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antibioticR
An R package to identify resistant populations in environmental bacteria

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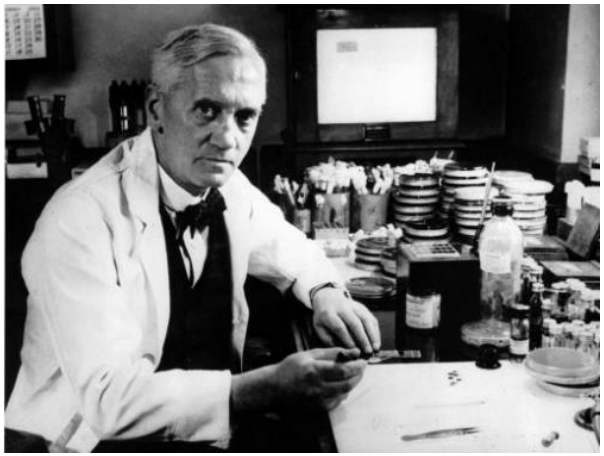
Antibiotics made modern medicine possible

Sir Alexander Fleming (1881 –1955)

- knighted by British king in 1944
- Nobel prize in medicine 1945

- (re-)discovered penicillin in 1928 "by accident"
- isolation of penicillin
  → made modern medicine possible



Calibuon at English Wikibooks [Public domain]
https://commons.wikimedia.org/wiki/File:Alexander_Fleming.jpg

- discovered already, that resistance develops if penicillin application is too low or too short

https://youtu.be/Eu61_KDMGLw

#Documentary #Anitibiotikakrise #ResistanceFighters
RESISTANCE FIGHTERS - The Global Antibiotics Crisis | Trailer (English, 1'30", HD)

„Drug resistant bacteria kill 700.000 citizens each year.“
„This figure is rising dramatically.“
„Resistant microbes will prevail the near future.“

https://www.broadview.tv/en/production/resistance-fighters-the-global-antibiotics-crisis/

Our contribution

Clinical context

- Susceptibility of microbial species
- Selection of suitable antibiotics
- Effective dosing

Large international organizations, e.g. US-FDA, CLSI, EUCAST

Careful characterisation of resistance with Excel-Tools and expert judgment

Environmental context

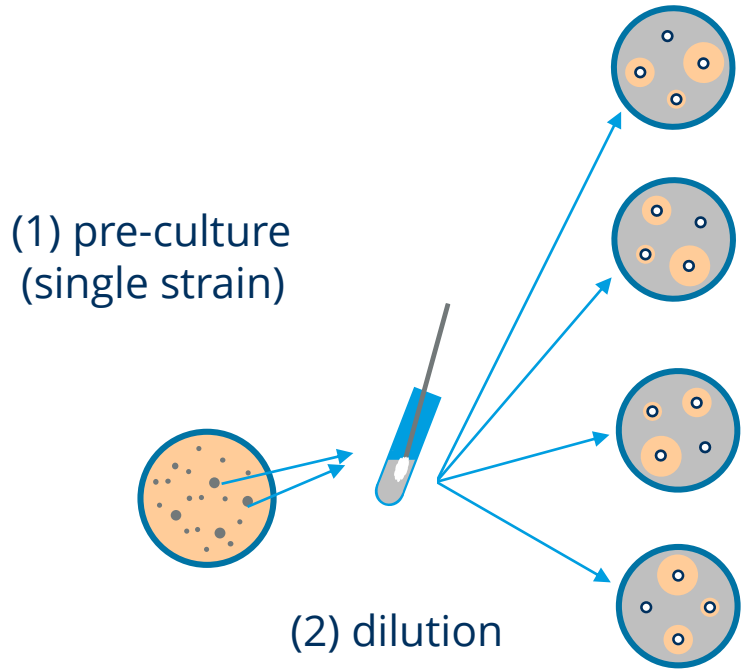
- Sources of resistance
- Influence of environmental factors
- Effectivity of reduction measures
- Evolution and transmission of genes

Aquatic and Environmental Sciences

→ need automatic and reproducible tools for screening and systems understanding.

