



NordicAST webinar 5 December 2024:

Upcoming changes in EUCAST benzylpenicillin breakpoints and testing of *S. pneumoniae*

Today's program:

- Background for breakpoint changes as proposed in the EUCAST consultation (Christian Giske)
- Testing methodology incl. updated flowchart (Erika Matuschek)
- Implications for the Nordic countries
- Questions and discussion

Please stay muted.

Type your questions in the chat function.

The webinar will be recorded and available on the NordicAST homepage.

Why did we start the revision?

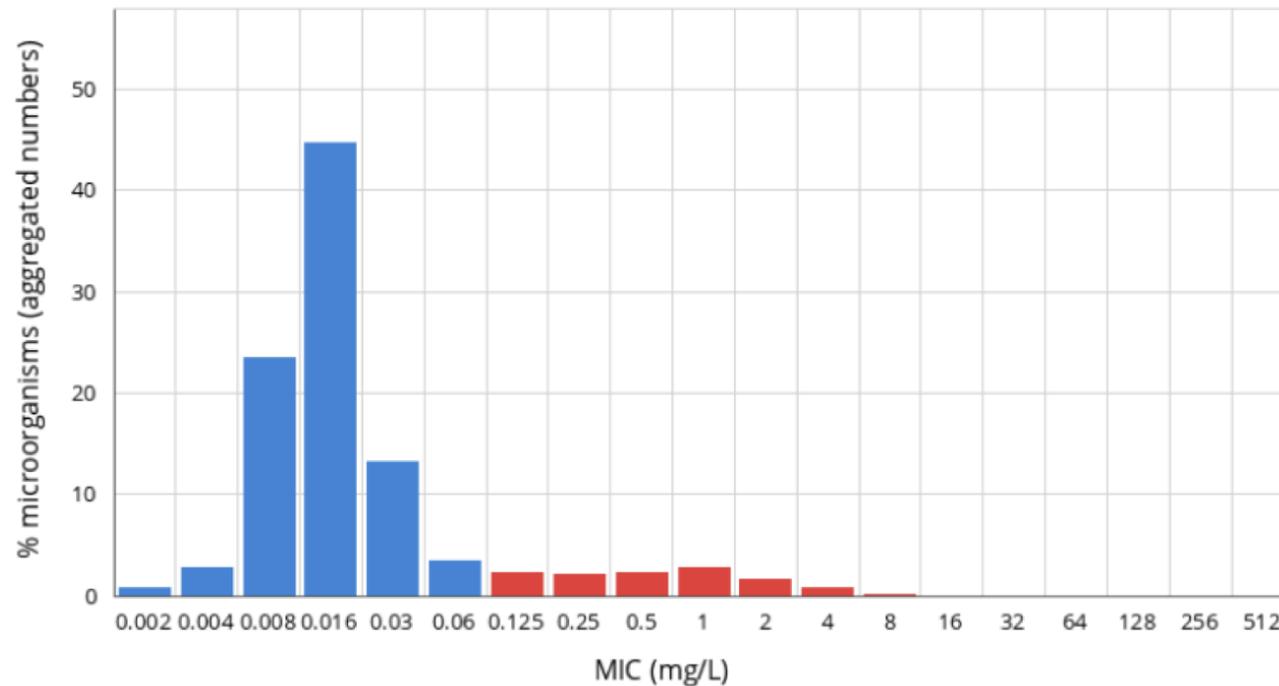
Penicillins	Standard dosage	High dosage	Uncomplicated UTI	Special situations
Benzylicillin	0.6 g (1 MU) x 4 iv	1.2 g (2 MU) x 4-6 iv		<p>Meningitis caused by <i>S. pneumoniae</i>: For a dose of 2.4 g (4 MU) x 6 iv, isolates with MIC ≤0.06 mg/L are susceptible.</p> <p>Pneumonia caused by <i>S. pneumoniae</i>: breakpoints are related to dosage: For a dose of 1.2 g (2 MU) x 4 iv, isolates with MIC ≤ 0.5 mg/L are susceptible. For a dose of 2.4 (4 MU) g x 4 iv or 1.2 g (2 MU) x 6 iv, isolates with MIC ≤1 mg/L are susceptible. For a dose of 2.4 g (4 MU) x 6 iv, isolates with MIC ≤2 mg/L are susceptible.</p>

- You could use whatever breakpoint you wanted in the previous version...
- The breakpoints required laboratories to frequently perform MIC-testing
- Gradient diffusion tests for benzylpenicillin against *S. pneumoniae* tend to undercall the MIC as measured in reference broth microdilution.
- If the MIC of a clinical isolate is determined and used for patient management decisions, the intrinsic variation (+/- one 2-fold dilution) in the MIC measurement did not allow the granular approach to dosing presented above
- Additionally
 - Comparison of surveillance data for penicillin-resistance was very difficult due to the various cut-offs used as R-breakpoint
 - Clinical data were not robust at higher MIC-values – poor quality of the data
- Could we make a simple system that did not require routine MIC-testing?

