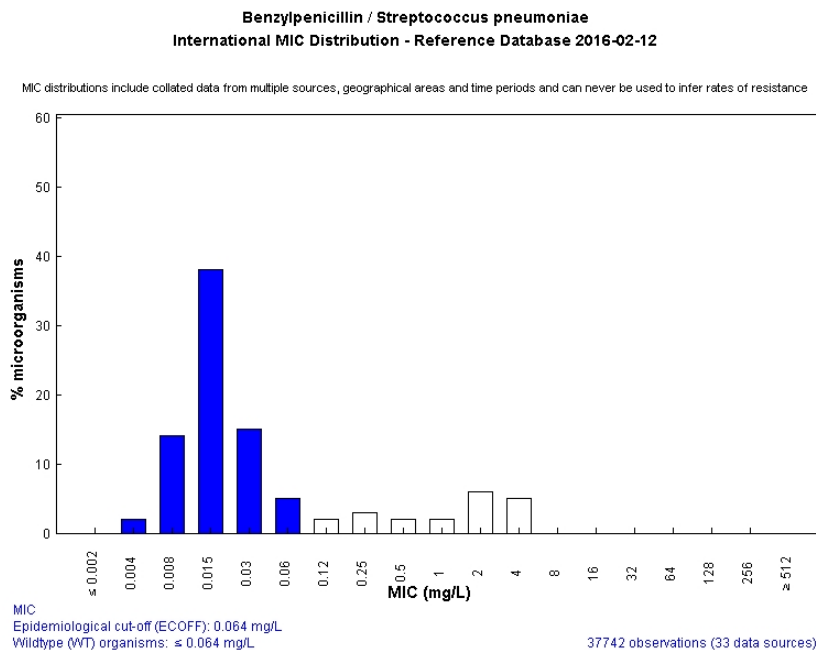


## Implications of breakpoints splitting the wild type and/or resistant populations

A microorganism is defined as wild type for a species by the absence of phenotypically detectable acquired resistance mechanisms to the agent in question. The MIC or zone diameter distribution for a collection of organisms devoid of phenotypically detectable acquired resistance is described as a wild type MIC or zone diameter distribution. The EUCAST MIC and zone diameter distribution website includes aggregated distributions for each species-agent combination. The constituent MIC distributions are aggregated only if they meet defined standards. A typical wild type MIC distribution is shown as blue bars in figure 1.

Figure 1: Benzylpenicillin MIC distributions for *Streptococcus pneumoniae*.



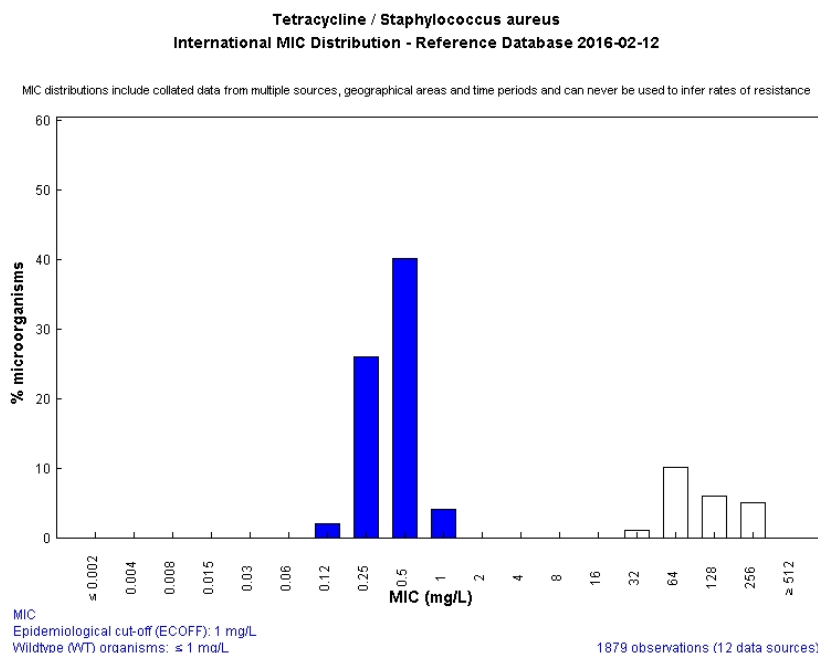
The range of MICs within the wild type is largely a consequence of technical variation within and between laboratories, with biological differences in susceptibility among isolates playing a lesser part. It is normal for the wild type MIC distribution to span 3-5 two-fold dilution steps.

Whenever possible, EUCAST avoids splitting the wild type when setting breakpoints because the technical variation within the wild type would result in susceptibility testing results being inherently non-reproducible. The closer the breakpoint is to the wild type median MIC, the greater the detrimental effect on reproducibility.

MIC distributions for resistant organisms may form a similar distribution to the wild type, but at higher MIC values, as for tetracycline with *Staphylococcus aureus* (figure 2), but

more commonly a variety of resistance mechanisms and different expression of resistance result in a spread of MIC values for resistant isolates as seen for benzylpenicillin and *Streptococcus pneumoniae* (figure 1).

Figure 2: Tetracycline MIC distributions for *Staphylococcus aureus*.



