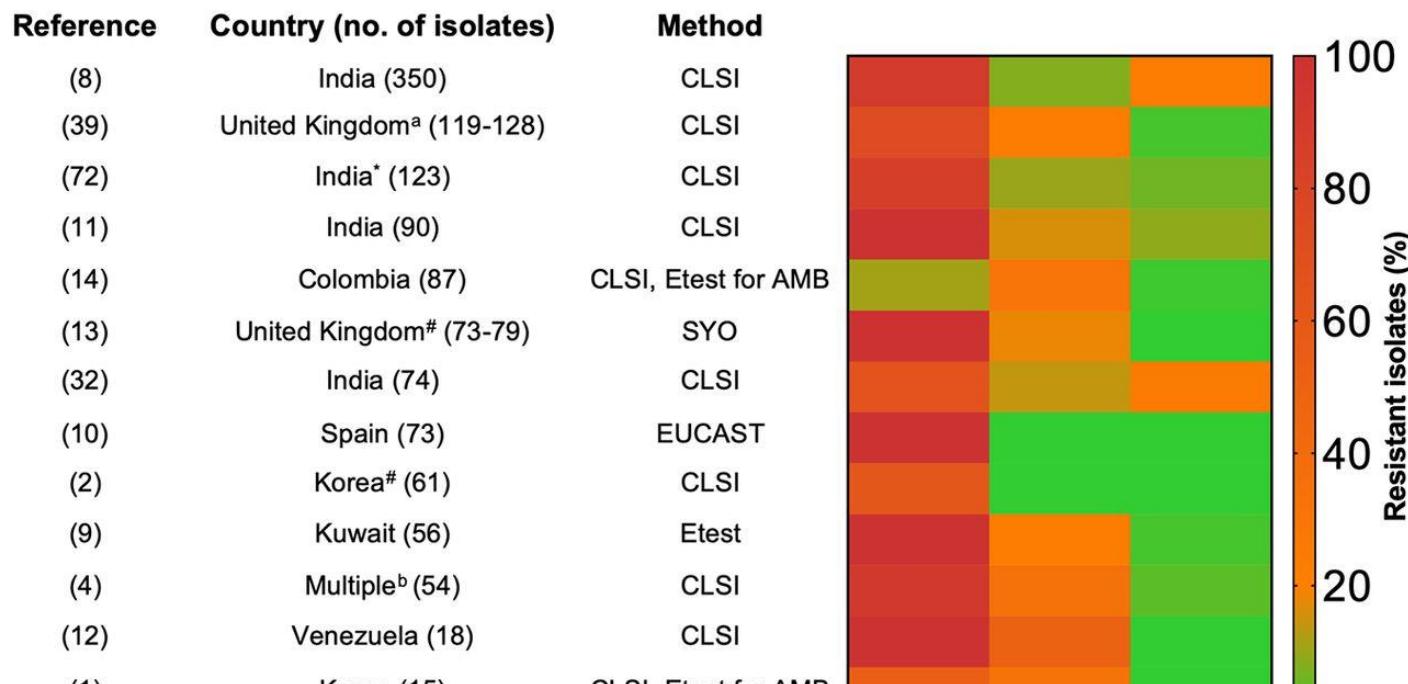
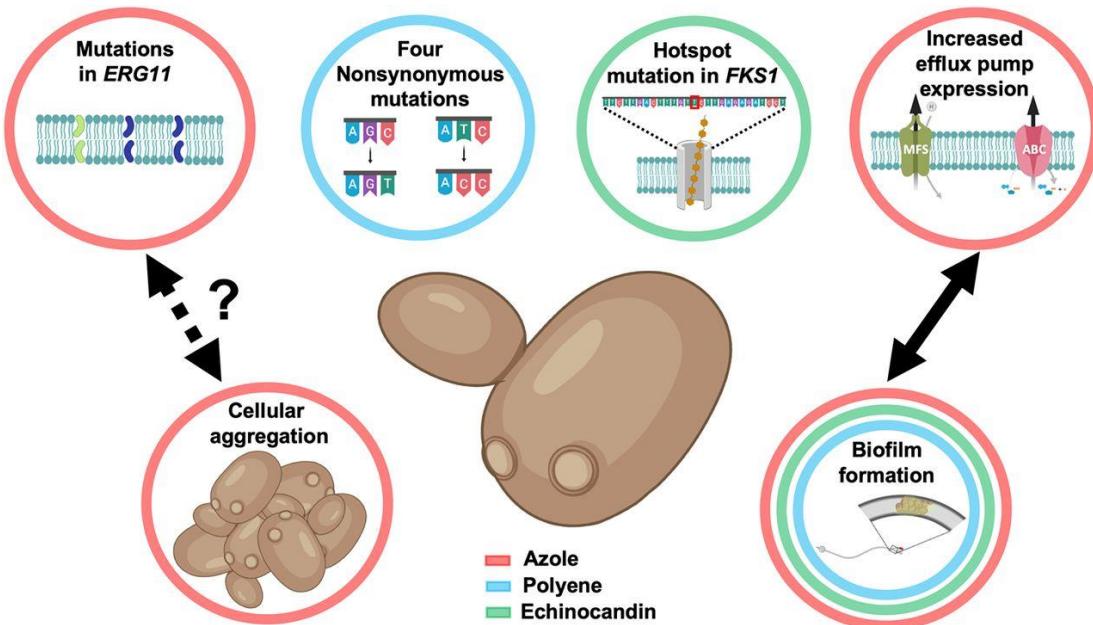
S. pneumoniae: 47% unter 18    H. influenzae: 53% unter 18    S. pyogenes: 60% unter 18

	<i>Streptococcus pneumoniae</i>	<i>Haemophilus influenzae</i>	<i>Streptococcus pyogenes</i>
2021	n=106 (%)	n=194 (%)	n=45 (%)
Erythromycin	19,0	-	20,0
Cefuroxim	4,8	21,8	0,0
Ceftriaxon	0,9	0,5	0,0
Ampicillin	2,8	32,0	0,0
Amoxicillin / Clavulansäure	2,8	14,9	0,0
Levofloxacin	0,0	1,5	2,2
Moxifloxacin	0,0	5,7	2,2
Tetracyclin	12,3	1,0	20,0
Piperacillin / Tazobactam	2,8	2,1	0,0
2022	<i>Streptococcus pneumoniae</i>	<i>Haemophilus influenzae</i>	<i>Streptococcus pyogenes</i>
	n=118 (%)	n=423 (%)	n=90 (%)
Erythromycin	9,3	-	13,3
Cefuroxim	0,9	17,7	0,0
Ceftriaxon	0,0	0,2	0,0
Ampicillin	0,8	29,1	0,0
Amoxicillin / Clavulansäure	0,0	9,2	0,0
Levofloxacin	0,0	2,1	2,2
Moxifloxacin	0,0	1,7	2,2
Tetracyclin	7,6	0,7	13,3
Piperacillin / Tazobactam	0,0	0,9	0,0

# *Candida auris*

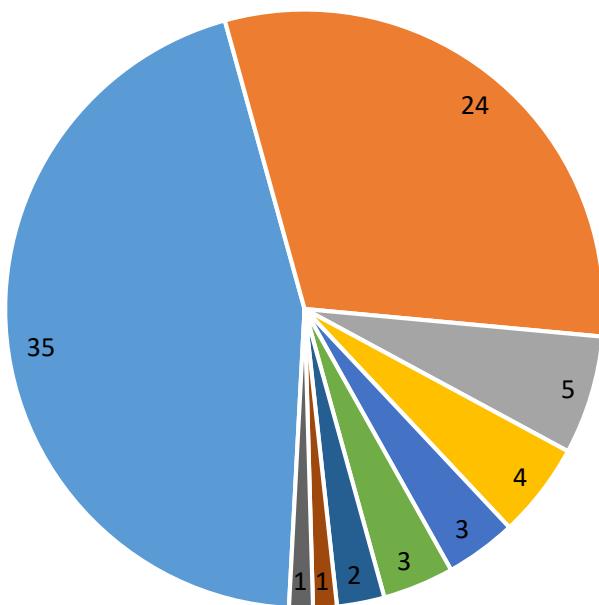


# *Candida auris* Problematik



# Hefepilze in Blutkulturen

- *Candida albicans*
- *Candida glabrata (Torulopsis glabrata)*
- *Candida parapsilosis*
- *Candida dubliniensis*
- *Candida tropicalis*
- *Clavispora lusitaniae (Candida lusitaniae)*
- *Pichia kudriavzevii (Candida krusei)*
- *Candida nivariensis*
- *Candida orthopsilosis*



LKI 2022

	Anzahl Isolate	In Prozent
Koagulase negative Staphylokokken	354	34,8%
<i>E. coli</i>	168	16,5%
<i>S. aureus</i> -Gruppe	74	7,3%
Andere Enterobakterien	67	6,6%
Andere grampositive Erreger	66	6,5%
<i>Klebsiella</i> spp.	55	5,4%
<i>Enterococcus</i> spp.	51	5,0%
<b>Hefepilze</b>	<b>44</b>	<b>4,3%</b>
Vergrünende Streptokokken	40	3,9%
Hämolsierende Streptokokken	27	2,7%
<i>Pseudomonas</i> spp.	25	2,5%
Anaerobier	19	1,9%
<i>Streptococcus pneumoniae</i>	17	1,7%
Andere Nonfermenter	7	0,7%
Andere gramnegative Erreger	3	0,3%
<b>Gesamt</b>	<b>1017</b>	<b>100,0%</b>

Table 1. Description of the clinical isolates detected in Austria.