MIC distribution

Benzylpenicillin / *Streptococcus pneumoniae*
International MIC distribution - Reference database 2024-01-15
Based on aggregated distributions

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC
Epidemiological cut-off (ECOFF): 0.06 mg/L
Wildtype (WT) organisms: ≤ 0.06 mg/L

Confidence interval: 0.016 - 0.06
15161 observations (31 data sources)

Pharmacokinetics and dynamics

The current EUCAST rationale document for benzylpenicillin (v1.0) reports the following PD target values:

- 25-35% $fT > MIC$ for stasis
- 35-45% $fT > MIC$ for cidal activity
- 40% from clinical data

Monte Carlo simulation of target attainment

A simulation was carried out in Pmetrics. The following assumptions were made:

-1 compartment model

-CL 24L/h, V 26L, 25% CV on each parameter, fraction unbound 55% (fixed) (based on Visser et al. 1993)

Dosage	0.6 g x 4	1.2 g x 4	1.2 g x 6	2.4 g x 6	3 g x 3	3 g x 4	3 g x 6
$f\%T > MIC$	40	40	40	40	40	40	40
0.06	97.1	98.3	100	100	99.3	99.1	100
0.125	93.3	97.1	100	100	98.3	98.8	100
0.25	81.9	93.0	100	100	97.0	97.6	100
0.5	61.0	81.9	99.8	100	93.7	94.5	100
1	26.8	61.0	99.5	99.8	84.9	86.1	99.9
2	6.6	26.8	95.0	99.5	65.6	68.4	99.8
4	0.9	6.6	49.6	95.0	32.8	38.8	97.9
8	0.1	0.1	8.1	49.6	8.6	10.5	72.0

The PTA analysis suggest the following PK-PD cut-off values:

- $S \leq 0.06 \text{ mg/L}$, with 0.6 x 4 as the lowest dose, assuming 40% $fT > MIC$
- $R > 1 \text{ mg/L}$ if 1.2g x 6 is considered