If PK-PD considerations indicate that breakpoints can clearly distinguish wild type and resistant populations, splitting the resistant population can be avoided, as with tetracycline and *S. aureus* (figure 2). However, if the MIC distribution for organisms with acquired resistance mechanisms is widely spread, particularly if it is closely adjacent to (figures 1, 3) or even overlapping the wild type (figure 4), it will not be possible to avoid overlap between the wild type distribution and low level resistant organisms or splitting the population with acquired resistance mechanisms.

Figure 3: Ciprofloxacin MIC distributions for *Klebsiella pneumoniae*

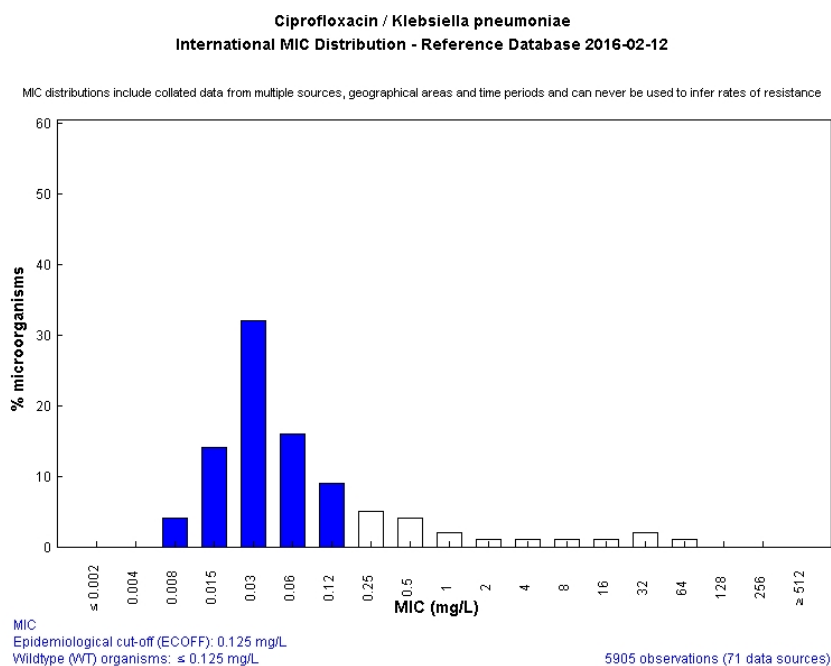
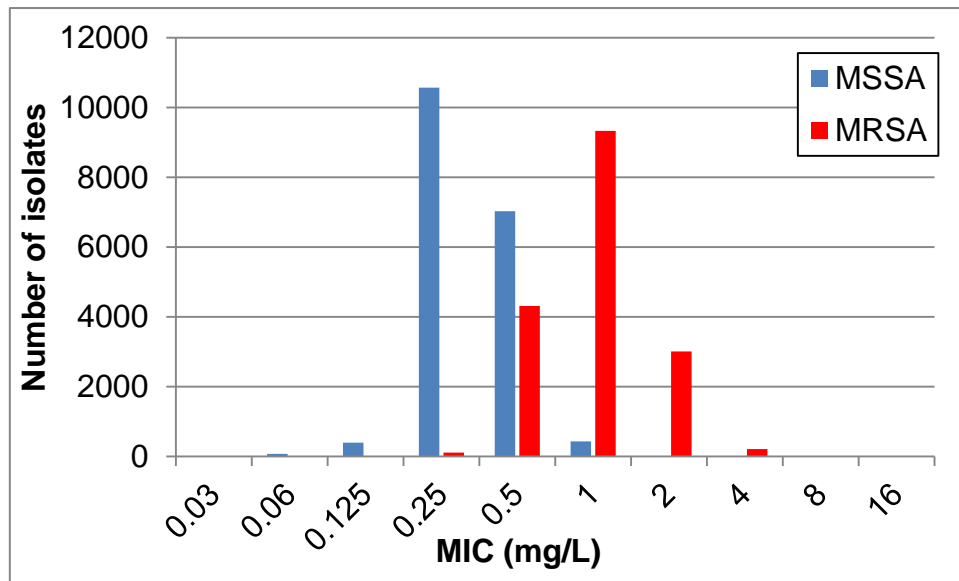


Figure 4: Ceftobiprole MIC distributions for methicillin resistant (MRSA) and methicillin susceptible (MSSA) *S. aureus*.



On occasion, mostly in local settings such as a ward or a hospital, a clonal outbreak will result in a large proportion of resistant isolates with the same MIC. With the expected technical variation of median  $\pm$  one to two two-fold dilutions (or median  $\pm$  3 to 6 mm for zone diameters) the distribution will appear as a Gaussian distribution close to or far from (depending on the inherent MIC for the clone) the wild type distribution. It has been suggested that it is more important to avoid splitting distributions of resistant bacteria than distributions of wild type organisms, but this is not always possible. Ideally, breakpoints should not split either wild type or resistant distributions but the wild type distribution is fundamental to decisions on breakpoints for all organism-agent combinations and will take priority over splitting resistant populations. Hence, wild type distributions must always be characterized and agreed. The EUCAST MIC distribution database was developed principally to enable definition of wild type distributions and now includes more than 25000 MIC distributions from all over the world (<http://mic.eucast.org/Eucast2/>).