Inhibition Zone Diameter (ZD)
Similar to the method of Fleming

(3) susceptibility tests
- single strain
- multiple antibiotics



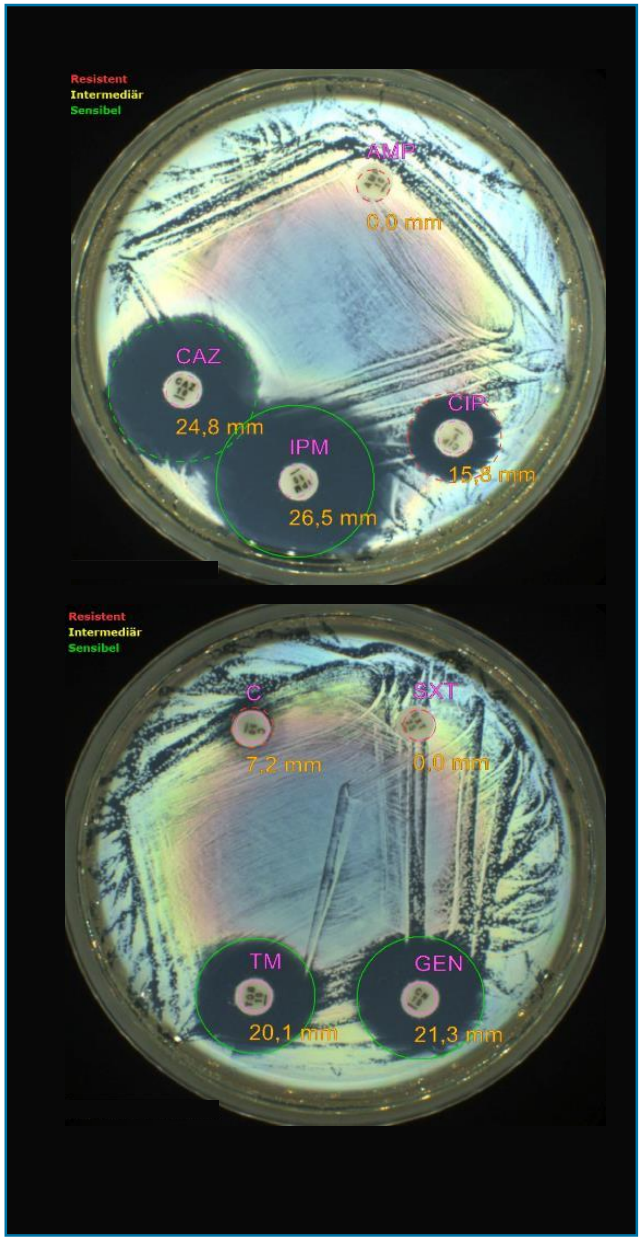
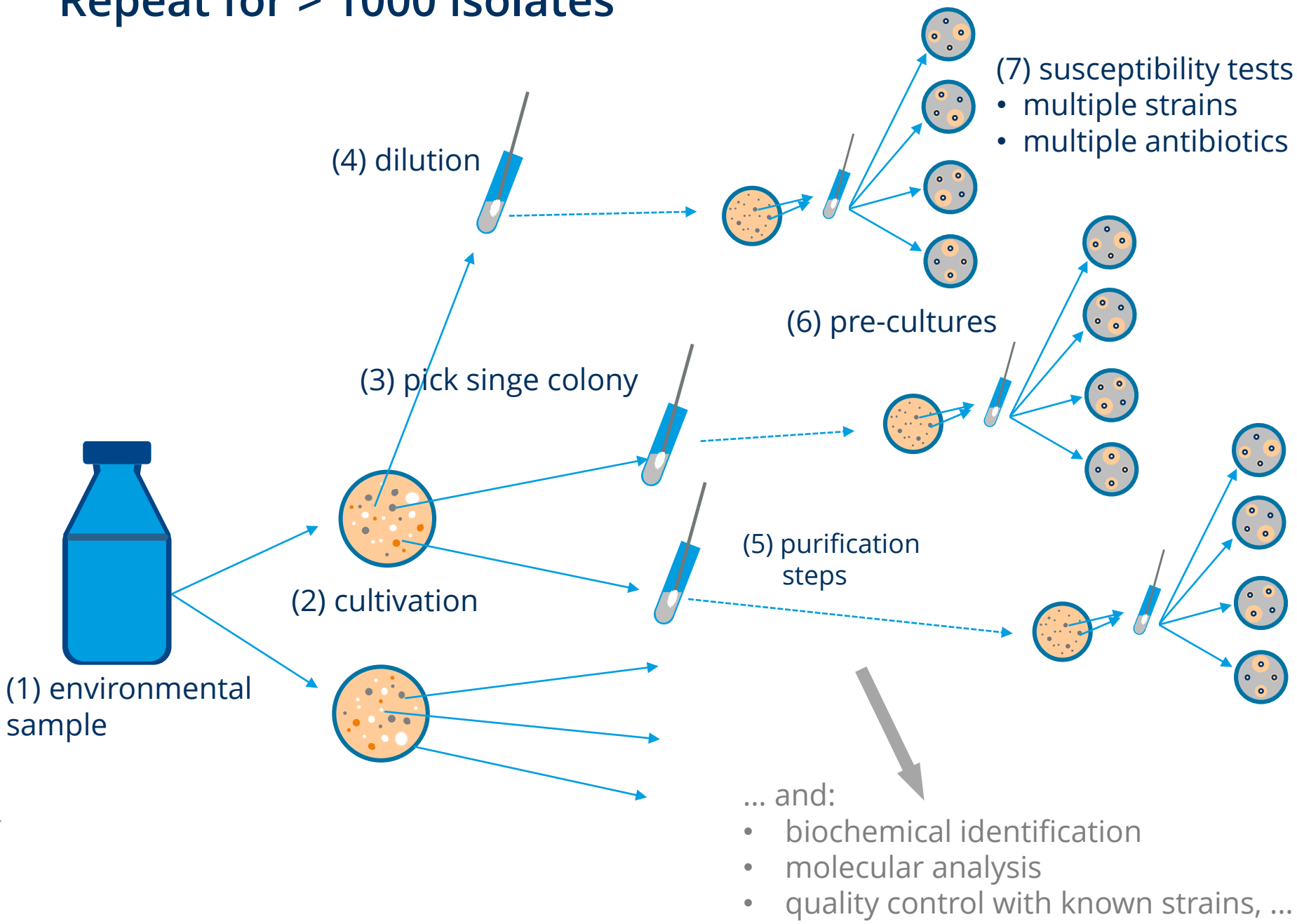
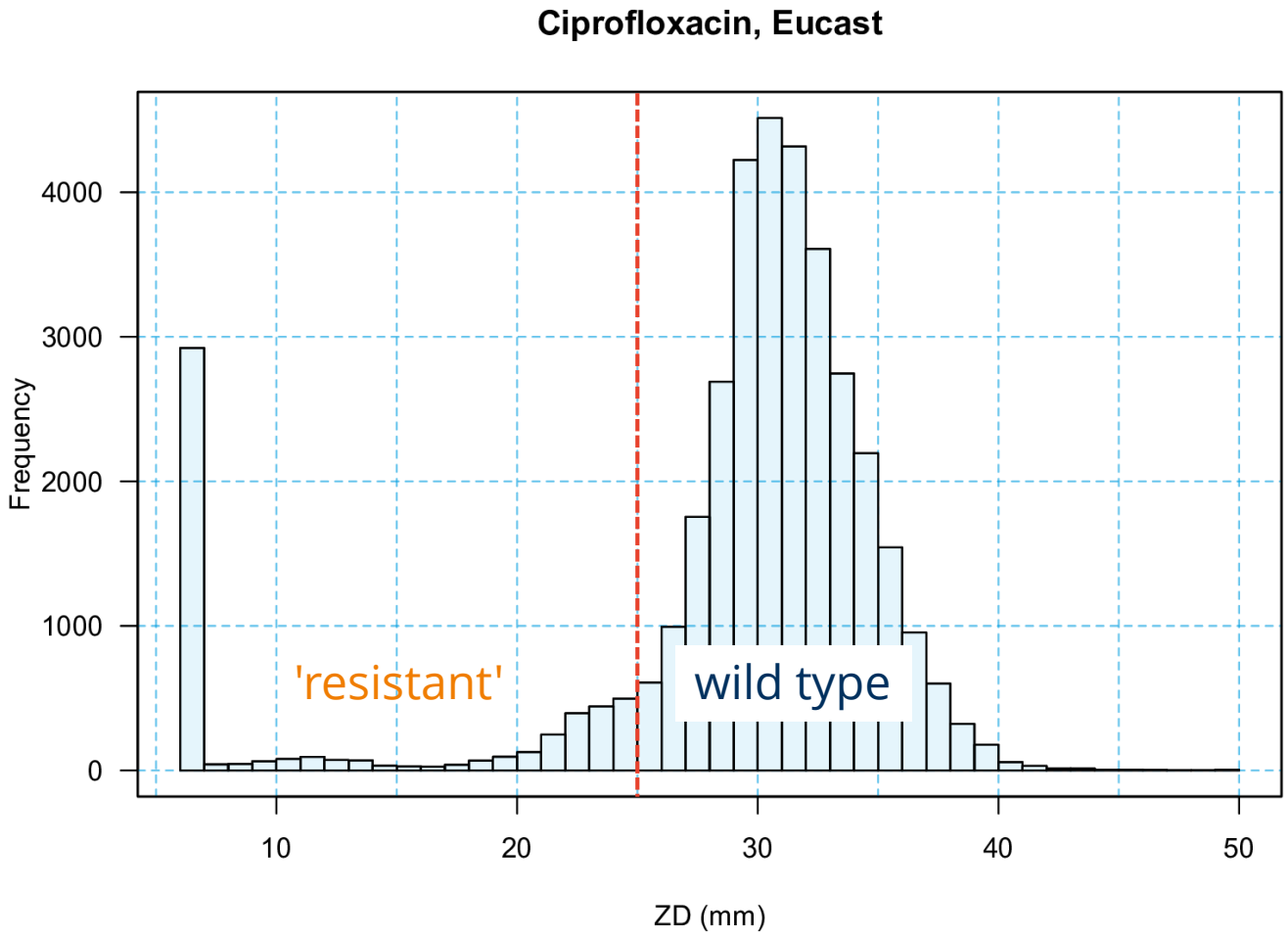