ID	Isolation Date	Patient Description	Underlying Medical Condition	Site of Isolation	Travel History
Cau1	01/2018	22-year-old male patient with Turkish ancestry	therapy-refractory otitis externa	external auditory canal	Turkey
Cau2	02/2020	61-year-old male patient	hematologic malignancy, colonization	external auditory canal	none
Cau3	05/2020	male patient with Indian ancestry	trauma, colonization	urinary tract	India
Cau4	10/2021	60-year-old female patient	hospitalization in Spain due to subarachnoid hemorrhage, colonization	throat	Spain
Cau5	04/2022	66-year-old female patient	hospitalization in Greece due to subarachnoid hemorrhage, colonization	urinary tract	Greece

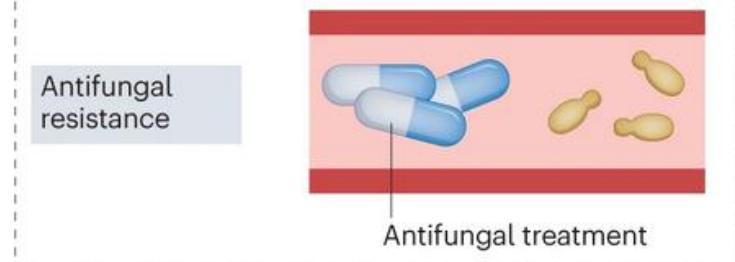
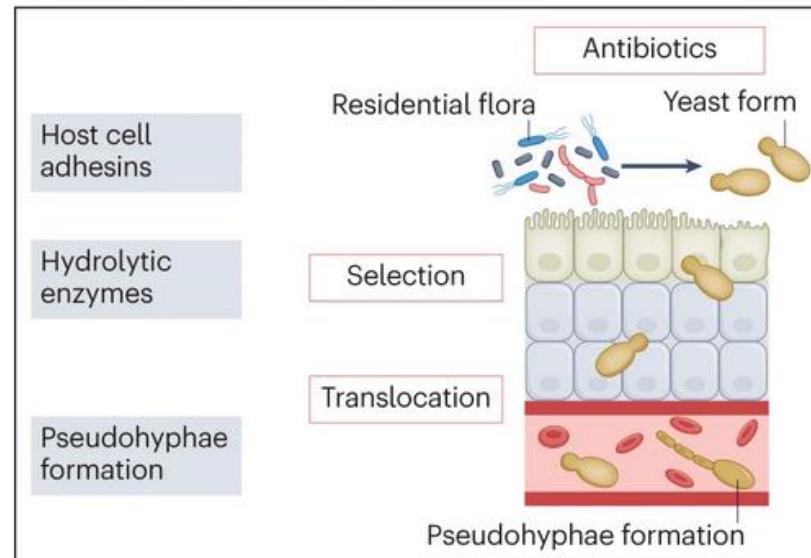
→ noch kein Nachweis von *C. auris* in Tirol

Innsbrucker Resistenzbericht 2022. <https://www.i-med.ac.at/hygiene/dokumente/Resistenzbericht-2022.pdf>

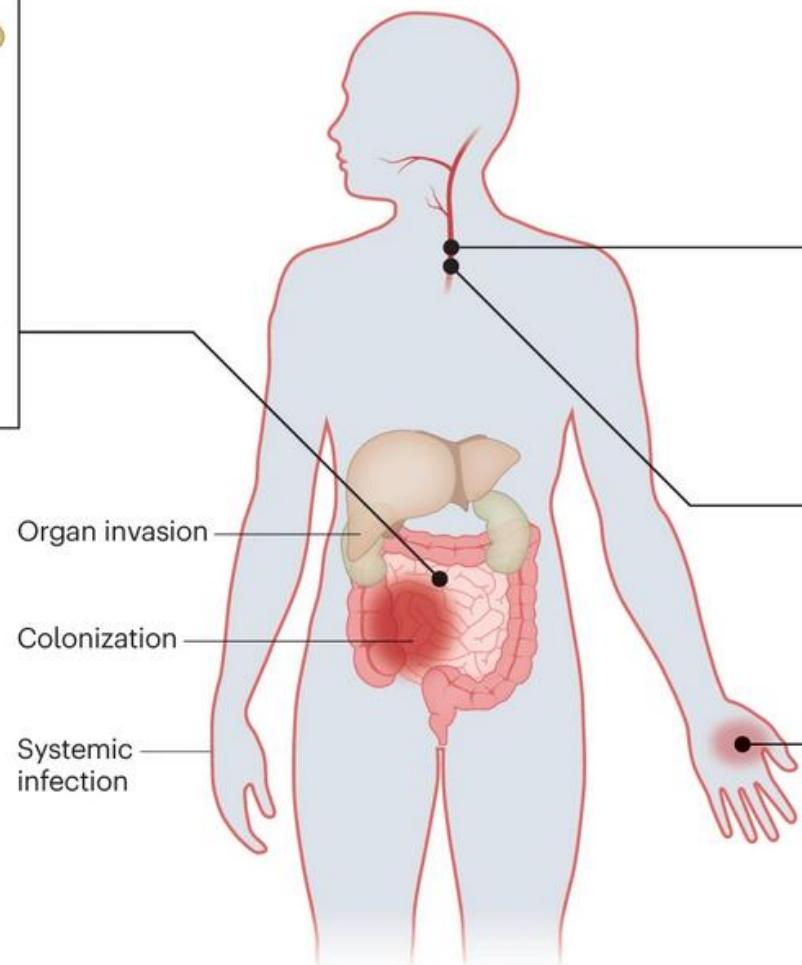
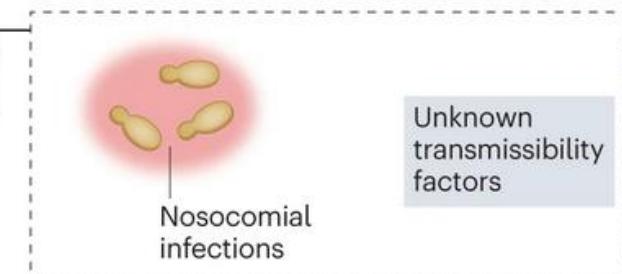
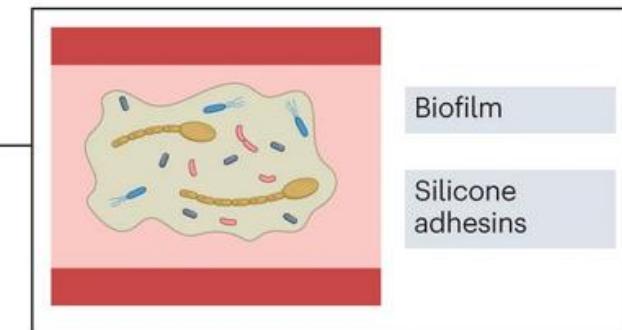
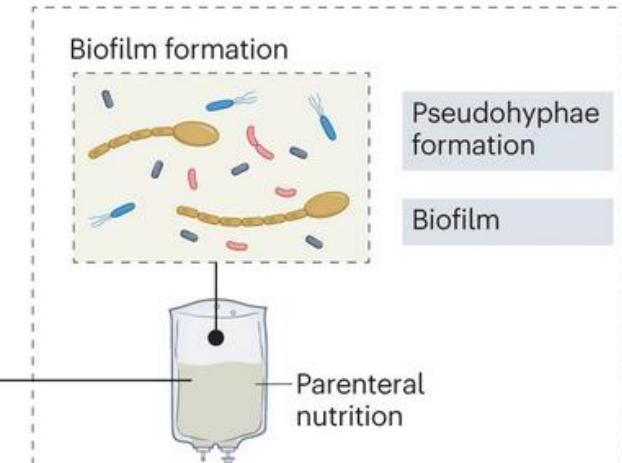
Spettel K et al, 2022. *J Fungi*, <https://doi.org/10.3390/jof9020129>