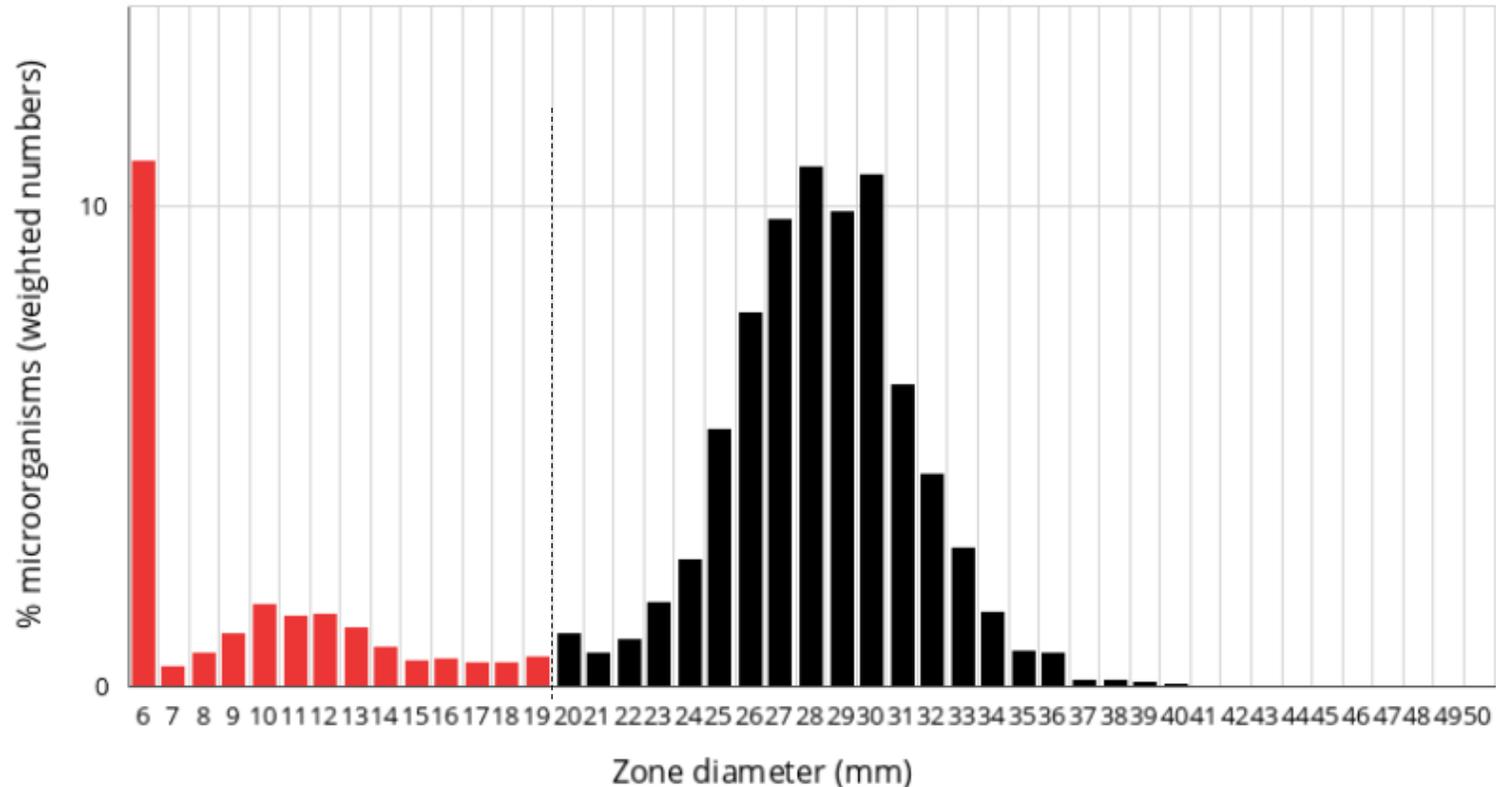
Conclusions

- The proposed breakpoints were
 - $S \leq 0.06$ mg/L (dosing minimum 0.6 g x 4)
 - $R > 1$ (dosing for the I-group 1.2 g x 6)
- But what about the consequences for AST?

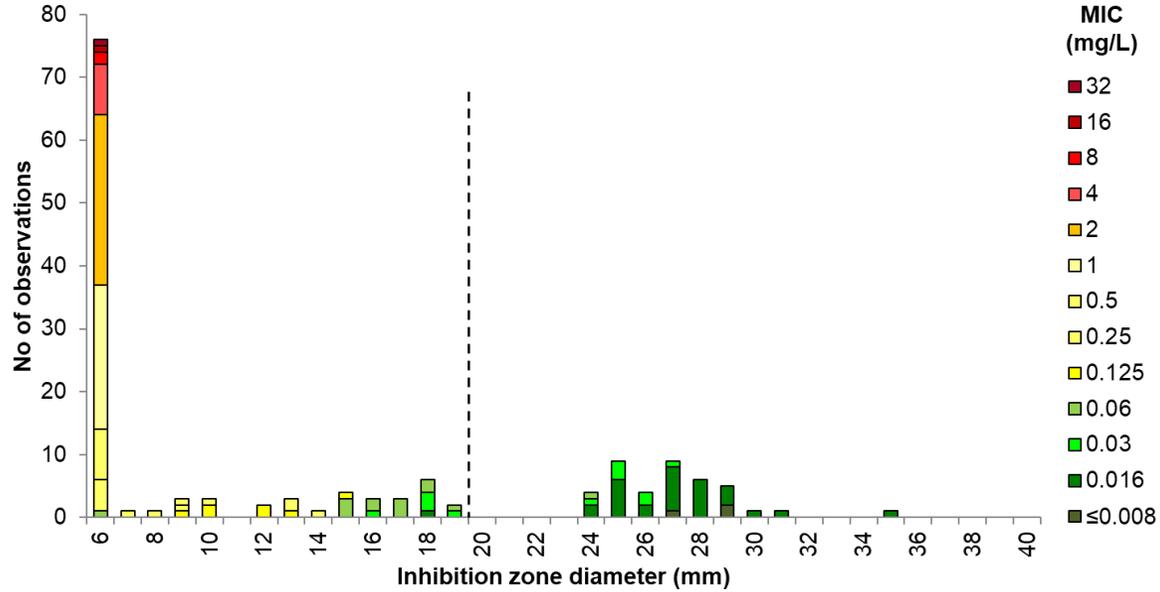
Antimicrobial susceptibility
testing of *S. pneumoniae* and
benzylpenicillin