Image:
Ioannis Kampouris, Institute of Hydrobiology
Standard: EUCAST 2015-01-01

Repeat for > 1000 isolates



Zone diameter test repeated thousands of times
→ multi-modal distribution



How to separate the sub-populations?

Ecosystems, rivers, wasterwater treatment:

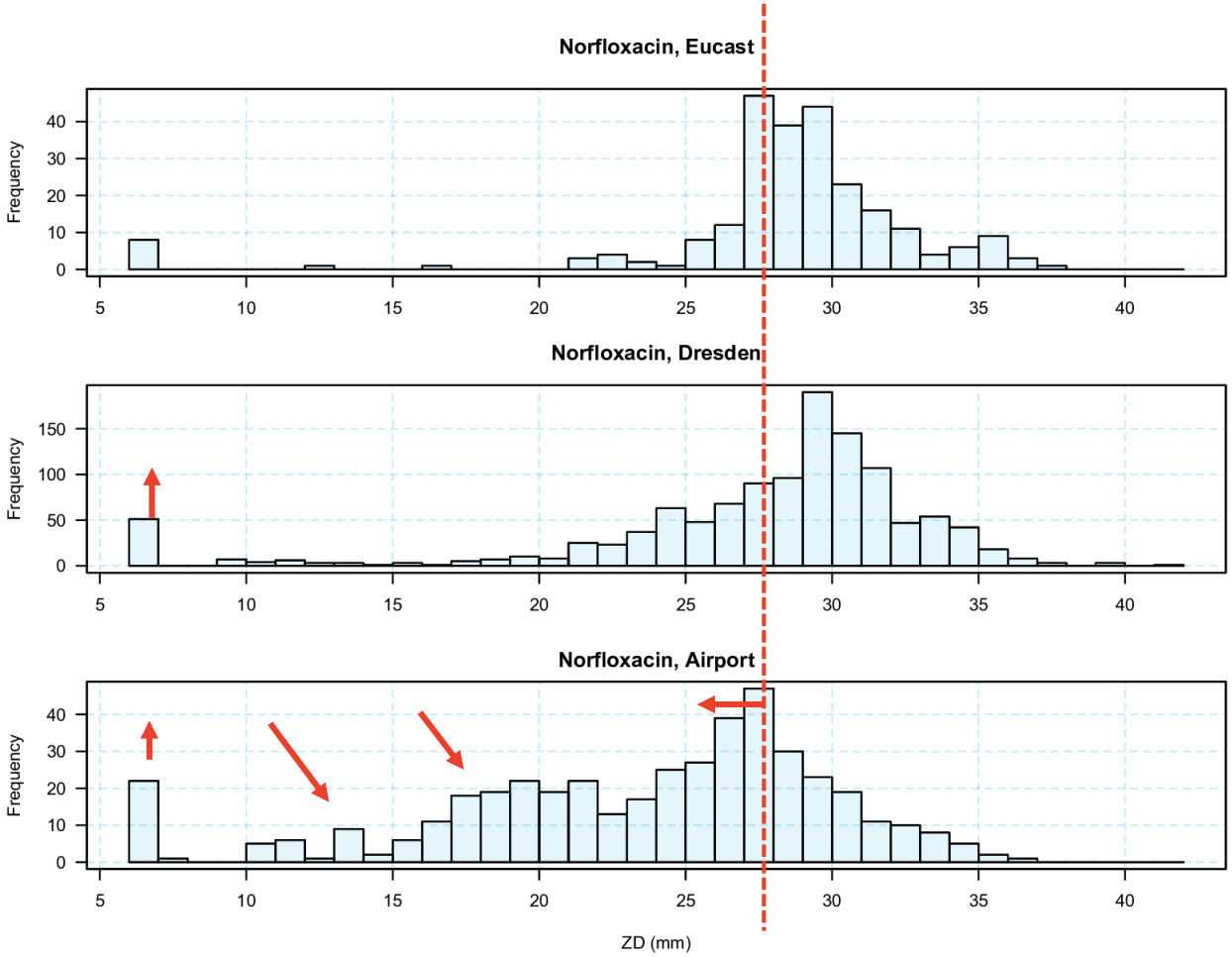
→ **Transmission, selection, gene transfer**