# *Candida parapsilosis* complex Infektionen

## Translocation from the gut

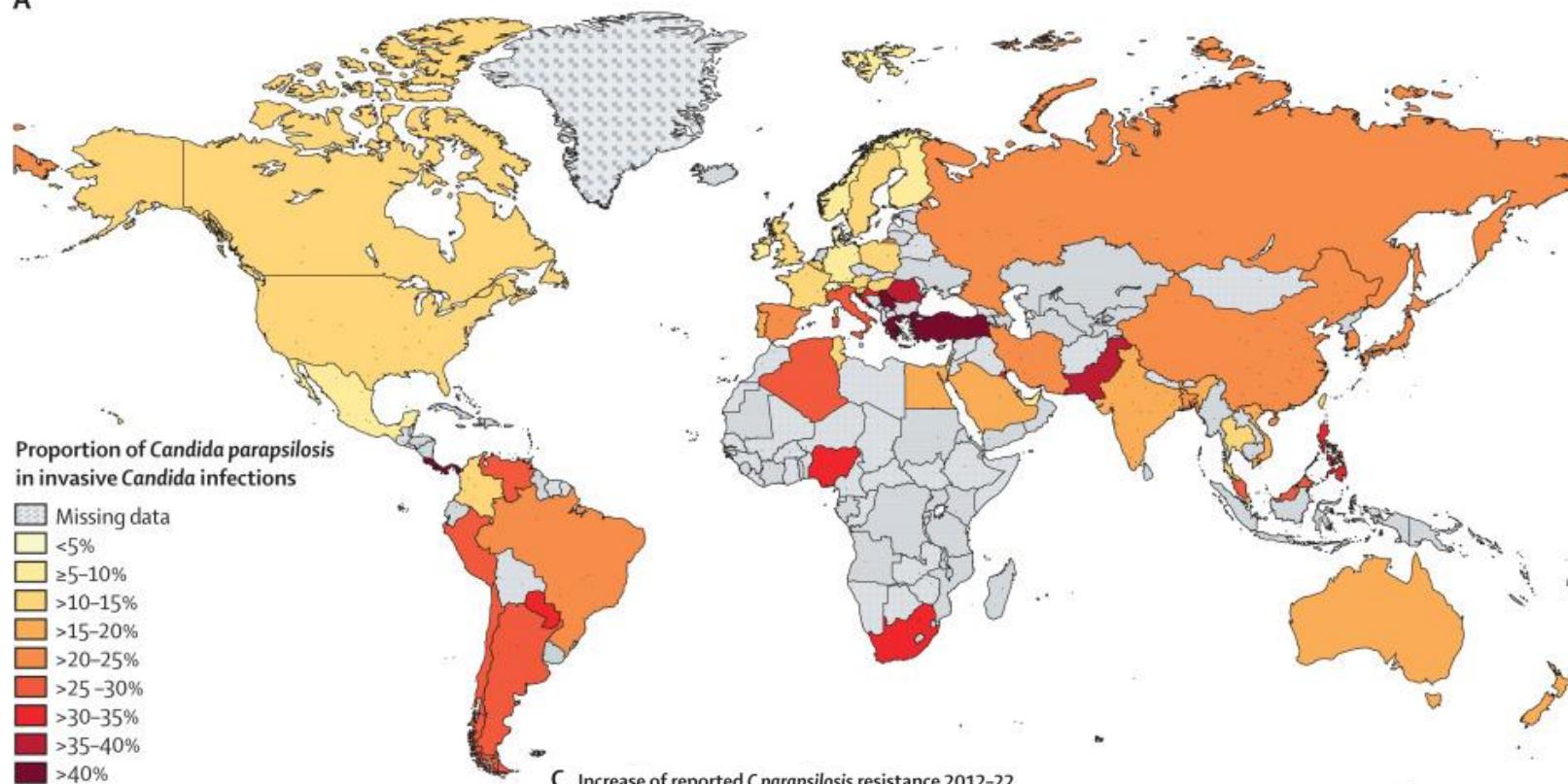


## Horizontal transmission

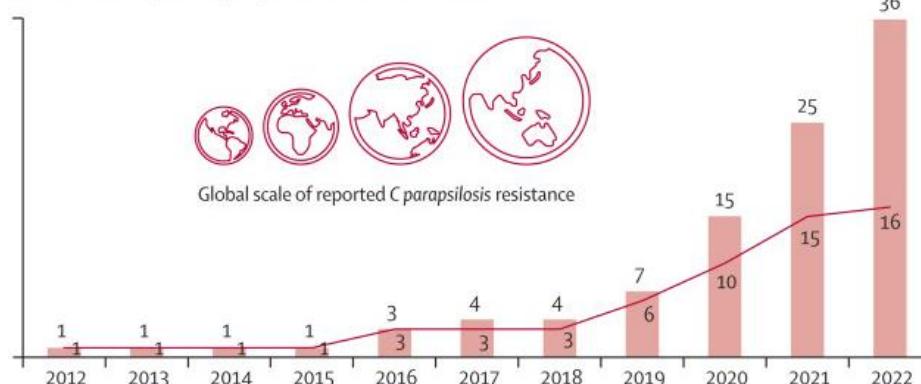


# *Candida parapsilosis* Problematik

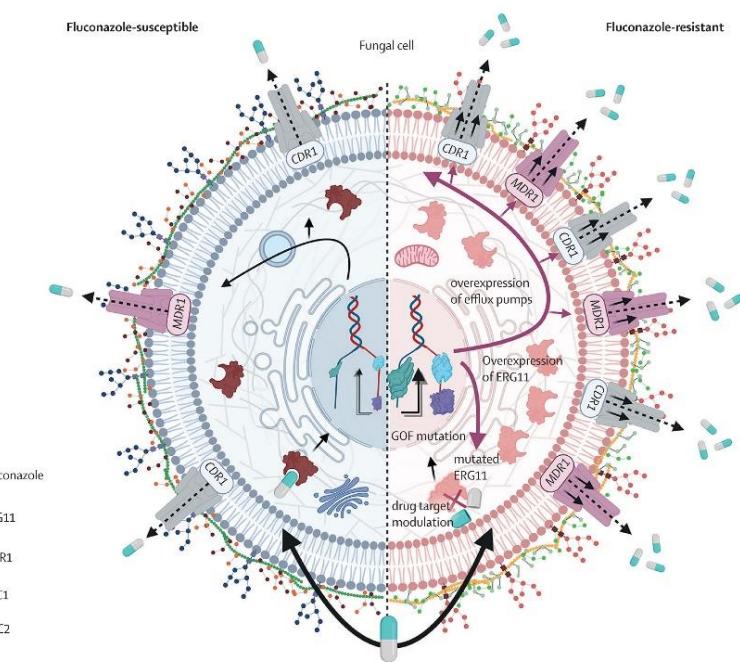