Screening for beta-lactam resistance in *S. pneumoniae*

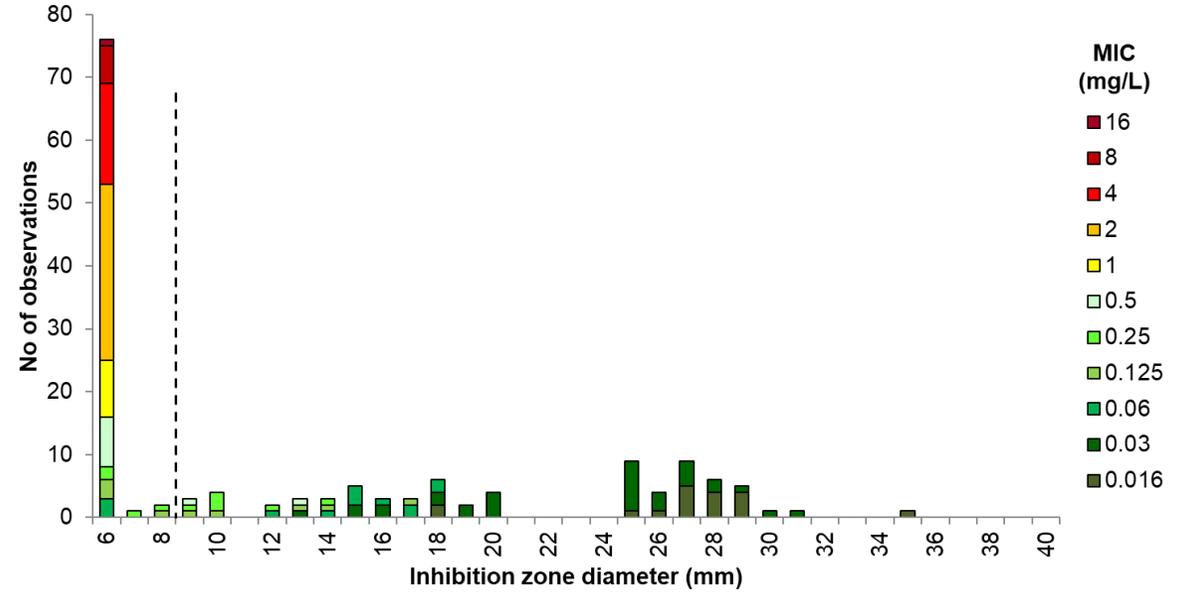
- Oxacillin 1 µg differentiates between wild-type and non-wild type for beta-lactam agents



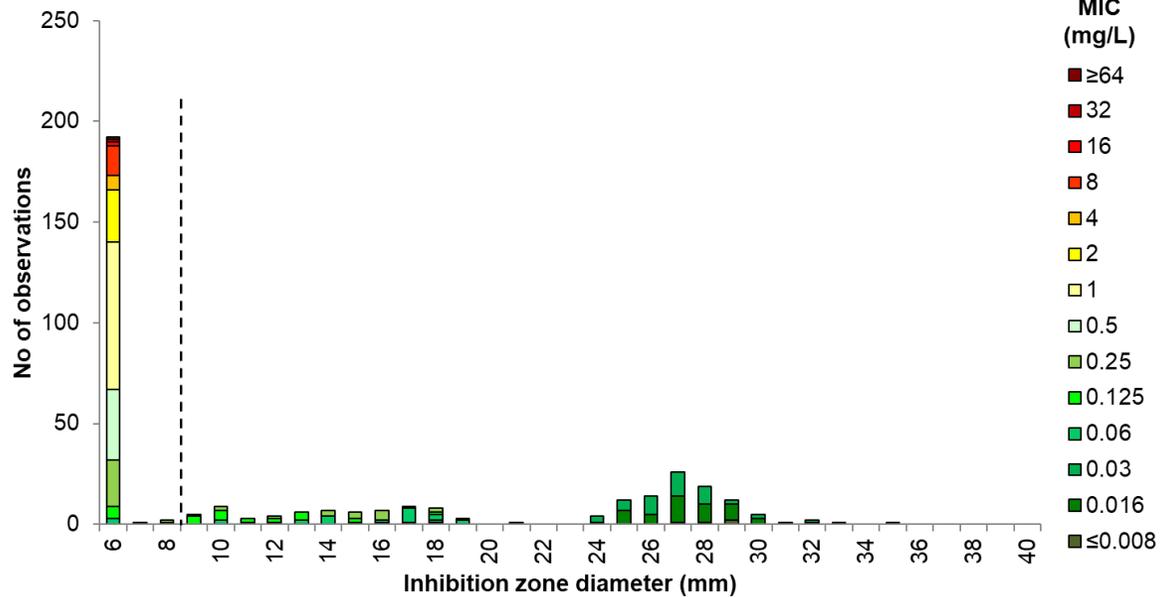
**Oxacillin 1 µg vs. Benzylpenicillin MIC
S. pneumoniae, 148 isolates**