EUCAST
Reference data

Own data

- Icrease of 'resistant' fraction

- Sub-Populations
- Shift

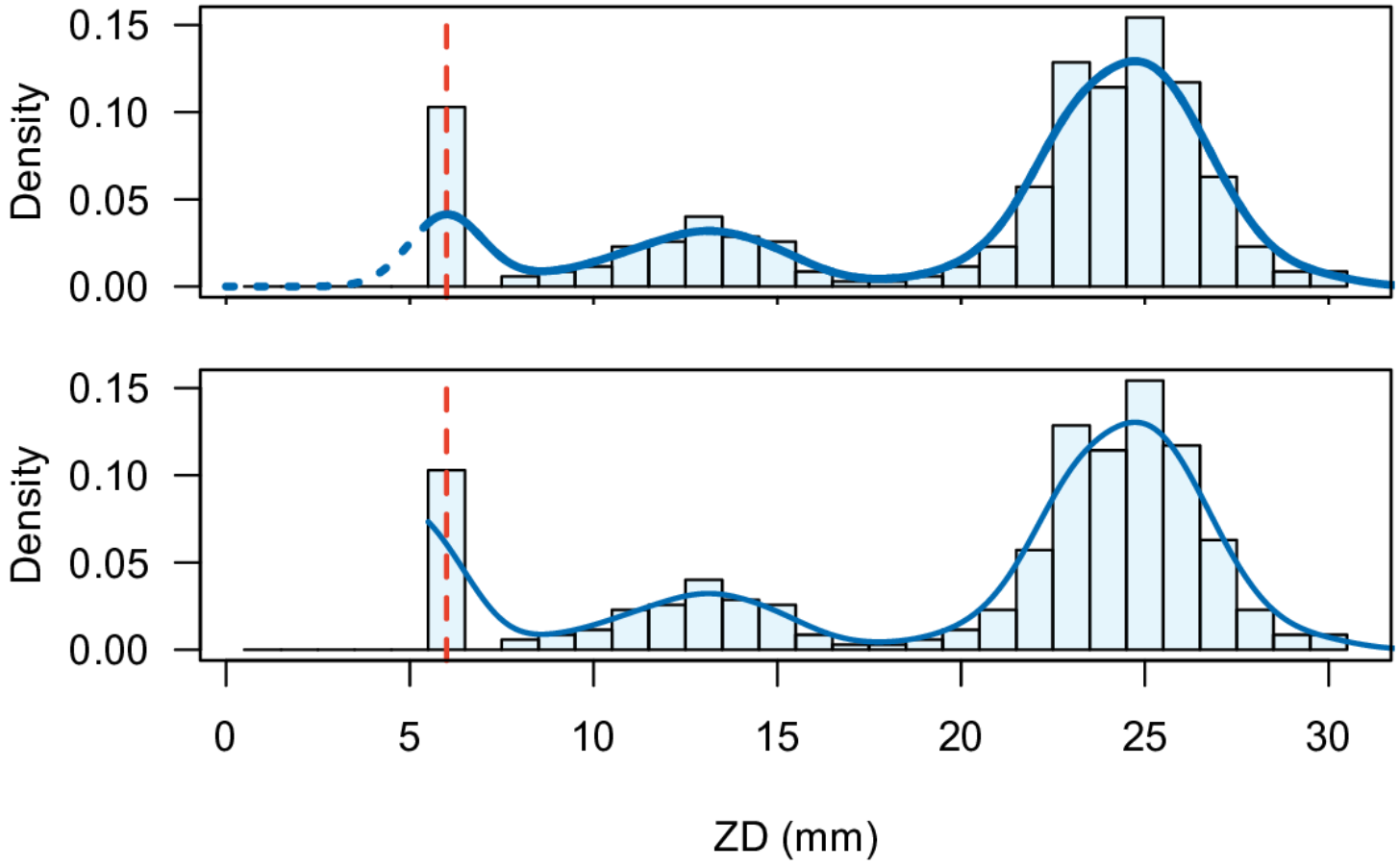


→ Reproducible indicators needed

Approach 1: Kernel density estimation

Gaussian

with boundary correction



→ allows estimation of quantiles (mode, 0.99, ...) and area

Approach 2: ECOFFinder algorithm

ECOFF

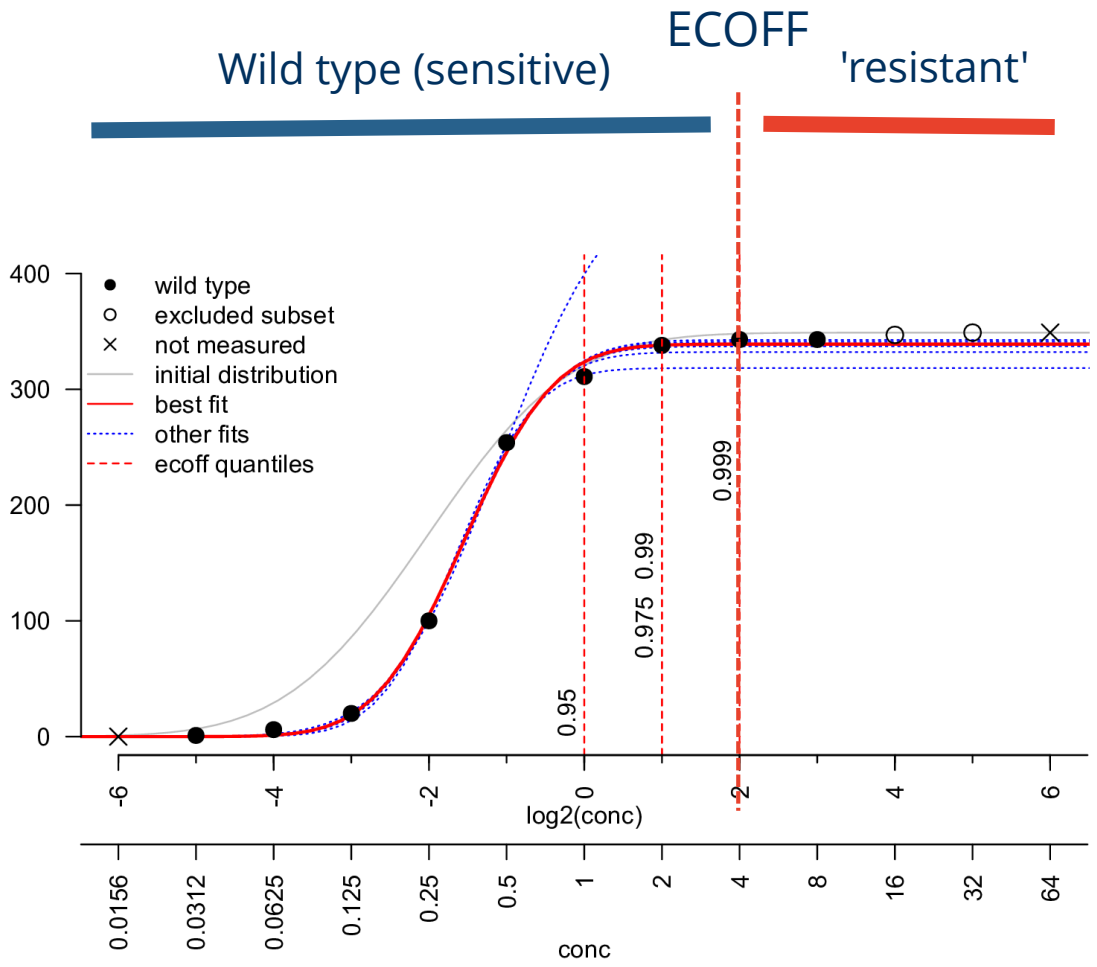
„epidemiological cut-off value“

Separates 2 groups

Software

Original: Excel VBA
official EUCAST tool
(Turnidge et al. 2006)

