

Programming issues in automated resistance testing devices can falsely increase carbapenem non-susceptibility rates in *Morganellaceae*

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BACKGROUND / AIM

- ❖ Carbapenem resistance rates in Enterobacterales are of substantial interest in national and international surveillance databases.
- ❖ In *Morganellaceae*, imipenem shows limited activity [1]. In 2019, EUCAST introduced "susceptible, increased exposure" (I) instead of "susceptible, standard dosing regimen" (S) and enlarged "I"-zones for some antibiotics and organisms, including imipenem in *Morganellaceae*, whereas meropenem breakpoints remained unchanged [2].
- ❖ In 2020, EUCAST completely removed category "S" for imipenem in *Morganellaceae*.
- ❖ Meropenem non-susceptibility rates in *Morganellaceae* increased from 0.7% (2018) to 2.4% (2019) and 6.3% (2020) in the ANRESIS database, which was not observed in other Enterobacterales.
- In this study, we investigated potential factors causing this increase.

MATERIAL & METHODS

- ❖ Meropenem susceptibility data of *Morganellaceae* isolates from 2017 to 2020 were extracted from the ANRESIS database.
- ❖ Data were inspected for outliers considering species, country areas, laboratories and susceptibility testing methods.
- ❖ For the most frequently reported genus, susceptibility data were inspected more closely to avoid selection bias due to low sample sizes.

ISOLATES

- ❖ A total of 57761 *Morganellaceae* isolates of 34 laboratories were investigated.
- ❖ *Proteus* species was most frequently isolated (76.9%) with *P. mirabilis* as the most common species (61.1%), followed by *Morganella morganii* (19.9%) and *Providencia* species (3.1%).

REFERENCES

1. Reviewed in Girlich, D. et al., Front. Microbiol. 2020. 11:256.
2. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. http://www.eucast.org/clinical_breakpoints/.

DO SUSCEPTIBILITY DATA DIFFER BETWEEN LABORATORIES?