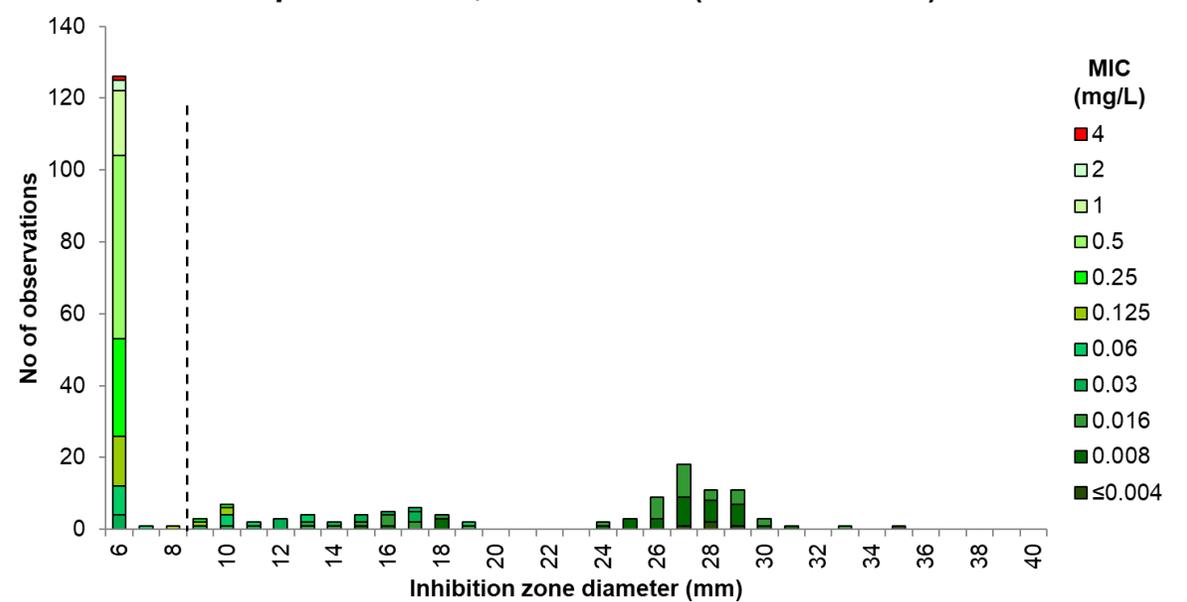
**Oxacillin 1 µg vs. Ampicillin MIC
S. pneumoniae, 153 isolates**



