

## [Extended Abstract]

# Surveillance of Antimicrobial Resistance: Can we Trust the Data?

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In a majority of patients antibiotic treatment is instituted based on presumed aetiology and antibiotic susceptibility, i.e., treatment is empirical. To avoid treatment failures due to antibiotic resistance, the prescribing physician must have access to surveillance data on frequencies of resistance in pathogens, which might cause the infection to be treated. This overview will deal with some quality aspects on surveillance of antibiotic resistance. In the future similar problems are likely to emerge also for antiviral drugs and has already been seen with antiparasitic and antifungal drugs.

**Definition of antibiotic resistance.** Antibiotic resistance can be defined as (i) presence of a resistance gene, (ii) a break-points based on pharmacokinetic (pk) and pharmacodynamic (pd) properties of the antibiotic and (iii) clinical resistance, i.e. the antibiotic is likely to fail if used. Genetic resistance is of importance to detect trends in emergence of resistance. For example a strain of *Escherichia coli*, which has a minimal inhibitory concentration (MIC) of ciprofloxacin of 0.1 mg/L has undergone a mutation and harbours a resistance gene but will be classified as fully sensitive by all systems used in clinical practice. However, if the strain mutates a second time MIC will increase 4- to 16-fold and the strain will be classified as resistant.

Susceptibility classified based on the basis of pk and pd parameters is the system normally used for defining break-points by CLSI (formerly NCCLS) in USA , BSAC in the UK and other similar organisations. Normally pk parameters are well known for all antibiotics. This is not the case for pd characteristics which are incompletely studied for many antibiotics. At this stage it is clear that for  $\beta$ -lactam antibiotics (penicillins, cephalosporins and others) the pd parameter predicting efficacy of treatment is the time during which concentrations above MIC are maintained at the site of infection. With such drugs low doses given with short intervals will be more effective than large doses with long intervals. The reverse is true for antibiotics such as the aminoglycosides and the fluoroquinolones for which the peak concentration or the area under the concentration curve decide efficacy. A factor complicating definitions of break-points based on pk/pd is that doses tend to vary between countries; for example in Japan doses used are normally much lower than in Western countries

For clinicians a definition of resistance based on predicted clinical efficacy would of course be ideal. This cannot always be achieved although the methods used today tend to predict fairly well when an antibiotic can be used. They may, however, fail to predict efficacy when pk/pd parameters are affected by patient factors such as very high or very low body weight, high age and/or renal failure. Also, in some infections (mainly urinary tract ones) accumulation of drug is achieved at the site of infection and the sensitivity tests will then often underestimate the possibility to use antibiotics such as  $\beta$ -lactams and aminoglycosides.

**Quality of antibiotic resistance surveillances.** Some surveillance projects have been seriously flawed by methodological errors. A common one is that repeat bacterial isolates

from one and the same patient are accepted. Normally only one isolate per patient should be included. For certain species, which tend to occur in nosocomial environments, e.g. *Pseudomonas* spp., *Burkholderia* spp., *Stenotrophomonas* spp. and *Acinetobacter* spp. acceptance of multiple isolates from one and the same unit may also result in falsely high or low frequencies of resistance since strains of these species tend to colonise multiple patients in a hospital ward. Therefore surveillances should avoid including multiple isolates of one and the same strain from a hospital unit.

When selecting strains for a surveillance project it should be considered if the susceptibility situation in out-patients or in hospitalised patients should be studied. Normally resistance is far more common in the hospital environment than in an out-patient setting. Differences may also exist between adults and children. In *Streptococcus pneumoniae* resistance tends to be more common in pre-school children than in adults. Extrapolation of data generated in children may therefore result in prediction of too high risk of resistance.

A common way of designing surveillance studies is to include consecutive strains isolated from samples sent by clinicians to a diagnostic laboratory. One should then be aware of the fact that in most countries bacterial cultures are not routinely taken from patients with common infections. Instead clinicians tend to take cultures when there is therapeutic failure or early recurrence of an infection, resulting in exaggeration of the frequencies of resistance. Also, with this study design there is a high likelihood that strains from out-patients and from hospital units will be mixed.

For objective assessment of a surveillance project it is of importance to know if it is sponsored by a pharmaceutical company. In the information about an antibiotic it is essential to provide data on its activity compared to those of the competitors. However by selecting the patients and the type of health care units from which bacterial strains are obtained it is possible to generate results, which show very high or very low frequencies of resistance. Extreme examples are patients in intensive care units who tend to harbour very resistant organisms and young females with sporadic uncomplicated urinary tract infections who normally have highly susceptible strains.

In this context it is also of major importance how resistance (R) is defined. In most cases strains studied are classified as susceptible (S), intermediately susceptible (I) or R. Often  $R = R + I$ , which means that frequencies of R will increase. For pneumococci and penicillin resistance the frequency of strains classified as R to penicillin increases dramatically and as a result other antibiotics tend to be chosen although a  $\beta$ -lactam might have been a better choice..

**Denominators.** Resistance is normally expressed as percent of something. Most often the denominator used is the number of strains tested. It would be much better if the denominator was more clinically relevant. In the EU programme for surveillance of antibiotic resistance, EARSS, only bacterial strains isolated from blood or cerebrospinal fluid are accepted. That means that the denominator is strains from patients with proven life-threatening infections, something which markedly increases the impact of the results generated.

A study which has not yet been performed but which would add important information is one in which all patients with a defined infection, e.g. otitis media, are sampled during a defined period irrespective of the severity of the infection.

## Conclusions

The above and some other aspects on antibiotic resistance surveillances are summarised in Table I

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**Table I.** Quality issues in antibiotic resistance surveillance studies

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Issue	Impact
Was the study prospective?	Retrospective studies normally of lower quality
Were repeat isolates allowed?	Repeat isolates result in false results and should normally not be accepted
Were the patient sources defined?	Results from in- and out-patients should be given separately
Were the patients representative?	The patients from whom the isolates were obtained should be as representative for the same type of patients elsewhere
How was susceptibility tested?	Bacterial inocula should be sufficiently high Routine agar or broth dilution techniques or E-test® should be used
How was “resistance” (R) defined?	If R includes intermediately susceptible strains frequencies of resistance will be over-estimated
Were clinically relevant denominators used?	Example of a relevant parameter is “blood and cerebrospinal fluid isolates”
Who sponsored the project?	Involvement of pharmaceutical companies should be transparent and possible conflicts of interest declared

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