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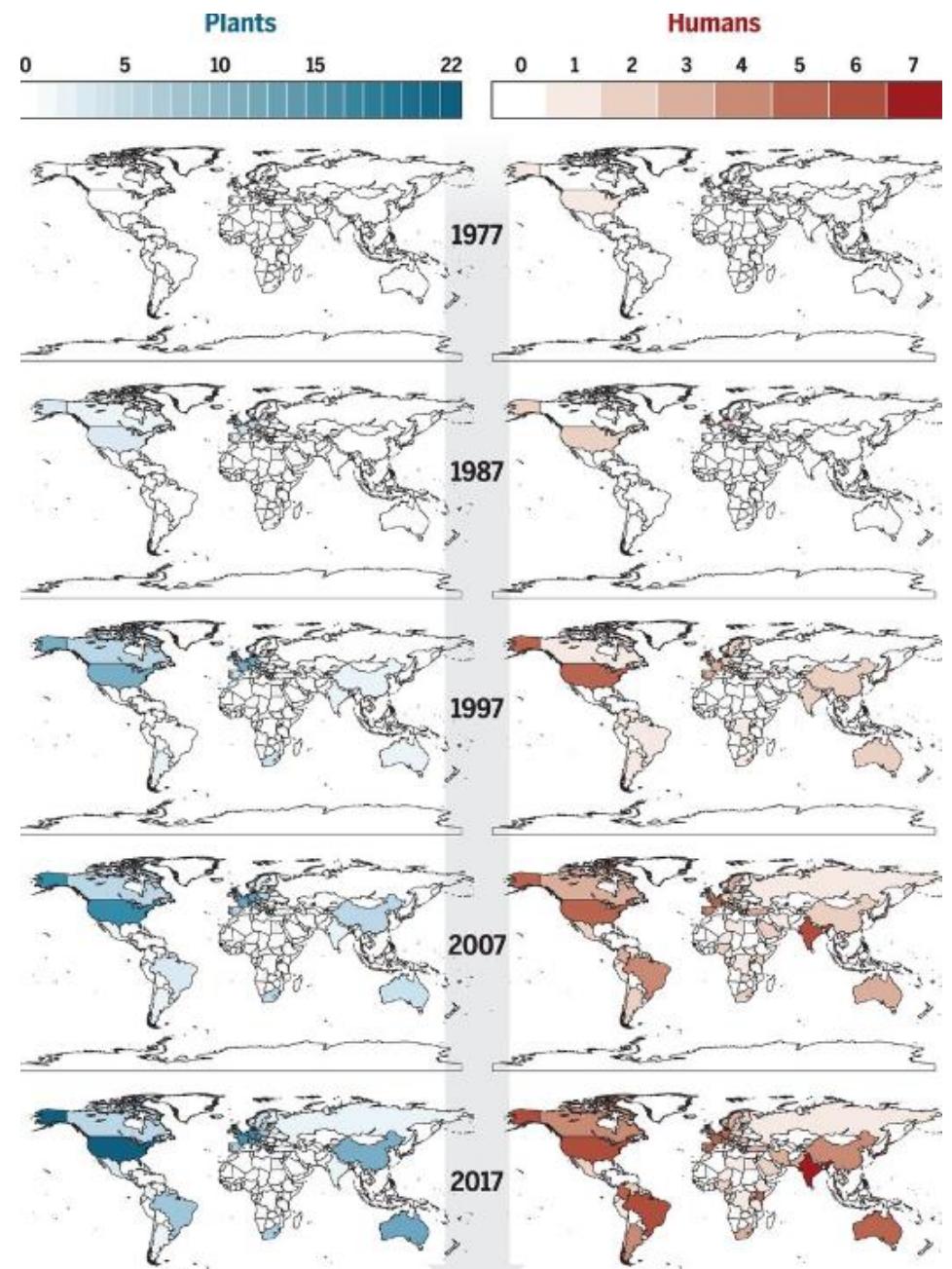
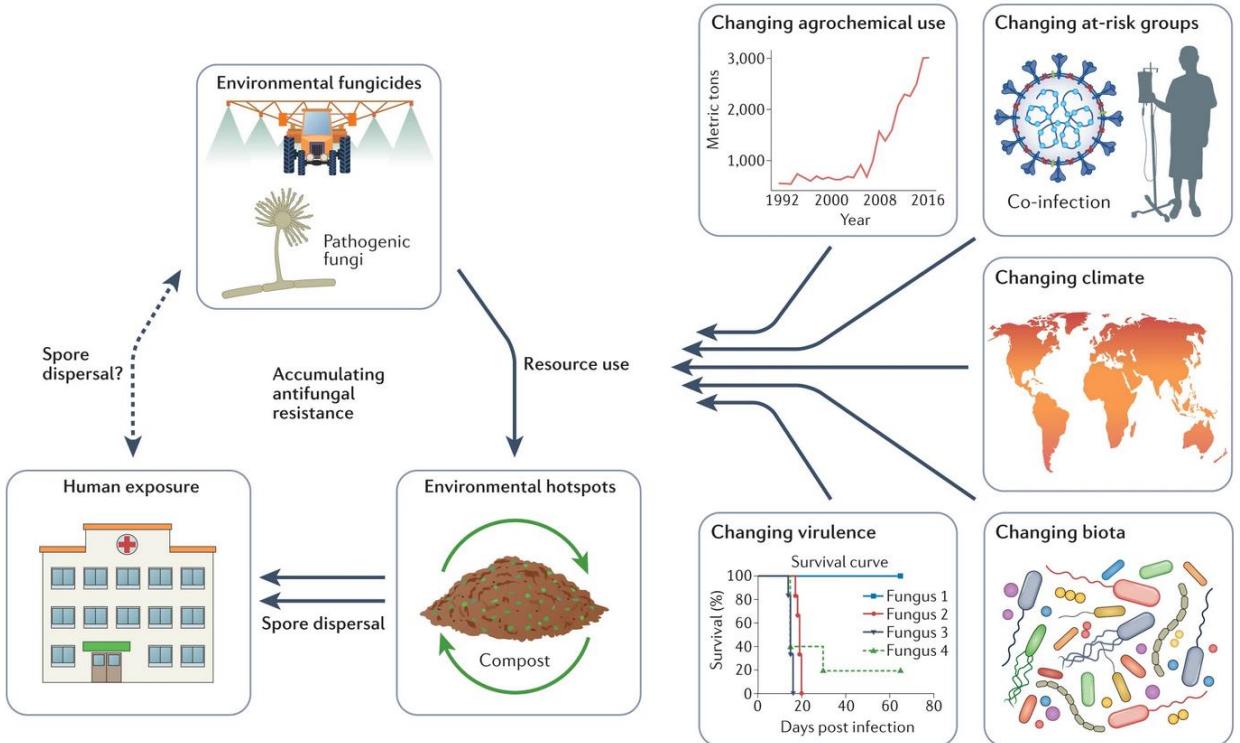
C Increase of reported *C parapsilosis* resistance 2012–22



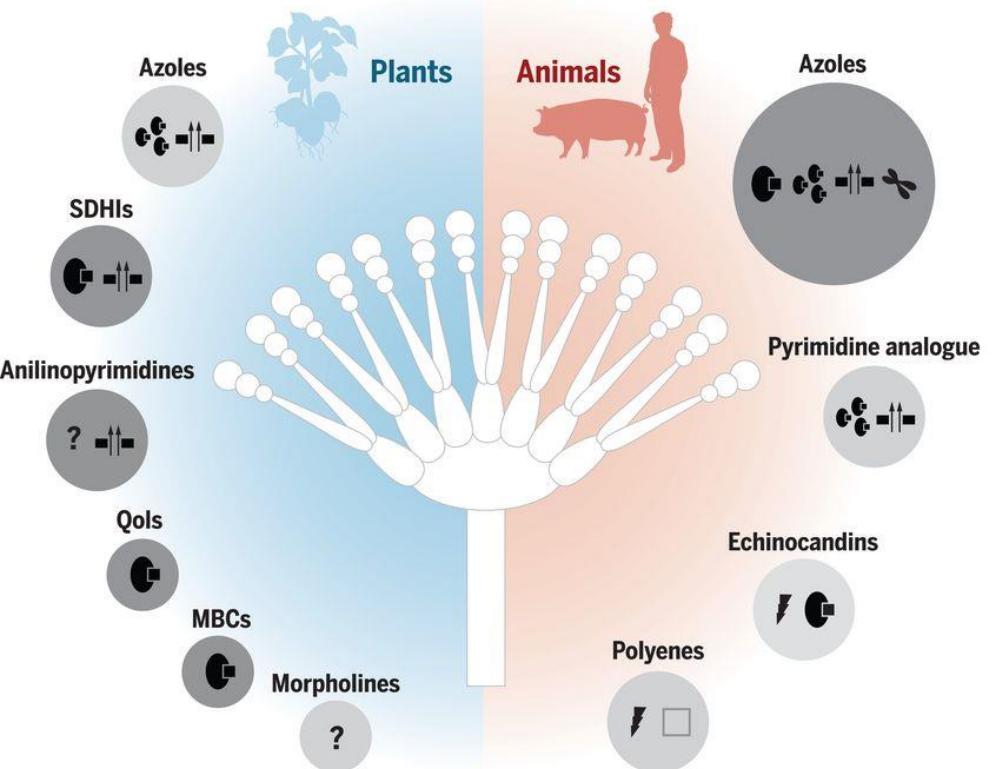
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# Antimykotische Resistenz