**Oxacillin 1 µg vs. Cefotaxime MIC
S. pneumoniae, 151 isolates (360 correlates)**



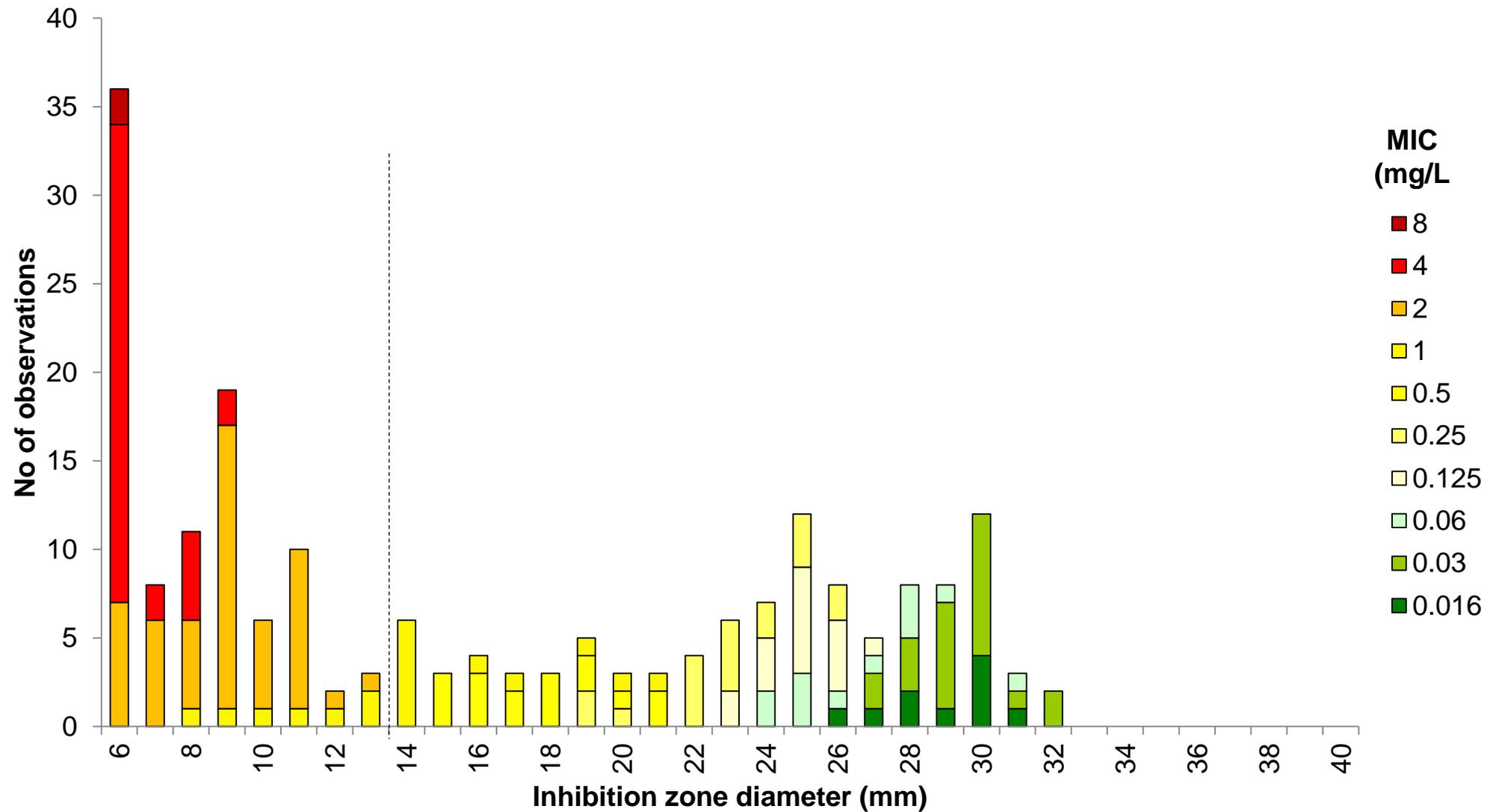
**Oxacillin 1 µg vs. Meropenem MIC
S. pneumoniae, 130 isolates (230 correlates)**



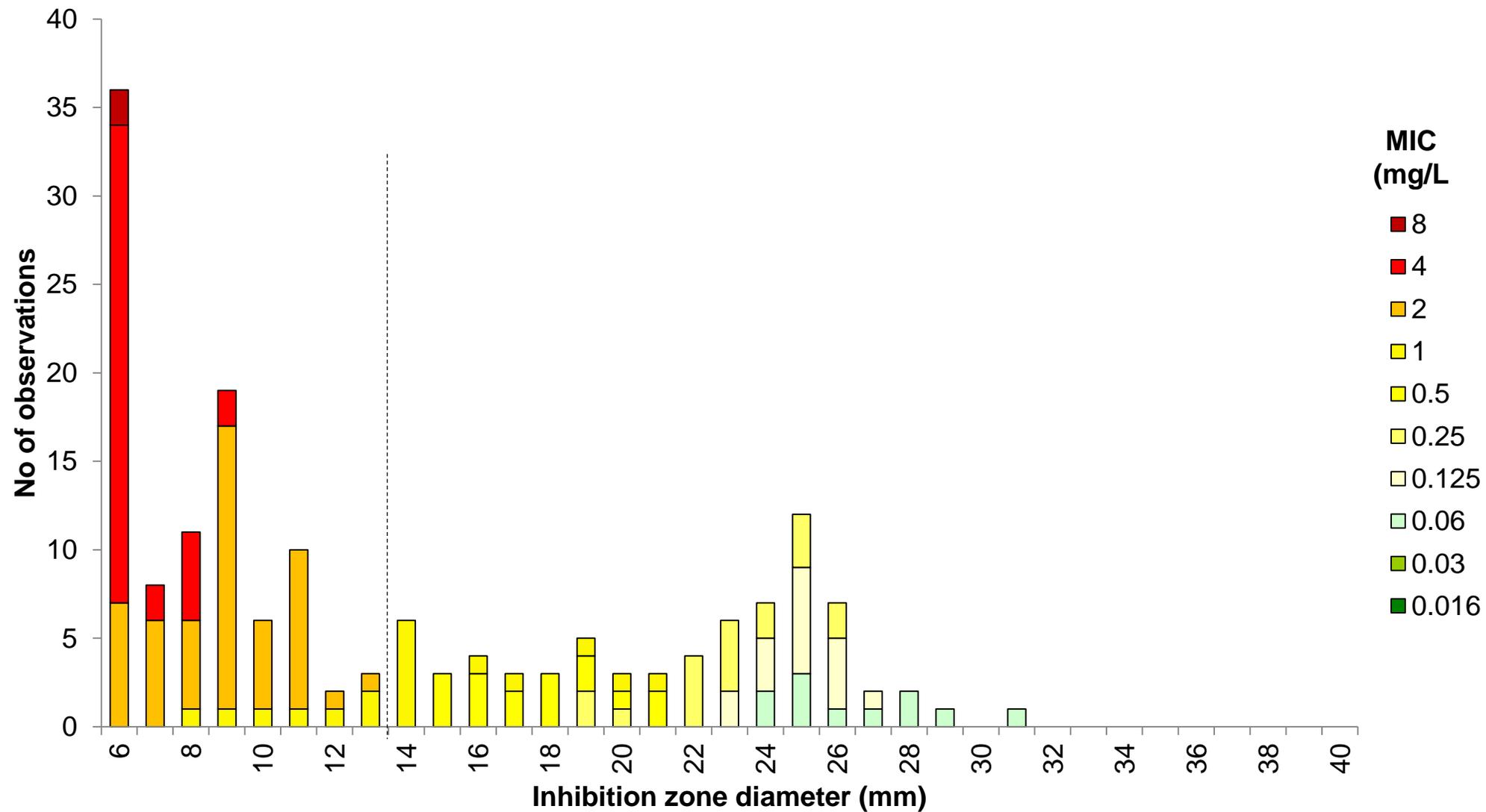
Development of a new method to categorise benzylpenicillin in *S. pneumoniae*