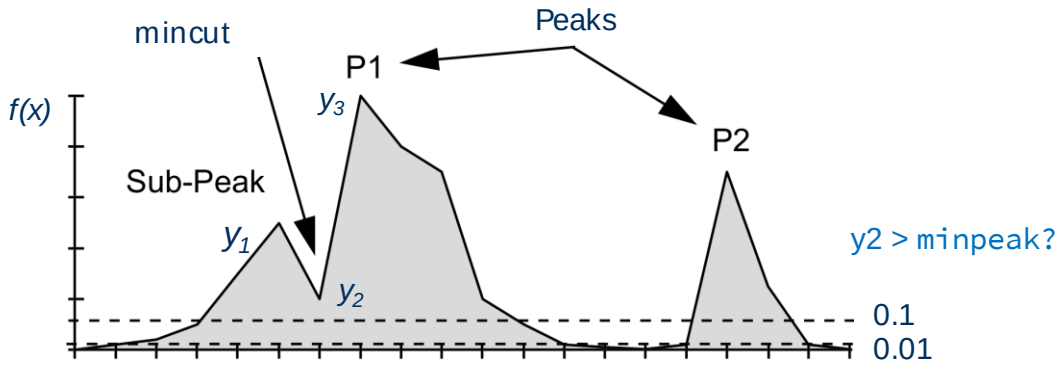
R/Shiny
package antibioticR



https://weblab.hydro.tu-dresden.de/ecoffinder/

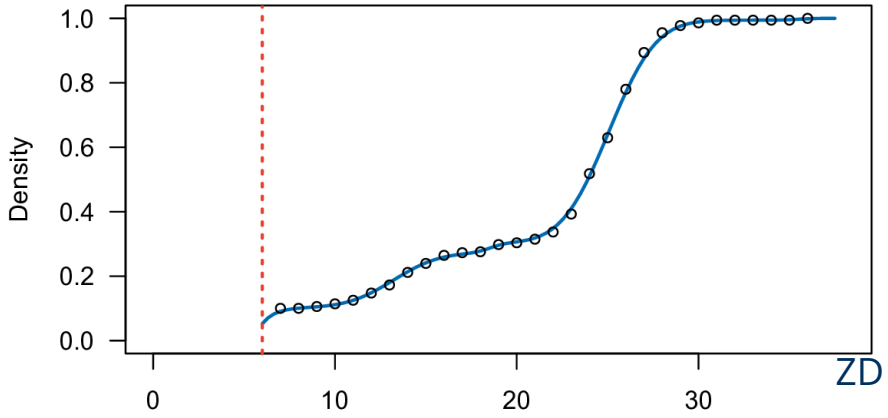
Approach 3: Fit the complete mixture distribution

Step 1:
peak hunting algorithm



Step 2:
Maximum likelihood estimation
for binned data
(personal thanks to Brian Ripley)

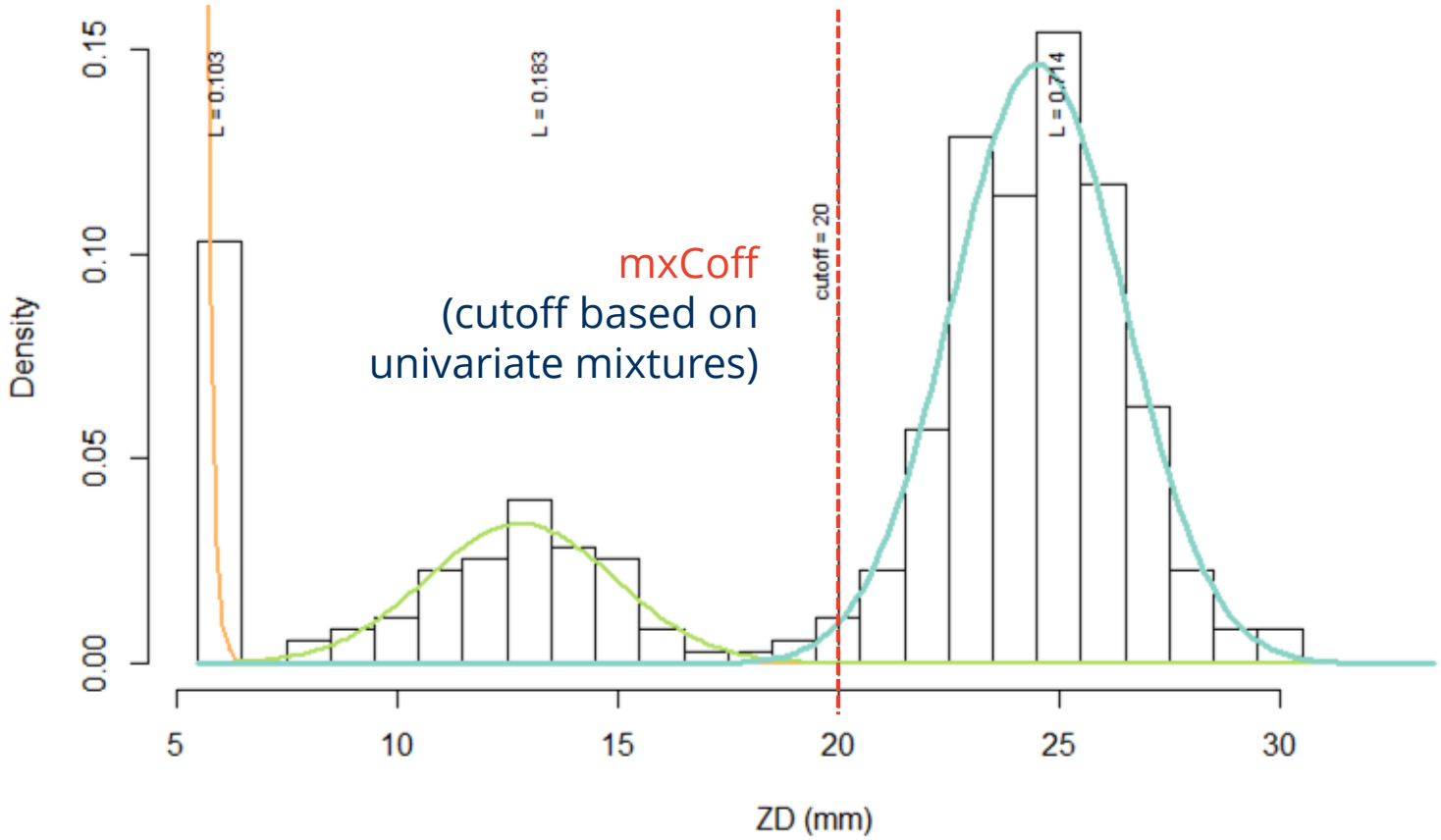
Leftmost component can be exponential,
all others normal distributions