# Antimykotische Resistenz



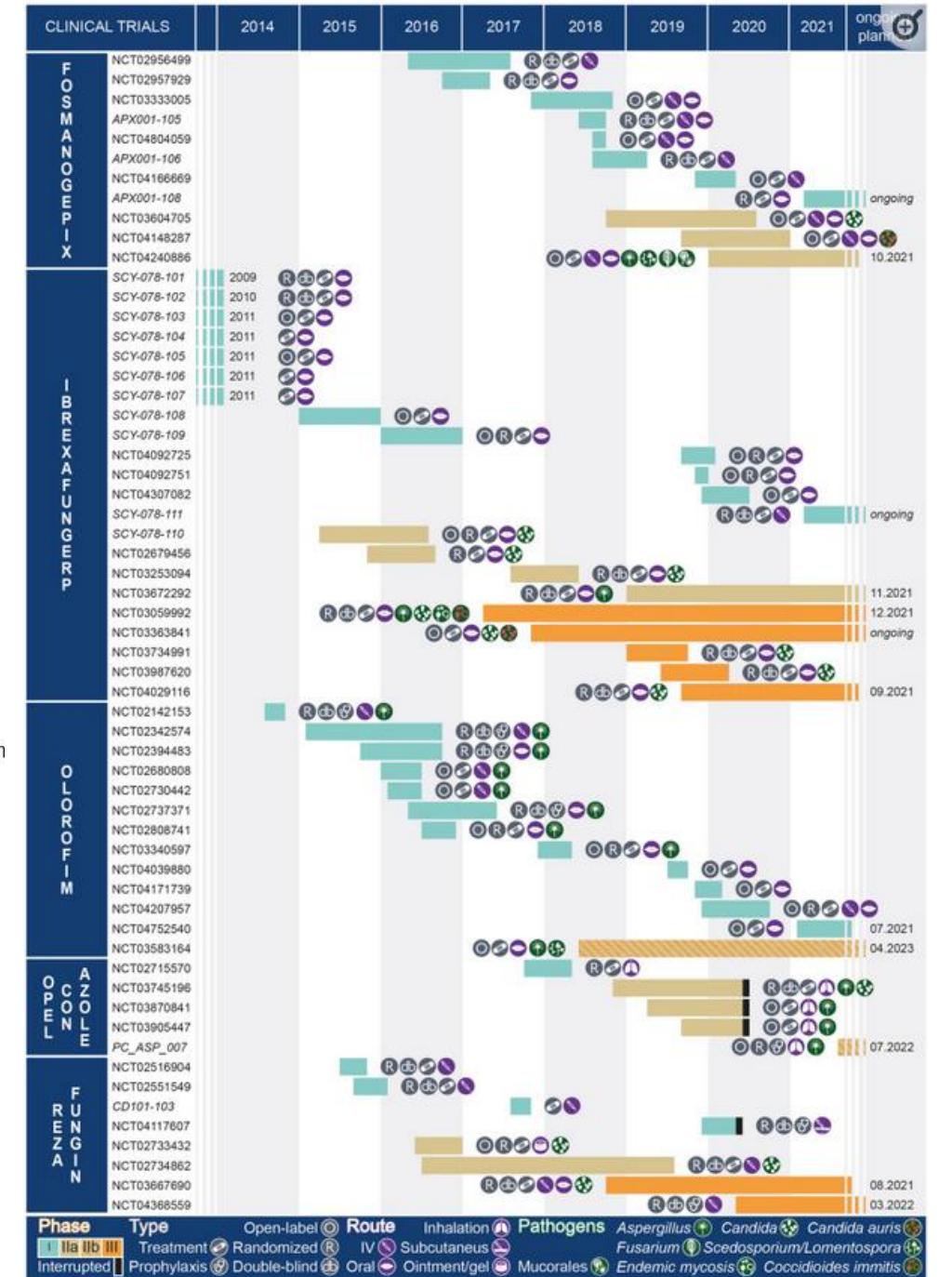
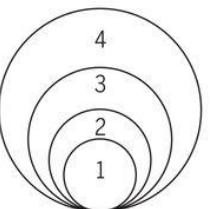
## Resistance Status

- Resistance
  - Partial resistance
  - No resistance

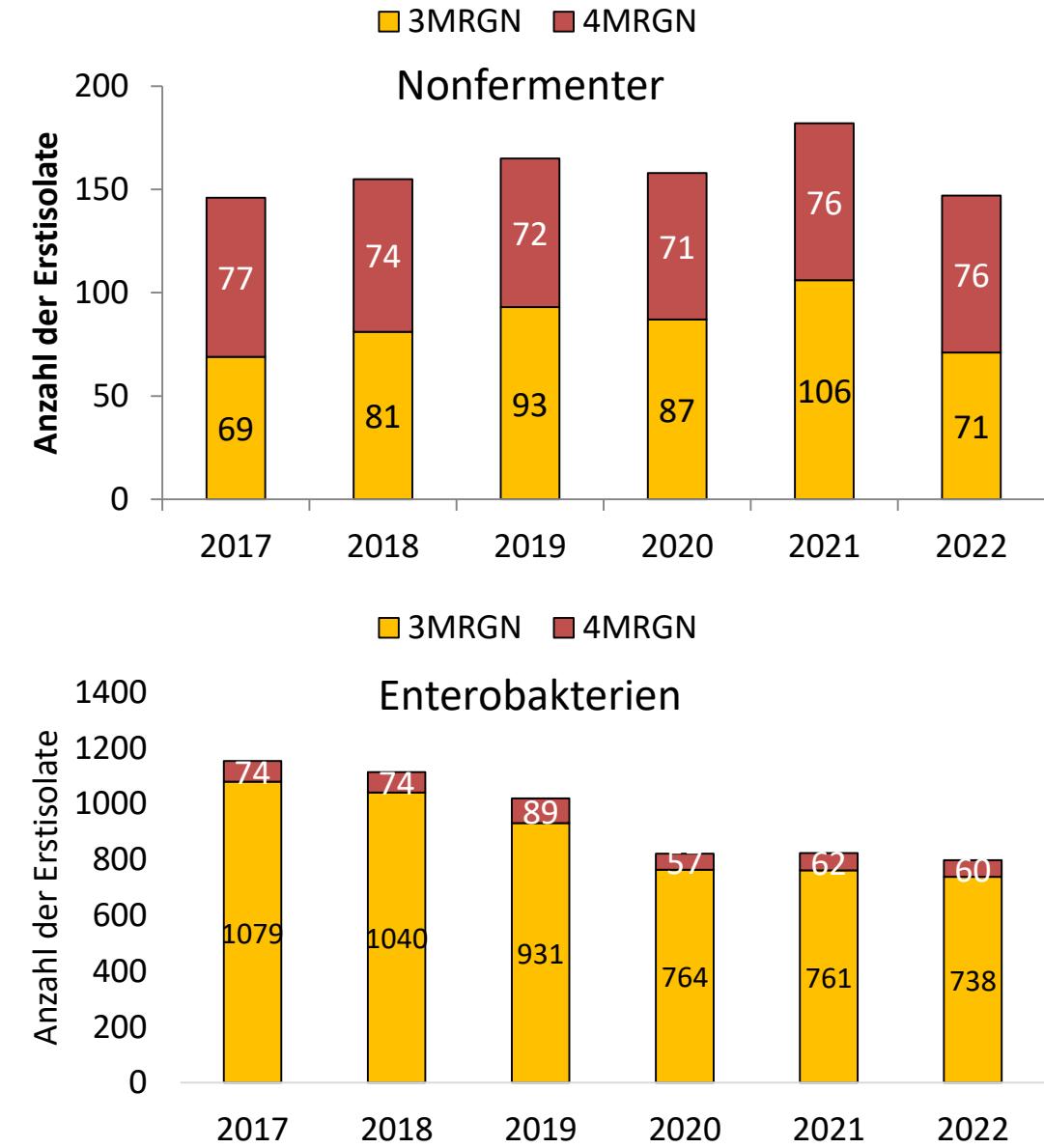
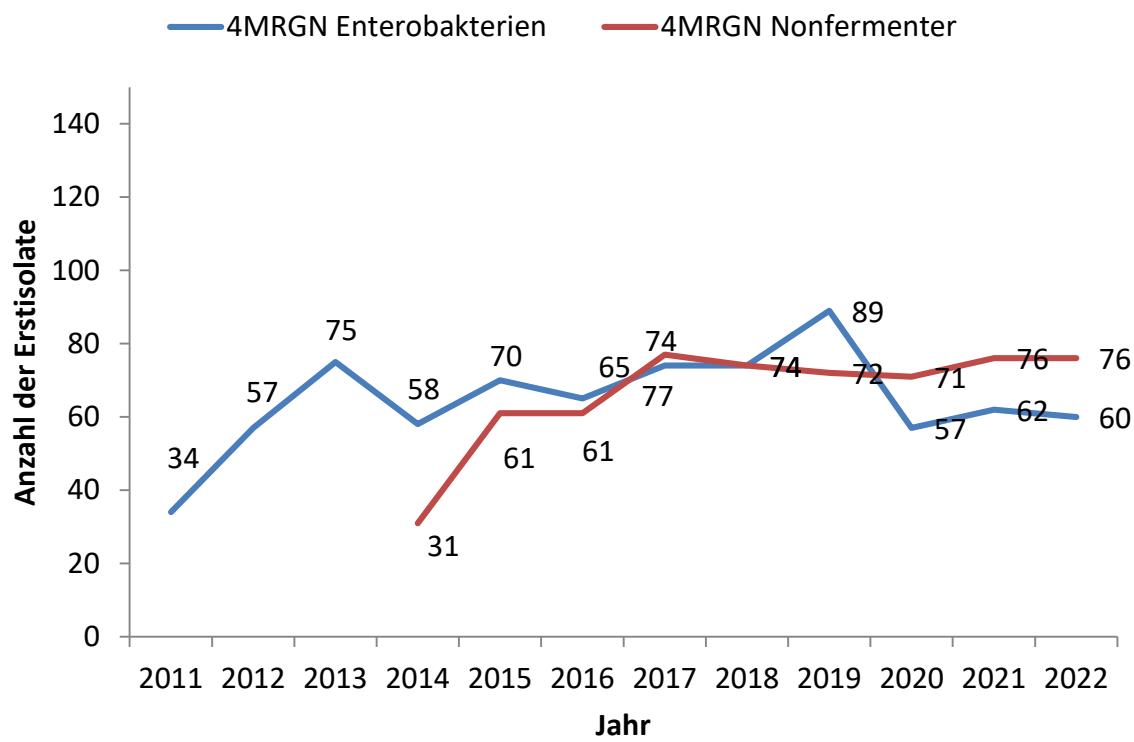
## Resistance Mechanisms