- 100 *S. pneumoniae* with PCG MICs 0.016-8 mg/L.
- Broth microdilution and disk diffusion performed in parallel
 - Disk diffusion on MH-F agar from 2 manufacturers
 - Benzylpenicillin 1 unit
 - Ampicillin 2 µg
 - Piperacillin-tazobactam 30-6 µg
 - Oxacillin 1 µg
 - Cefadroxil 30 µg
 - Cefaclor 30 µg
 - Cefoxitin 30 µg
 - Ceftazidime 10 µg
 - Cefotaxime 5 µg
 - Ceftaroline 5 µg

Benzylpenicillin 1 unit vs. MIC *S. pneumoniae*, 100 isolates (200 correlates)



Benzylpenicillin 1 unit vs. MIC, OXA <20 mm
***S. pneumoniae*, 84 isolates (167 correlates)**



**Oxacillin 1 µg zone diameter <20 mm
(or benzylpenicillin MIC >0.06 mg/L)**

Mechanism: beta-lactam resistance detected

Report resistant (R) to benzylpenicillin in endocarditis and meningitis and to phenoxymethylpenicillin (all indications).

For benzylpenicillin in indications other than endocarditis and meningitis,
read and interpret the benzylpenicillin disk:

If zone ≥14 mm, report benzylpenicillin “susceptible, increased exposure” (I),

If zone <14 mm, report benzylpenicillin resistant (R).

For other beta-lactam agents, see below.

Implications for the respective countries



Konsekvenser för de svenska labben

- Överensstämmelse mellan R och vad som ska rapporteras i Sminet, dvs isolat som är PCG R (MIC >1 mg/L eller R med lappdiffusion)
- Alla isolat med OXA zon <9 mm skickas till FoHM
- På alla isolat som utfaller I för PcG. Lägg på kommentar om högre dosering från RAF:
- *Isolatet har resistensmekanismer mot bensylpenicillin vilket kräver högre dosering, var god se RAFs doseringstabell. Vid svårt sjuk patient och/eller tecken på behandlingssvikt kontakta infektionskonsult.
- Se preliminärt flödesschema på nästa bild
- Se prel ny doseringstabell fr RAF på bilden därefter.



Streptococcus pneumoniae ALGORITM FÖR DETEKTION AV BETALAKTAMRESISTENS

NordicAST v. 15.0, 2025-01-xx

Se EUCAST varning om användning av
bensylpenicillin gradienttest:
<http://www.eucast.org/warnings/>.

Flödesschema för bedömning av betalaktamresistens baserat på screeningtest

Inkludera lappar med oxacillin (1 µg) OCH bensylpenicillin (1 unit) från början för snabbare svar
Läs och tolka bensylpenicillin enbart för isolat med oxacillin zon <20 mm

Oxacillin 1 µg zondiameter ≥20 mm (eller bensylpenicillin MIC ≤0.06 mg/L)

Exkluderar alla resistensmekanismer mot betalaktamer

Rapportera känslig (**S**) för betalaktamer med kliniska brytpunkter, inklusive preparat som har "Note".

