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Relationship between Antibiotic Consumption and *Clostridium difficile*-Associated Diarrhea: an Epidemiological Note

In a recent study, Aldeyab et al. determined the hospital-wide relationship between antimicrobial drug consumption and occurrence as well as spread of *Clostridium difficile*-associated diarrhea (CDAD) in a teaching hospital in Belfast, Northern Ireland (1). A major advantage of the methods used (time series analysis) is the establishment of a hospital-wide cause-effect relationship, with a clear direction and determination of the strength of the observed correlation.

We compared the study results reported by Aldeyab et al. with data from a 1,600-bed teaching hospital in Freiburg, Germany, and found comparable dose-response rates for the two studies (1, 4).

The dose-response relationship between antibiotic consumption and emergence of resistance was first described in 1989 by Phelps, who defined this relationship as "the percentage change in the probability of an organism being resistant following a 1% change in the level of antibiotic use" (6). In economic science, the time series analysis is used extensively for analysis of economic relationships (econometrics). In this context, the dose-response rate is termed elasticity and can easily be deduced from the coefficients estimated by time series analyses (3). In the studies conducted by Aldeyab et al., elasticity $E_{\mathrm{CDAD},q}$ is defined as

$$E_{\mathrm{CDAD},q} = \frac{\partial \mathrm{CDAD}(q)}{\partial q} \cdot \frac{q}{\mathrm{CDAD}(q)} \quad (1)$$

where CDAD(q) stands for the incidence of CDAD, which is a dependent function of the consumption of q. The variable q represents the independent variable used in the time series analysis, i.e., a series associated with the consumption of a class of antimicrobials. Following this concept, the coefficients estimated by Aldeyab et al. can be transformed into elasticities, thus facilitating comparisons between different study settings. First, estimated coefficients are inserted into the first fraction of equation 1 [$\partial\mathrm{CDAD}(q)/\partial q$]. Second, averages of the dependent variable CDAD and the independent variable q (i.e., antibiotic use series) are inserted into the second fraction [$q/\mathrm{CDAD}(q)$].

In contrast, the study conducted in Southern Germany used a log-linear modeling approach for the estimation of the multivariate model (4). According to this, elasticity $E_{\mathrm{CDAD},q}$ is defined as

$$E_{\mathrm{CDAD},q} = \frac{\log \mathrm{CDAD}(q)}{\log q} \quad (2)$$

which means that all estimated coefficients may be interpreted as dose-response rates without transformation. For the two studies investigated here, elasticities are shown in Table 1. A 1% increase in the use of fluoroquinolones in Belfast, for instance, was followed by a 0.4% increase in the incidence of CDAD, while a 1% increase in the use of fluoroquinolones in Freiburg was followed by a 1% increase in the incidence of CDAD.

Unfortunately, both studies do not distinguish between community-acquired and health care-associated cases of CDAD. Therefore, both analyses may be biased by a proportion of patients admitted with CDAD whose diarrhea was not caused by prior in-hospital antibiotic use. Differences in this proportion could act as an explanation for differences in the dose-response rates.

An analysis of the influence of *Clostridium difficile* colonization pressure from outside the hospital that includes the incidence of patients admitted with CDAD as an independent variable would be a challenge for future analyses in the same way as was recently done for methicillin-resistant *Staphylococcus aureus* and extended-spectrum-β-lactamase-producing strains (2, 4, 5).

TABLE 1. Coefficients estimated by time series analyses for Belfast and Freiburg and their corresponding elasticities[a]

Independent variable	M. A. Aldeyab et al. (Belfast, Northern Ireland)[b]			K. Kaier et al. (Freiburg, Germany)[c]	
	Coefficient	q/CDAD	Elasticity (dose response rate)	Coefficient	Elasticity (dose response rate)
Expanded-spectrum cephalosporin use	0.010299*** (lag 2)	2.82/0.06	0.48		
Broad-spectrum cephalosporin use	0.018226*** (lag 2)	0.61/0.06	0.19	1.41*** (lags 0 and 1)	1.41
Fluoroquinolone use	0.003835*** (lag 3)	6.95/0.06	0.44	1.01* (lags 2 and 3)	1.01
Macrolide use	0.001835** (lag 5)	9.96/0.06	0.25	1.19*** (lags 2 and 3)	1.19
Amoxicillin-clavulanic acid use	0.001518*** (lag 1)	24.5/0.06	0.62		
H2 receptor antagonist use	0.001035*** (lag 1)	7.99/0.06	0.14		

[a] ***, significant at the 1% level; **, significant at the 5% level; *, significant at the 10% level; lag, the delay necessary to observe the effect (in months).
[b] Reference 1.
[c] Reference 4.

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