-  Target site conformational changes
  -  Target site overexpression
  -  Absence of target
  -  Efflux pump overexpression
  -  Regulation of stress response pathways
  -  Genomic plasticity: aneuploidy/hypermutation
  -  Unknown mechanism

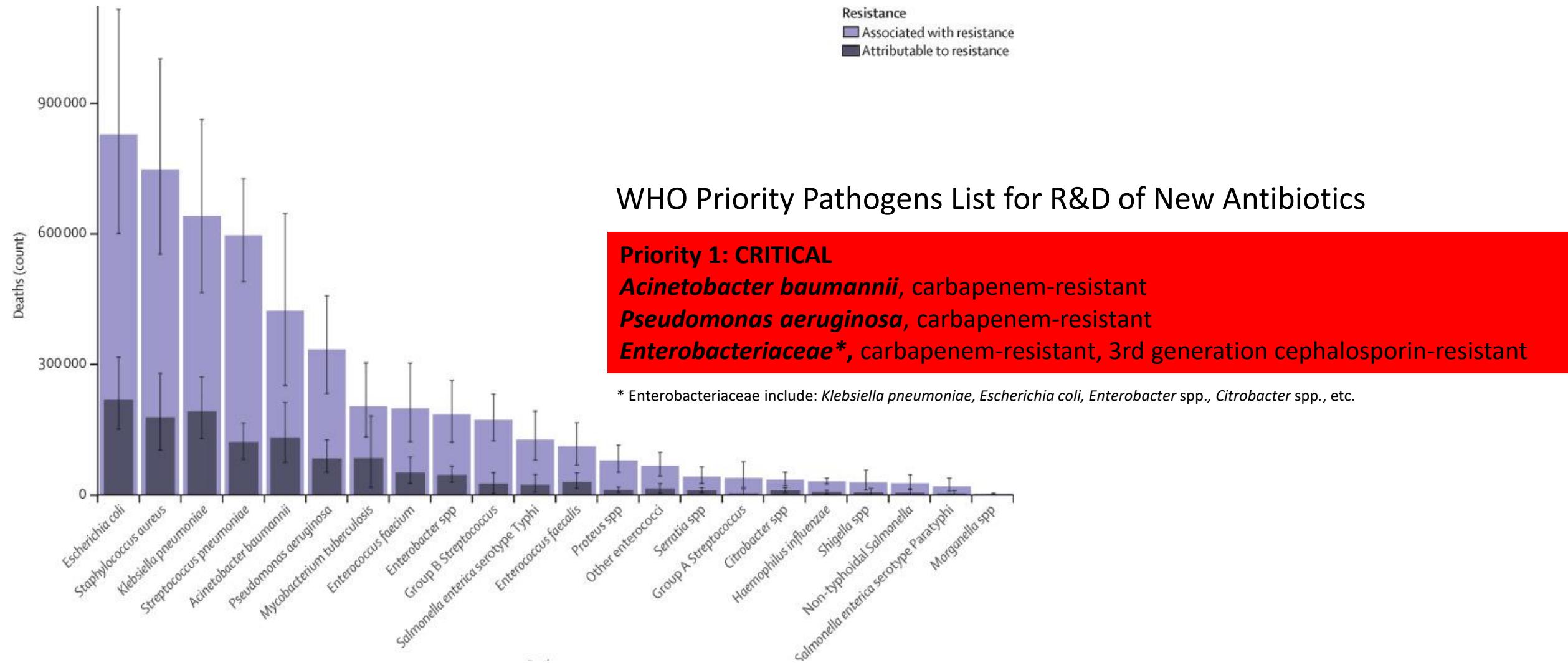
## **Number of Resistance Mechanisms**



# Entwicklungen im gramnegativen Bereich



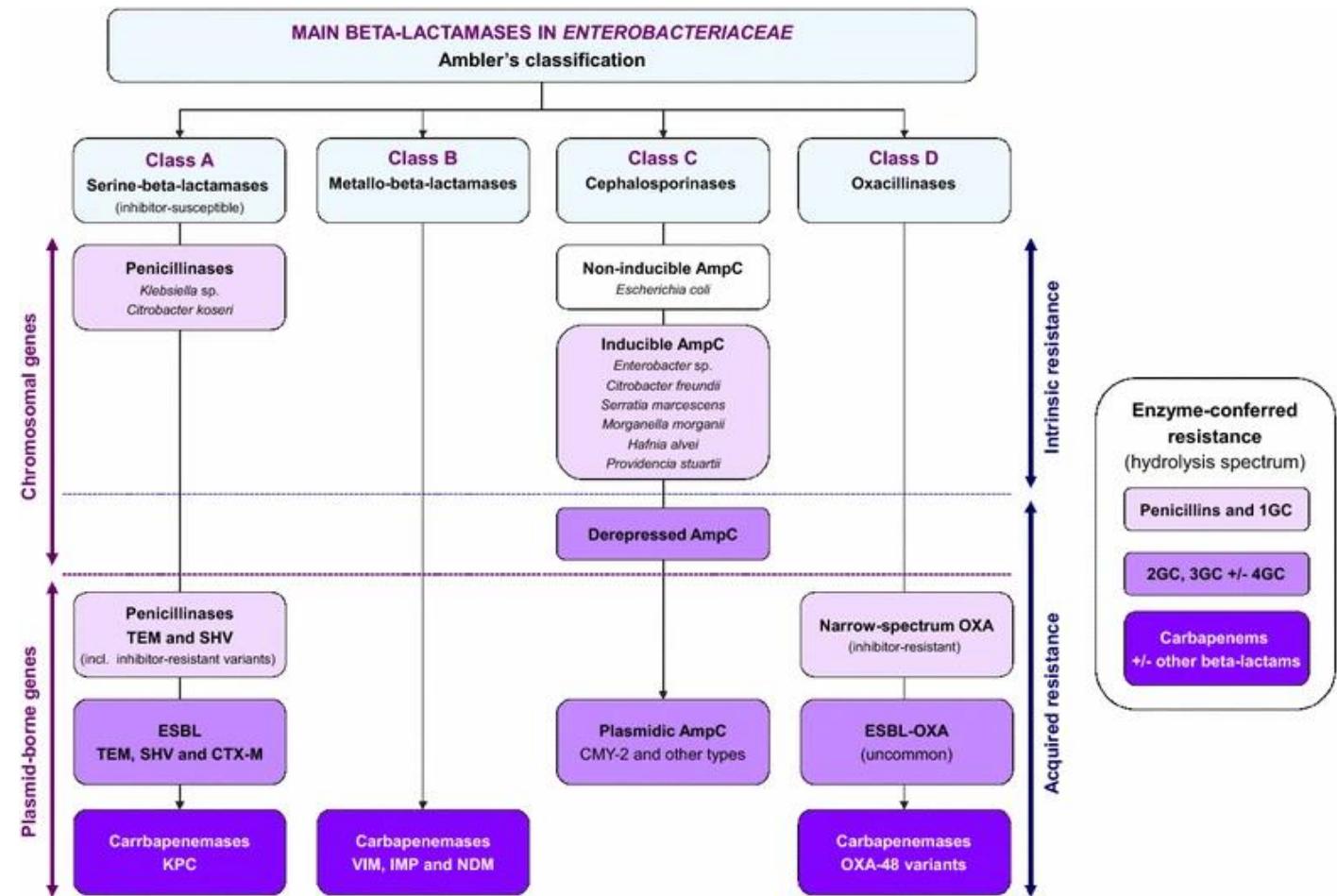
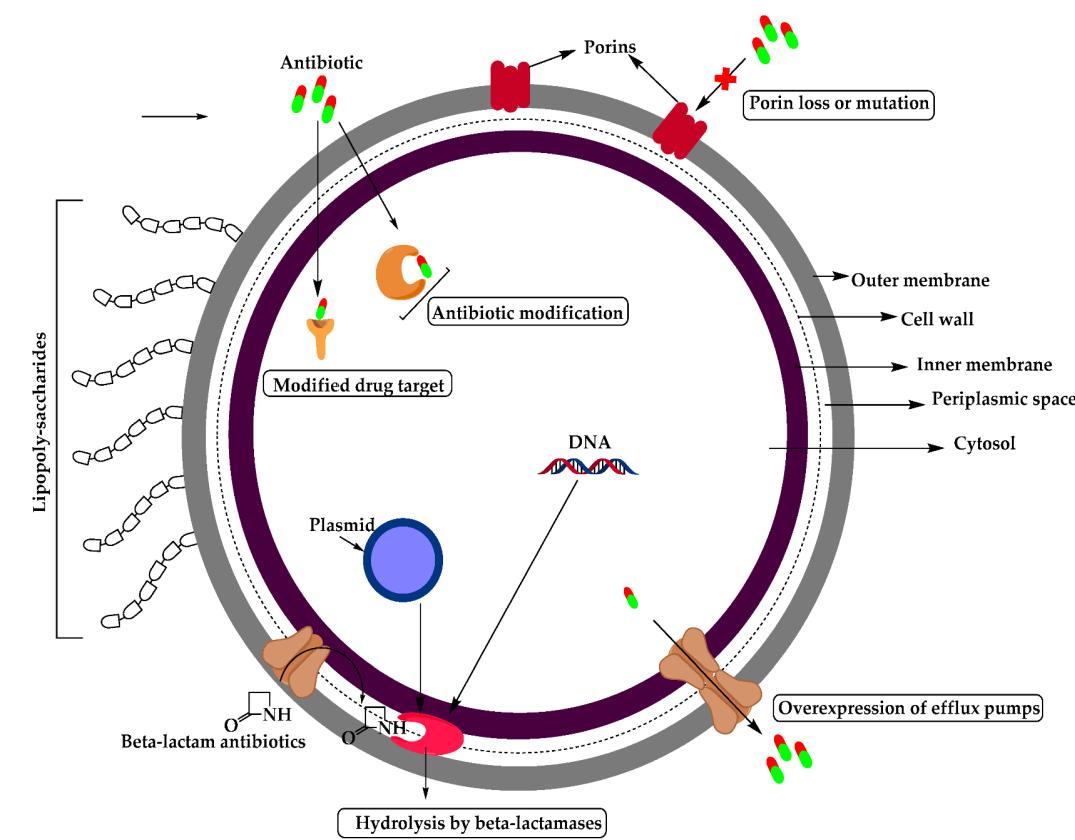
# Gramnegative Resistenzen



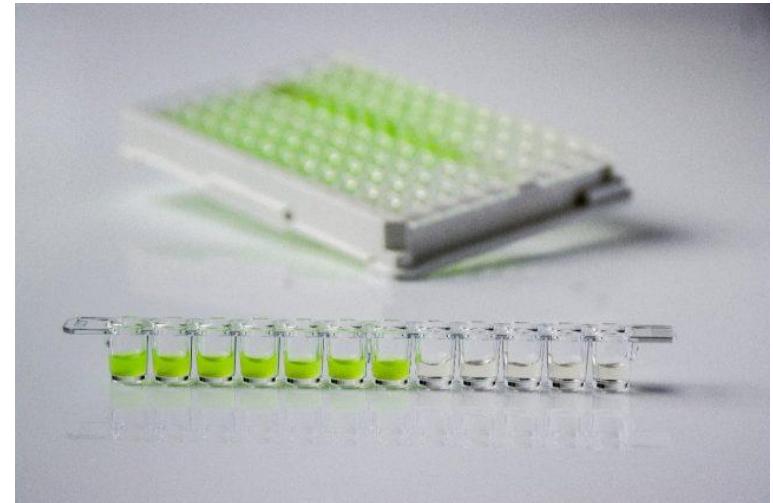
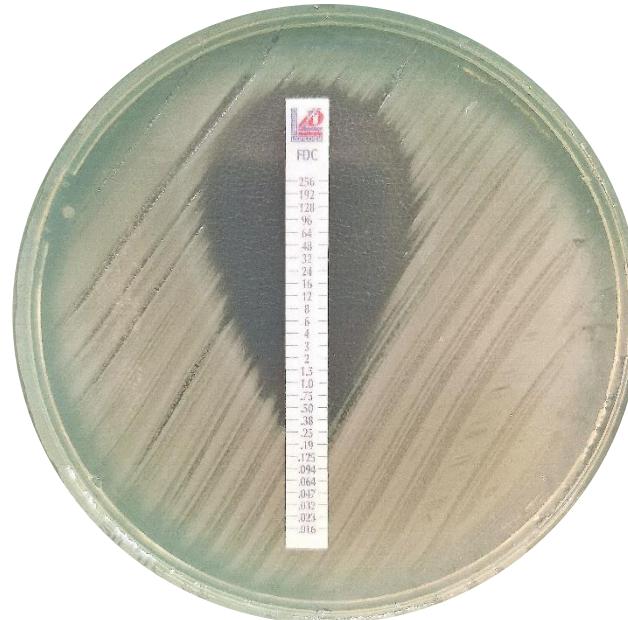
Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by pathogen, 2019

Murray CJL et al, 2022. *Lancet*, [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)

# Resistenzmechanismen bei *Enterobacteriales* (*E. coli*, *Klebsiella* etc.)



# Methodik der Resistenztestung



Source: <https://www.bruker.com/de/products-and-solutions/microbiology-and-diagnostics/antimicrobial-susceptibility-testing/mic-strip.html>

Carbapenems	Disk content ( $\mu\text{g}$ )	Zone diameter breakpoints (mm)		
		S $\geq$	R <	ATU
Doripenem	10	50	22	
Ertapenem		-	-	
Imipenem	10	50	20	