en, nn, enn, nnn, ennn, ..., ennnnn

Result

Univariate mixture with overlapping components
Quantiles of all distribution components
Plotting functions

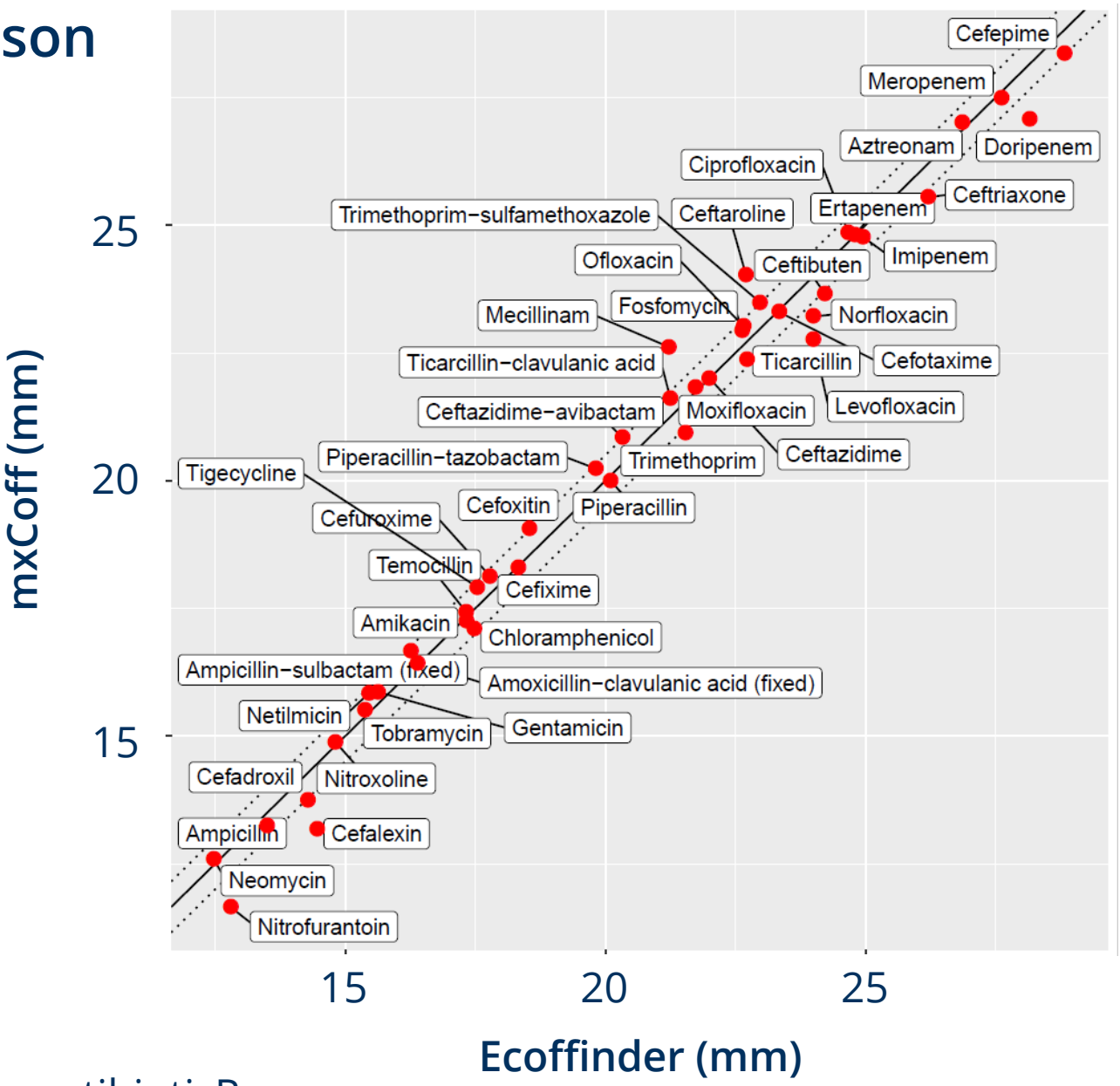


ZD distribution with resistant (orange), intermediate (green) and wild-type sub-population (blue), L = proportions of the components, cutoff = 1% quantile of the wild type

Method comparison

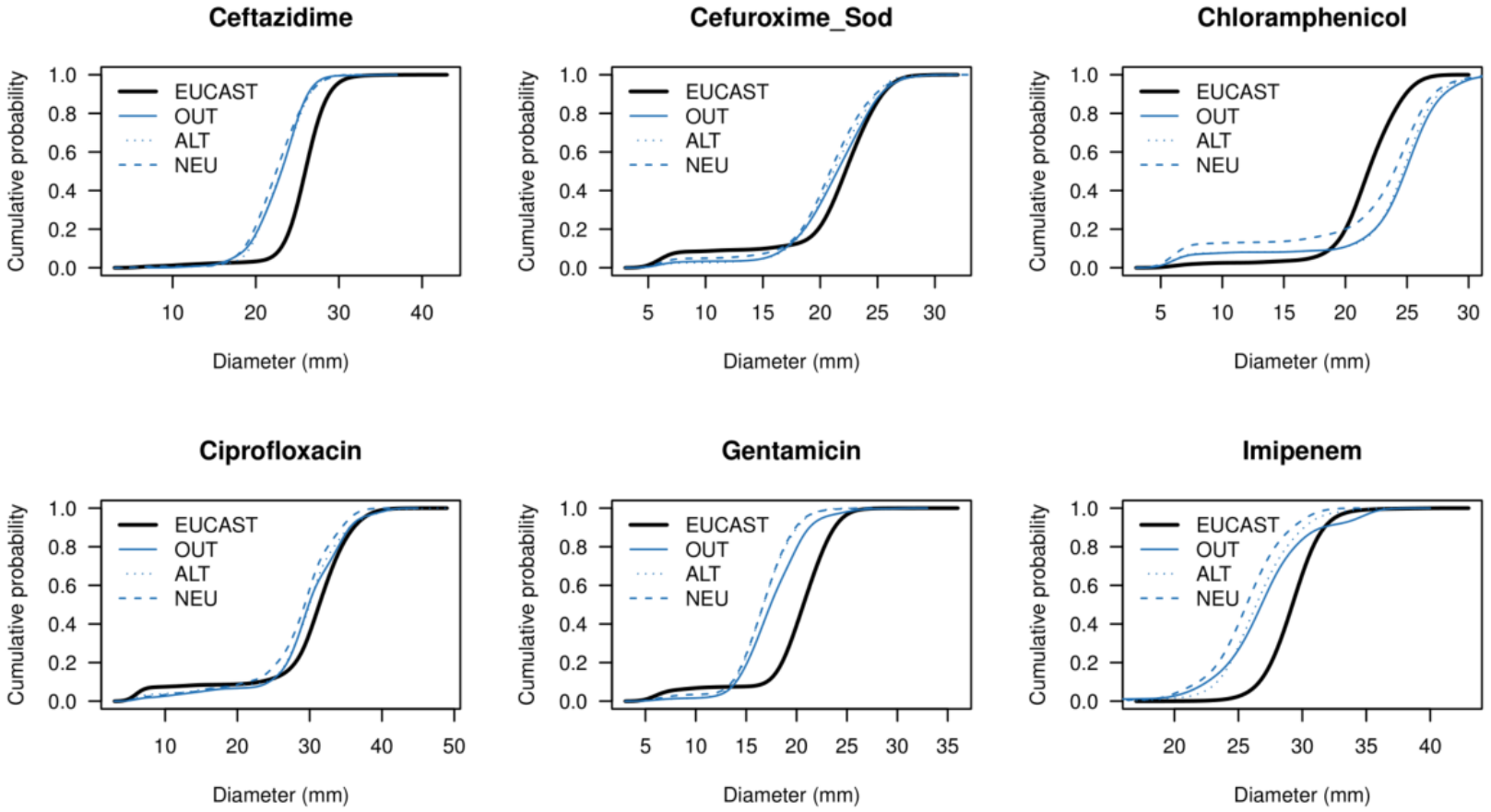
Own method

- Automatic
- Scriptable
- All distribution components



Both methods available in antibioticR

Comparison between own data from a sewer system with EUCAST reference data from clinical populations



Hypothesis, that the wild type of bacteria in a sewer system shifted to higher resistance with repect to common antibiotics.

(E. coli, Sewer System of Dresden, Germany, Data: Project antiResist)

Questions?

https://github.com/tpetzoldt/**antibioticR**

https://weblab.hydro.tu-dresden.de/ecoffinder/