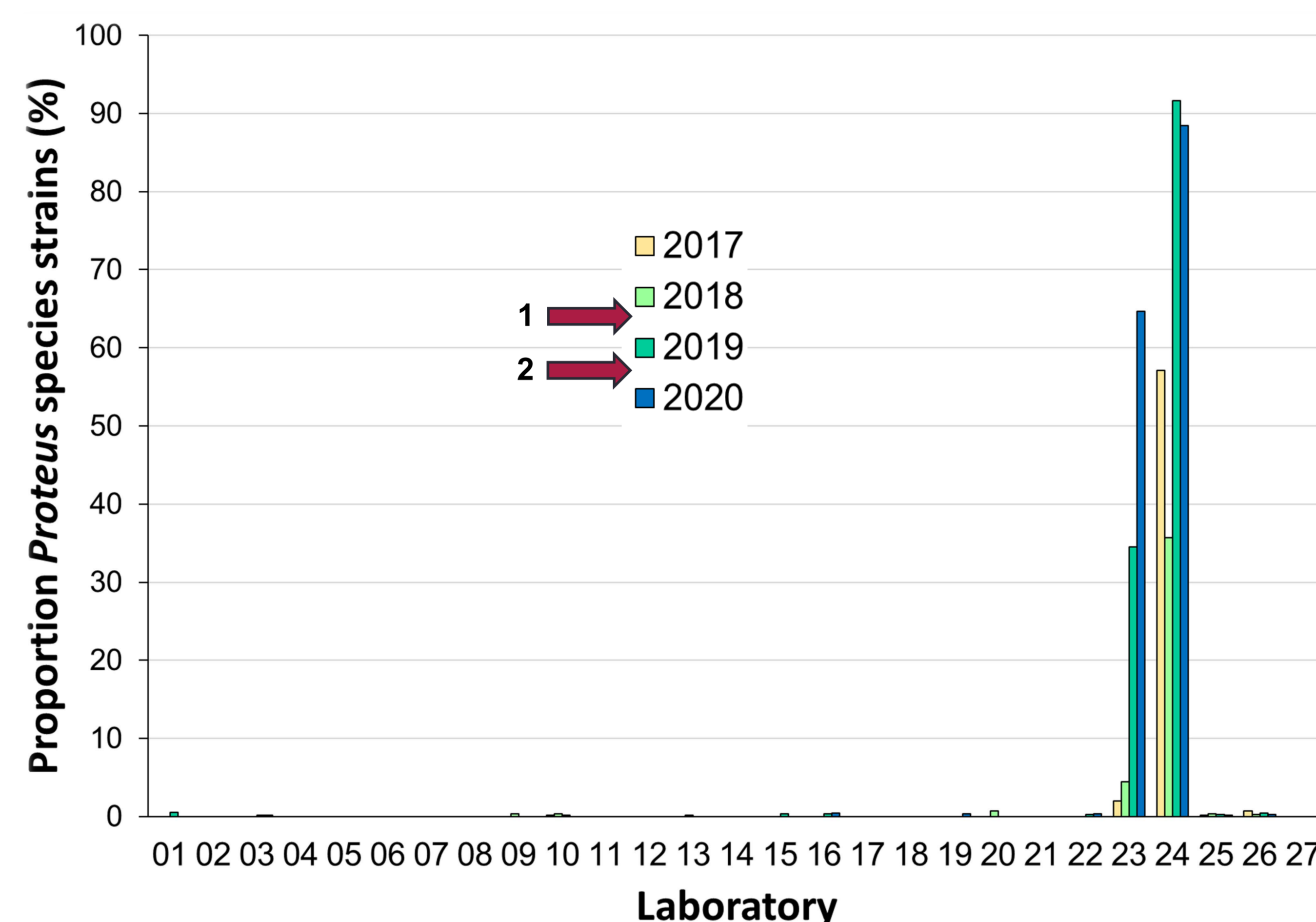


Figure 1. Percentage of *Proteus* species strains classified as meropenem "I" (susceptible, increased exposure) or "R" (resistant) by laboratories reporting a minimum of 20 isolates/year to the ANRESIS database. Arrows 1 and 2 indicate introduction of changes in imipenem breakpoints by EUCAST in January 2019 and 2020, respectively.

- Two laboratories showed a pronounced increase in meropenem "I" or "R" classified *Proteus* species isolates in 2019 and 2020.
- Both laboratories used Vitek automated antibiotic susceptibility testing. Inspection of breakpoint tables used by Vitek revealed imipenem, instead of meropenem breakpoints were implemented for meropenem susceptibility categorisation.
- Causes of relatively high rates of meropenem "I" or "R" isolates in 2017 and 2018 reported by laboratory 24 remained unclear.

DO ERRONEUS BREAKPOINTS AFFECT MEROPENEM DATA?