Imipenem-relebactam, P. aeruginosa	10-25	22	22	
Meropenem (indications other than meningitis)	10	24	18	
Meropenem (meningitis)	10	24	24	
Meropenem-vaborbactam, P. aeruginosa	IP	IP	IP	

Carbapenems	MIC breakpoints (mg/L)		
	S $\leq$	R >	ATU
Doripenem	0.001	2	
Ertapenem	-	-	
Imipenem	0.001	4	
Imipenem-relebactam, P. aeruginosa	2 <sup>1</sup>	2 <sup>1</sup>	
Meropenem (indications other than meningitis)	2	8	
Meropenem (meningitis)	2	2	
Meropenem-vaborbactam, P. aeruginosa	8 <sup>2</sup>	8 <sup>2</sup>	

# I – Intermediär bisher

Empfindlichkeitskategorie „I“ (**intermediär**) bisher:

1. Therapeutischer Effekt unsicher
  2. Therapieerfolg mit diesem Antibiotikum bei Gabe einer hohen Dosis bzw. einer erhöhten Exposition des Erregers möglich
  3. Pufferzone für methodische Schwierigkeiten
- „I“ eher Richtung „R“ interpretiert



# I NEU – Sensibel bei erhöhter Antibiotika-Exposition

## New definitions of S, I and R from 2019

EUCAST has changed the definitions of susceptibility testing categories S, I and R as shown below. Results of several consultations on the new definitions are available on the EUCAST website under "Consultations".