Undantag: Cefaklor rapporteras "känslig vid ökad exponering" (**I**).

Ingen ytterligare testning krävs.

Oxacillin 1 µg zondiameter <20 mm (eller bensylpenicillin MIC >0.06 mg/L)

Resistensmekanismer mot betalaktamer är påvisade

Rapportera resistent (**R**) för bensylpenicillin vid meningit/endokardit och fenoximetylpenicillin (alla indikationer).

För bensylpenicillin vid andra indikationer än meningit eller endokardit,

Läs och tolka bensylpenicillinlappen

Om zonen är ≥14mm, rapportera bensylpenicillin "känslig vid ökad exponering" (**I**) och lägg på kommentar*

Om zonen är <14 mm, rapportera bensylpenicillin som resistent (**R**)

För övriga betalaktamantibiotika se nedan.

Oxacillin 1 µg zondiameter 9-19 mm

Rapportera känslig (**S**) utan ytterligare testning: ampicillin, amoxicillin och piperacillin (med och utan betalaktamashämmare), cefepim, cefotaxim, ceftarolin, ceftobiprol, ceftriaxon, imipenem och meropenem.

Övriga betalaktamer, ej listade ovan: utför resistensbestämning för de preparat som ska svaras och tolka enligt kliniska brytpunkter.

Oxacillin 1 µg zondiameter <9 mm

Utför resistensbestämning för andra betalaktamer som ska svaras och tolka enligt kliniska brytpunkter.

*Isolatet har resistensmekanismer mot bensylpenicillin vilket kräver högre dosering, var god se RAFs doseringstabell. Vid svårt sjuk patient och/eller tecken på behandlingssvikt kontakta infektionskonsult.



RAF doseringstabell, preliminär version

Dosering

	Normaldos (dos för S)	Högdos (dos för I)	Dos vid okomplicerad UVI	Särskilda överväganden
Bensylpenicillin	1g x 3 i.v. alternativt 1g x 4 i.v.	3 g x 4 i.v. alternativt 1g x 6 i.v.		<i>Vid allvarliga infektioner med pneumokocker som besvaras I, kan 3gx4 ge för låga antibiotikakoncentrationer. Överväg därför 6-dos särskilt till unga njurfriska patienter.</i> Cornebacterium spp. :endast högdos Meningit: 3 g x 4 iv Endokardit: 3 g x 4 alternativt 2 g x 6 iv



Implications for Denmark

- Referral of isolates to reference lab at SSI: all invasive isolates are sent. (No referral of non-invasive resistant isolates.)
- Infection prevention and control: no national recommendation on isolation precautions.
- Dosing: in most regions benzylpenicillin high dose is 5 MU x4 iv
→ add comment on report and/or dosing table



Implications for Norway

- The proportion of isolates categorized as R will remain more or less the same
- Referral to FHI:
 - All invasive isolates (as before)
 - FHI is working on new criteria for referral of resistant isolates
- Dosing:
 - High dose 3g x 4 or 1.2g x 6 as before
 - Guidelines for targeted therapy for
 - Endocarditis: already x 6
 - Meningitis: will be updated to x 6
 - Severe pneumonia: will be updated to x 6 (?)
- A comment on ensuring sufficient dosing for I-category will be added to the flow chart

What about Finland?



- The new flowchart could be implemented in all laboratories performing AST for *Streptococcus pneumoniae*
- Reference laboratory (THL): no changes. All *S. pneumoniae* strains isolated from bloodculture and other sterile sites should be sent to THL
- The new high dosage for benzylpenicillin already correspond to benzylpenicillin prescription in Finland
- Adding a comment for benzylpenicillin I-isolate will help the AST interpretation by clinicians:
 - Penisilliini I tulkitaan meningiitissä ja endokardiitissa R:ksi ja pneumoniassa S:ksi, jos käytetään riittävää annostusta (4 milj. IE x 6 iv)
- FinRes: the change of the benzylpenicillin breakpoint will probably lead to an increase in % of resistant strains in FinRes report
- Any further questions could be send to Kaisu Rantakokko-Jalava, Heikki Ilmavirta and Nathalie Friberg



Thanks for joining today!

Save the dates:

Webinar "What is new in the breakpoint table v15.0?"

31st January 2025, 13.00-14.30 CET

NordicAST Workshop

27-28th May 2025, Malmö Hyllie