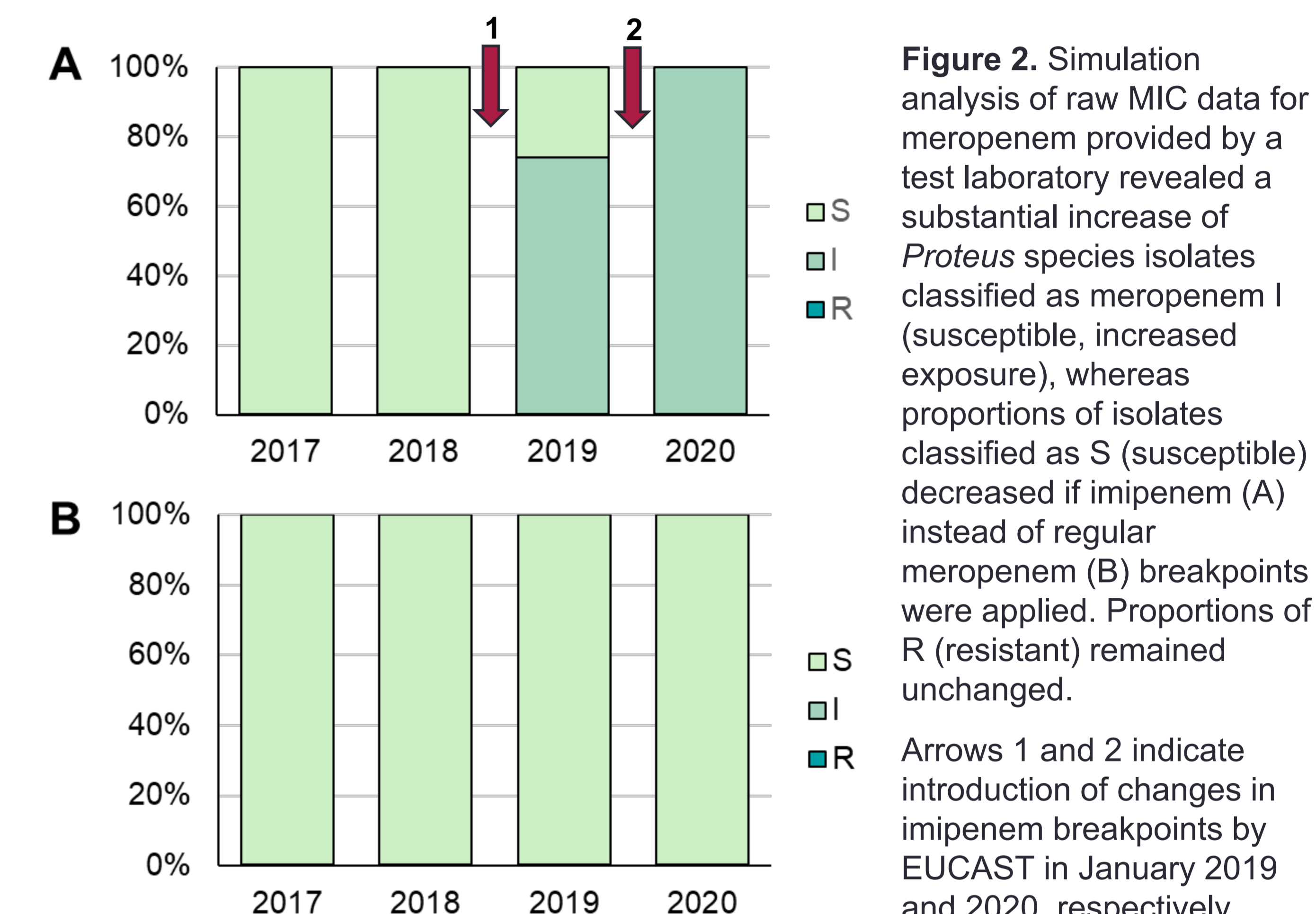


Figure 2. Simulation analysis of raw MIC data for meropenem provided by a test laboratory revealed a substantial increase of *Proteus* species isolates classified as meropenem I (susceptible, increased exposure), whereas proportions of isolates classified as S (susceptible) decreased if imipenem (A) instead of regular meropenem (B) breakpoints were applied. Proportions of R (resistant) remained unchanged. Arrows 1 and 2 indicate introduction of changes in imipenem breakpoints by EUCAST in January 2019 and 2020, respectively.

- If "I" is interpreted as non-susceptible, resistance rates will increase substantially.
- Isolates falsely categorised "I" can lead to therapies with unnecessarily increased dosage.

CONCLUSION

- ❖ Isolates categorised meropenem "I" (susceptible, increased exposure) due to programming issues in automated testing devices may cause unnecessary higher dosage treatments and substantial errors in resistance surveillance statistics, if non-susceptibility rates (including "I") are reported.
- ❖ Caution should be used, in general, when operating automated susceptibility testing systems with black box like in-built breakpoint tables and especially after implementing revised breakpoint guidelines.