- S - Susceptible, standard dosing regimen: A microorganism is categorised as "Susceptible, standard dosing regimen", when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
- I - Susceptible, increased exposure\*: A microorganism is categorised as "Susceptible, Increased exposure\*\*" when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.
- R - Resistant: A microorganism is categorised as "Resistant" when there is a high likelihood of therapeutic failure even when there is increased exposure.

Fluoroquinolones	Standard dosage	High dosage
Ciprofloxacin	0.5 g x 2 oral or 0.4 g x 2 iv	0.75 g x 2 oral or 0.4 g x 3 iv
Delafloxacin	0.45 g x 2 oral or 0.3 g x 2 iv	None
Levofloxacin	0.5 g x 1 oral or 0.5 g x 1 iv	0.5 g x 2 oral or 0.5 g x 2 iv
Moxifloxacin	0.4 g x 1 oral or 0.4 g x 1 iv	None
Norfloxacin	None	None
Ofloxacin	0.2 g x 2 oral or 0.2 g x 2 iv	0.4 g x 2 oral or 0.4 g x 2 iv

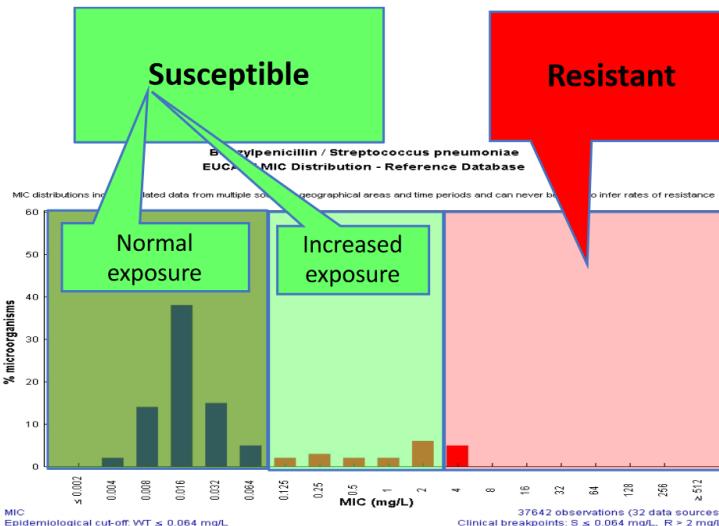


# S-Bereich erreichbar

## New definitions of S, I and R from 2019

EUCAST has changed the definitions of susceptibility testing categories S, I and R as shown below. Results of several consultations on the new definitions are available on the EUCAST website under "Consultations".

- S - Susceptible, standard dosing regimen: A microorganism is categorised as "Susceptible, standard dosing regimen", when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
- I - Susceptible, increased exposure\*: A microorganism is categorised as "Susceptible, Increased exposure\*" when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.
- R - Resistant: A microorganism is categorised as "Resistant" when there is a high likelihood of therapeutic failure even when there is increased exposure.



## Enterobacteriales\*

### Expert Rules and Intrinsic Resistance Tables

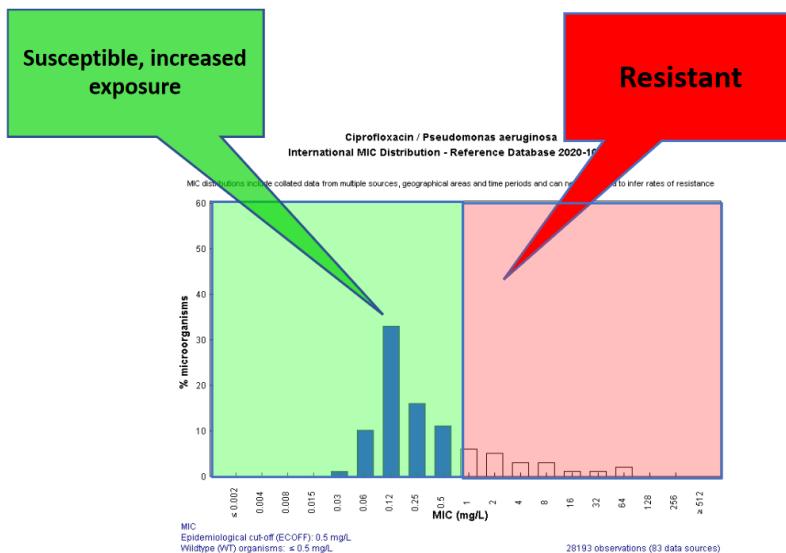
Carbapenems <sup>1</sup>	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Doripenem	1	2		10	24	21	
Ertapenem	0.5	0.5		10	25	25	
Imipenem, Enterobacteriales except Morganellaceae	2	4		10	22	19	
Imipenem <sup>2</sup> , Morganellaceae	0.001	4		10	50	19	
Imipenem-relebactam, Enterobacteriales except Morganellaceae	2 <sup>3</sup>	2 <sup>3</sup>		10-25	22	22	
Meropenem (indications other than meningitis)	2	8		10	22	16	
Meropenem (meningitis)	2	2		10	22	22	
Meropenem-vaborbactam	8 <sup>4</sup>	8 <sup>4</sup>		IP	IP	IP	

# S-Bereich nicht erreichbar

## New definitions of S, I and R from 2019

EUCAST has changed the definitions of susceptibility testing categories S, I and R as shown below. Results of several consultations on the new definitions are available on the EUCAST website under "Consultations".

- S - Susceptible, standard dosing regimen: A microorganism is categorised as "Susceptible, standard dosing regimen", when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
- I - Susceptible, increased exposure\*: A microorganism is categorised as "Susceptible, Increased exposure" when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.
- R - Resistant: A microorganism is categorised as "Resistant" when there is a high likelihood of therapeutic failure even when there is increased exposure.



## *Pseudomonas* spp.

### Expert Rules and Intrinsic Resistance Tables

Fluoroquinolones	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S <	R >	ATU		S >	R <	ATU
Ciprofloxacin	0.001	0.5		5	50	26	1
Delafloxacin	IE	IE			IE	IE	
Levofloxacin	0.001	1		5	50	22	
Moxifloxacin	-	-			-	-	
Nalidixic acid (screen only)	NA	NA			NA	NA	
Norfloxacin (uncomplicated UTI only)	-	-			-	-	
Oflloxacin	-	-			-	-	

# Antibiogramme über die letzten Jahre

2019

1. spärlich muköser **Pseudomonas aeruginosa**

Antibiotikum/Antimykotikum	1.
Amikacin	S
Aztreonam	S
Cefepim	S
Ceftazidim	S
Ciprofloxacin	S
Gentamicin	S
Imipenem	S
Meropenem	S
Piperacillin-Tazobactam	S
Tobramycin	S
Trimethoprim + Sulfonamid	R



2023

1. **Pseudomonas aeruginosa**

Antibiotikum/Antimykotikum	1.
Amikacin	(S)
Aztreonam	I
Cefepim	I
Ceftazidim	I
Ciprofloxacin	I
Imipenem	I
Meropenem	S
Piperacillin-Tazobactam	I
Tobramycin	(S)
Trimethoprim + Sulfonamid	R



Seit 2022:

S = sensibel, I = sensibel bei erhöhter Antibiotika-Exposition, R = resistent, (S) = wirksam nur in Kombinationstherapie

**Hinweis:** als sensibel zu werten sind die Kategorien S (sensibel bei Standardexposition) und I (sensibel bei erhöhter Antibiotika-Exposition) bezogen auf die Dosierungsempfehlungen gemäß EUCAST, siehe:

[https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST\\_files/Breakpoint\\_tables/Dosages\\_v\\_12.0\\_Breakpoint\\_Tables.pdf](https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Dosages_v_12.0_Breakpoint_Tables.pdf)

# Fazit



hmm  
institut für hygiene und  
medizinische mikrobiologie

RESISTENZBERICHT 2022

Resistenzverhalten von Bakterien  
und Pilzen gegenüber Antibiotika  
und Antimykotika

MEDIZINISCHE  
UNIVERSITÄT  
INNSBRUCK

- ❖ Problematik durch multiresistente Grampositive (VRE, LRS), besonders in europäischen Nachbarländern
- ❖ Anstieg ambulant erworbbener respiratorischer Pathogene auf das Vor-Pandemie-Niveau
- ❖ Candida auris und Fluconazol-resistente C. parapsilosis noch nicht nachgewiesen
- ❖ Kein Anstieg gramnegativer Resistenzen im letzten Jahr



<https://i-med.ac.at/hygiene/bakteriologiehome.html.de>