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Surveillance of antimicrobial consumption data: Development of an early warning system for carbapenem resistance derived from a retrospective analysis of an OXA-48 producing *K. pneumoniae* outbreak

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Background: This study describes the development of an automated surveillance system using antimicrobial consumption data for the prediction of potential emergence of carbapenem-resistant organisms. It was derived from a retrospective analysis of an intervention to contain a prolonged OXA-48 producing *K. pneumoniae* outbreak.

Methods & Materials: A time series analysis (May 2005-April 2013) was conducted around an intervention to contain an outbreak (Jan 2008-April 2010) of an OXA-48-producing *K. pneumoniae* in the renal unit of a West London teaching hospital. The intervention focused on reinforcement of the renal antimicrobial policy and the decrease of carbapenem usage, as part of the overall stewardship strategy. Three mechanisms were promoted: awareness, education and feedback. A multivariate ARIMA model was developed utilising meropenem consumption data (defined daily dose per 100 occupied bed-days; DDD/100OBD) as a predictor of the incidence of OXA-48-producing organisms.

Results: Meropenem usage was increasing by 7.13DDD/100OBD/year (95%CI 3.46-10.80; $p < 0.001$) from 6.30DDD/100OBD/year prior to the intervention but decreased steadily for 4 years thereafter. The changes in slope of the time series were -10.18DDD/100OBD/year (95% CI, -16.63-3.73). Analysis of consumption of other gram negative antimicrobials was also undertaken and showed a significant increase in amikacin usage post-intervention from 0.56 to 4.07DDD/100OBD/year (slope = +0.83; 95%CI, 0.13-1.53). The incidence of OXA-48-producing organisms was significantly increasing by 2.2 cases per year pre-intervention, and decreased thereafter. Meropenem usage at lag-1 year was highly correlated to the incidence of OXA-48-producing organisms ($r = 0.74$, pvalue = 0.04) and was included as a predictor within the ARIMA model for forecasting the incidence of resistant isolates.

Conclusion: Our findings support an association between reinforcement of a specific antimicrobial policy and both meropenem usage, and a decreasing incidence of OXA-48-producing *K. pneumoniae*. Meropenem usage at lag-1 year was found to be a good predictor of the incidence of OXA-48-producing *K. pneumoniae* in the ARIMA model, although we need to remain cautious about the causality. This prediction model requires further development but shows early signs of how close surveillance of antimicrobial consumption can act as a warning indicator to anticipate potential outbreaks of drug resistance organisms and should be considered as part of healthcare organisations' antimicrobial stewardship programmes.

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Detection of antibiotic resistances of *Mycobacterium tuberculosis* on DNA microarrays

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Background: The infection with the bacterium *Mycobacterium tuberculosis* is one of the biggest challenges of healthcare systems, especially in South Africa or India. Associated with the extensive use of antibiotics the spread of resistances is promoted. Due to this a reliable and sensitive detection of infection and classification of resistances are needed.

Methods & Materials: DNA samples of South-African patients, provided by the Stellenbosch University, are amplified via isothermal amplification and hybridized on a DNA microarray. The array consists of specific sequences of TB and genes involved in developing resistances against known drugs. First of all, genes leading to resistances for first line drugs lie in the focus. The immobilization of the sequences is done with a non-contact spotter that requires low amount of material. Finally a fluorescent read-out is done for a qualitative statement of infection and resistances. Advantages of this assay are e.g. a constant temperature for the isothermal amplification, avoiding heating steps and the sensitive fluorescent detection of the hybridized DNA.

Results: It is possible to detect low amounts of TB-DNA using isothermal amplification coupled with a DNA microarray. The quantity of DNA in a typical saliva or blood sample is more than sufficient. Furthermore major gene mutations responsible for resistances against first line drugs are detectable.

Conclusion: The presented method depicts a novel way to diagnose TB infection and allows a prediction about resistances to the most used antibiotics, i.e. all first line drugs. As a perspective the detection of further antibiotic resistances should be added to the assay. The explained assay has the potential to give rise to new diagnostic tools for detecting TB infection and drug resistances.

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