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Interventions to control MRSA: high time for time-series analysis?

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Time-series methods are useful in quasi-experimental study designs in which rates of antibiotic-resistant infections are ascertained before and after an intervention. However, uncertainties remain regarding the use of time-series analysis as an appropriate research methodology for analysing the effect of infection control interventions and antibiotic policies on the epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA). In particular, there is still a substantial gap in our understanding of what actually happens to MRSA incidence when a planned intervention is made on use of one or more antibiotic drug classes.

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In 1960, Berntsen and McDermott[1] published a report demonstrating that 'The transmissibility of the staphylococci, principally drug-resistant staphylococci, was considerably increased among patients receiving therapy with an antimicrobial drug [tetracycline]'. A few years later, Ehrenkranz[2] provided further evidence that the 'spread of tetracycline-resistant *Staphylococcus aureus* in man is enhanced by tetracycline treatment of the carrier'. Since the publication of these landmark studies, a multitude of observational studies using different study designs have confirmed the effect of antibiotic selection pressure on acquisition and transmission of methicillin-resistant *S. aureus* (MRSA), especially in the healthcare setting.[3–5] Taken together, the evidence generated by these studies fulfils most of the criteria outlined by McGowan[6] for a causal relationship between antibiotic use and MRSA rates: consistent associations, dose–effect relationships, concomitant variations (changes in antimicrobial use lead to parallel changes in incidence of MRSA), and biological plausibility based on experimental models.

Many antibiotic classes used for common infectious conditions are now ineffective against pandemic healthcare-associated MRSA strains. Consequently, antibiotic treatment can have different negative ecological effects on MRSA acquisition, persistence and transmission: (i) eradication of the susceptible skin flora including coagulase-negative staphylococci will increase the likelihood of MRSA acquisition, especially in healthcare settings with endemic MRSA; (ii) antibiotics directly select for pre-existing MRSA in carriers and enhance the likelihood of transmission; (iii) antibiotic selection pressure may transform low-level carriers to persistent high spreaders of MRSA; and (iv) antibiotics active against methicillin-susceptible *S. aureus* (MSSA) may convert MSSA

carriers to non-carriers, indirectly promoting the spread of MRSA within the population.[7] Furthermore, at the level of the individual host, antibiotic exposure may increase the risk of endogenous MRSA infection related to changes in colonization resistance and bacterial virulence.[8]

Despite this strong evidence for a causal link between antibiotic selection pressure and MRSA incidence, surprisingly few intervention studies have attempted to decrease MRSA rates by active antibiotic policies.[9–13] Table 1 summarizes selected intervention studies published within the last 2 years, most of them uncontrolled and of rather weak levels of evidence. The intervention effects were not unidirectional, since several investigations did not observe an impact of antibiotic control interventions on MRSA rates.[13,14] As a further important limitation, the majority of these studies did not take into account the added effect of pre-existing or newly introduced infection control measures, such as active screening cultures or compliance with standard precautions and hand hygiene guidelines. Not surprisingly, a Cochrane review published in 2005 did not present strong evidence to support MRSA control by antibiotic stewardship interventions.[15]

In this issue, two articles from Ireland and Switzerland report interesting findings on the combined effect of antibiotic use and infection control interventions on MRSA rates in their hospitals. Although these two study groups were not aware of each other's analyses, they observed similar findings by using comparable multivariate time-series models. Aldeyab *et al.*[16] explained 79% of the variance in monthly MRSA incidence by practices related to antibiotic use and infection control practices, including active screening cultures and use of alcohol-

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Table 1. Recently published intervention studies to decrease MRSA rates by active antibiotic policies

Reference	Country	Design	Interventions	Main results/outcome
Fowler et al.[13]	UK	interrupted time-series	'narrow-spectrum' antibiotic policy plus audits and feedback of antibiotic usage	decrease in C. difficile incidence, stable MRSA rates
Madaras-Kelly et al.[12]	USA	interrupted time-series	computer-assisted intervention to limit the use of fluoroquinolones	lower nosocomial MRSA infection rate
Bosso and Mauldin[11]	USA	interrupted time-series	changes in the hospital's fluoroquinolone formulary	substitution of gatifloxacin for levofloxacin reversed the upward trend in MRSA isolation rate
Apisarnthanarak et al.[10]	Thailand	uncontrolled before–after study	education, antibiotic-control program	significant reduction in the incidence of MRSA infections
Charbonneau et al.[9]	France	interrupted time-series	hospital-wide fluoroquinolone restriction	significant downward trend in observed monthly rates of clinical MRSA isolates

MRSA, methicillin-resistant *Staphylococcus aureus*.

containing wipes and hand rubs. Vernaz et al.[17] explained 57% of the MRSA variance over time by analysing data on antibiotic consumption, MRSA colonization pressure and alcohol-based hand rubs. Interestingly, both studies found evidence of a role of the usual suspects in driving MRSA acquisition and transmission: fluoroquinolones, macrolides and broad-spectrum cephalosporins. However, except for fluoroquinolones (antibiotic effect delayed for 1 month), the lag times between antibiotic use and changes in MRSA rates varied between 1 and 5 months. Limitations of the study by Vernaz et al.[17] were the lack of detailed data on the number of admission cultures, whereas Aldeyab et al.[16] were not able to include monthly data on the use of alcohol-based hand rubs.

As in any good research, these studies are thought-provoking and merit further discussion. Traditional epidemiological studies of resistant organisms examine individual patient level associations between antibiotic use and colonization or infection with resistant organisms. In contrast, time-series methods rely on aggregated, ecological level data. In the case of transmissible diseases, this avoids the problem of erroneously assuming independence of events and may also mitigate confounding. Time-series methods are particularly useful in quasi-experimental study designs in which infection rates have been ascertained before and after an intervention.[18] The interventions implemented in these two studies related to infection control practices but not to antibiotic use. Thus, the analysis of antibiotic use and MRSA incidence relied on 'natural' variation in antimicrobial use. However, because the a priori hypotheses are less well-specified compared with the situation of a defined intervention, there may be a problem of multiple statistical hypothesis testing. The fitted regression coefficients are also not easily interpreted, in part because they are not translatable into familiar measures of relative risk. As described above, there is still a substantial gap in our understanding of what actually happens to MRSA incidence when an intervention is made on the use of one or more antibiotic drug classes.

Further studies are also required to better understand the impact of interventions such as active surveillance cultures. Aldeyab et al.[16] suggest that active surveillance cultures decreased MRSA incidence, in line with another recently published time-series analysis.[19] However, two recent high-quality studies did not suggest that universal rapid screening was effective in reducing MRSA acquisition and infection.[20,21] Thus, more research is required to establish whether and for which type of patients and settings MRSA screening offers more benefit than other general preventive measures. Probably, intensive promotion of alcohol-based hand rubs and behavioural change interventions represent a more cost-effective approach compared with universal screening policies.[22] Several time-series studies have now shown the immediate impact of increased hand hygiene compliance and the use of alcohol-based hand rubs, if properly promoted.[16,17,23–25] Clearly, as suggested by Aldeyab et al.,[16] combined interventions are most likely to be successful.

Moving forward, an emphasis on multi-institutional research is required to tackle issues of generalizability and facility-to-facility variation in baseline infection rates and hygiene practices. Advancing the use of mechanistic models to improve the interpretability and, possibly, validity, of statistical analyses of epidemiological data is also important.[26] Our ultimate goal is to understand what works to prevent and control infections due to pathogens such as MRSA and *Clostridium difficile*.

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