

# Antimicrobial Breakpoints- An Area for Clarification

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## Introduction

•The breakpoint Minimum Inhibitory Concentration (MIC) for an antimicrobial agent and a bacterial pathogen has traditionally been the threshold above which the pathogen is unlikely to respond to treatment with the specified drug.

•Breakpoints are becoming contentious because of differing and incompatible demands being placed on what has until now been a single parameter.

•In particular, the needs of the clinician and the epidemiologist are different.

## What the clinician needs

•A clinician choosing an antimicrobial agent to treat an animal suffering from a specific infection needs to know that the compound chosen should be effective against the pathogen involved.

•The MIC is ideally obtained for the pathogen *in vitro*, and this is compared with the pre-determined clinical breakpoint to determine whether the organism is likely to respond *in vivo*.

•The clinical breakpoint should have taken account of the behaviour of the drug following administration, and assumes that if an isolate shows an MIC below the allocated clinical breakpoint for the pathogen, then a clinical response should be obtained if the drug is dosed as recommended.

## What the epidemiologist needs

•The MIC distribution pattern often enables identification of two or more populations of microorganisms that can be differentiated by the presence or absence of resistance factors. This is illustrated in Fig 1.

•The wild-type (WT) “susceptible” subpopulation is assumed to show the antibiogram profile before any resistance has developed or has been acquired, and its distribution can be differentiated clearly from the “resistant” subpopulation.

•A dividing or cut-off MIC can thus be established to indicate the MIC above which the pathogen has some reduction in susceptibility. This point will normally be placed close to the WT population, and tend to be lower than if used for clinical prediction. In that case, taking the hypothetical illustration in Fig 1, an isolate with an MIC of, say 4 mg/L may yet be expected to respond clinically.

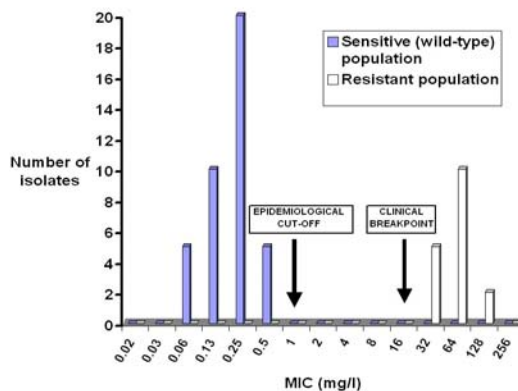


Fig 1. Illustrative distribution showing wild (susceptible) and resistant bacterial sub-populations

## The need for clear terminology

•The objective of a single universal breakpoint to achieve both (i) detection of the early stages of resistance development among a bacterial population and (ii) predicting outcome of therapy, will continue to fail in many circumstances, and will be a source of confusion among clinicians, clinical microbiologists and regulators.

•MIC breakpoints for clinical purposes are defined against a background of data, including therapeutic indications, clinical response data, dosing schedules, pharmacokinetics and pharmacodynamics.

•MIC cut-off points for epidemiological studies can be determined by suitable surveillance studies, but may be separate from, and lower than, clinical breakpoints

## Conclusions

•The term “breakpoint” should be retained solely for clinical breakpoints and be distinguished from “epidemiological cut-off point”, where the latter shows that a change away from the wild-type population may have occurred in a subpopulation. This terminology is used by European Committee on Antimicrobial Sensitivity Testing (EUCAST, Kahlmeter *et al* 2003).

•Universal adoption of such terminology would enable clinicians to choose appropriate treatment based on information relevant to the individual patient, yet would recognise that epidemiologists need to be aware of small changes in bacterial sensitivity which may indicate emerging resistance, and allow for appropriate control measures to be considered.

## Reference

Kahlmeter, G. *et al.*, 2003. European harmonisation of MIC breakpoints for antimicrobial susceptibility testing of bacteria. *Journal of Antimicrobial Chemotherapy*, 52, 145-148.