

Changes in the use of broad-spectrum antibiotics after withdrawal of cefepime from the market : an interrupted time series analysis

C. Plüss-Suard¹, A. Pannatier¹, G. Zanetti², for the Swiss Antibiotic Monitoring Study Group
Departments of Pharmacy¹ and Hospital Preventive Medicine², University Hospital, Lausanne, Switzerland

Background and Objective

Cefepime was one of the most used broad-spectrum antibiotics in Swiss public acute care hospitals. The drug was withdrawn from market in January 2007, and then replaced by a generic since October 2007.

The goal of the study was to evaluate changes in the use of broad-spectrum antibiotics after the withdrawal of the cefepime original product.

Design

A generalized regression-based interrupted time series model^{1,2} incorporating autocorrelated errors assessed how much the withdrawal changed the monthly use of other broad-spectrum antibiotics (ceftazidime, imipenem/cilastatine, meropenem, piperacilline/tazobactam) in *defined daily doses* (DDD)/100 bed-days from January 2004 to December 2008.

Setting

10 Swiss public acute care hospitals (7 with < 200 beds, 3 with 200 – 500 beds). 9 hospitals (group A) had a shortage of cefepime and 1 hospital had no shortage thanks to importation of cefepime from abroad.

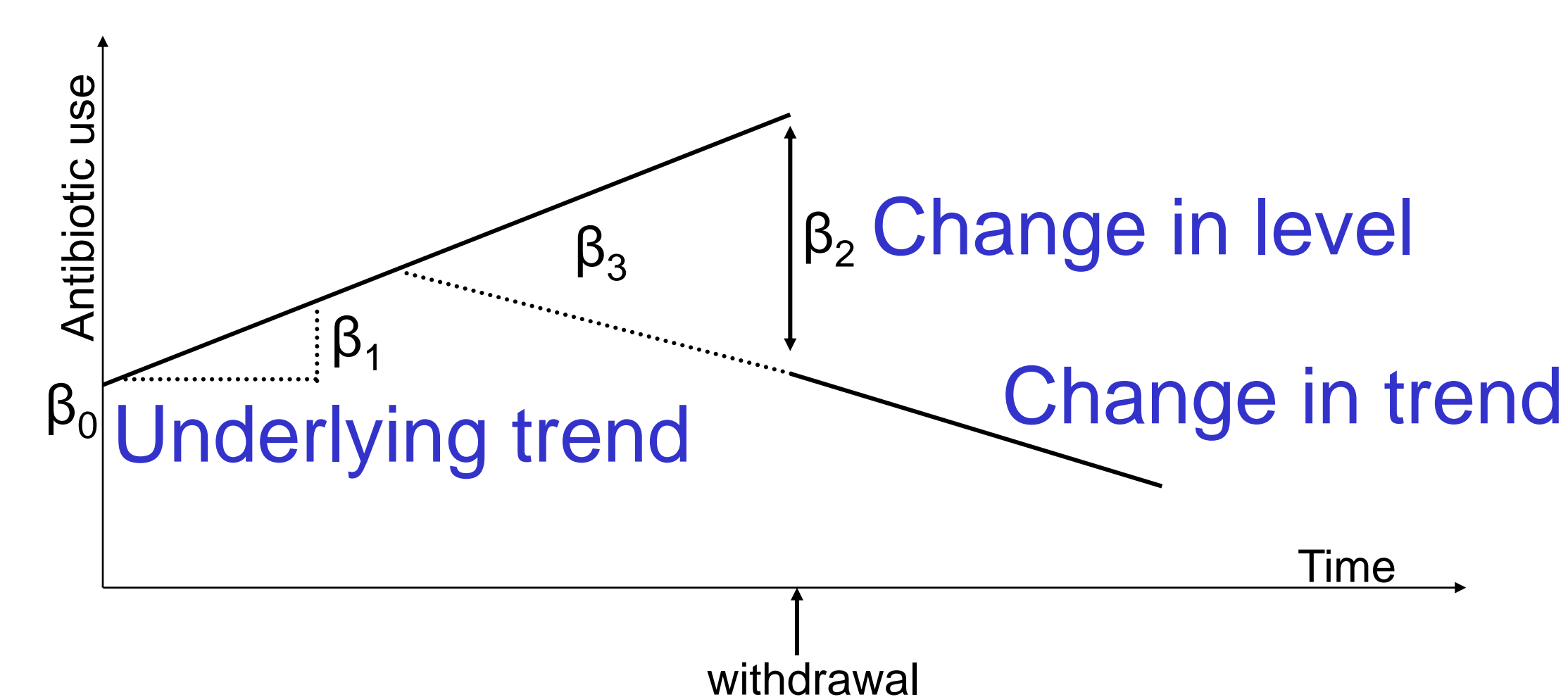
Main Outcome Measures

Underlying trend of use before the withdrawal, and changes in the level and in the trend of use after the withdrawal (Fig.1).

Results

Before the withdrawal, the average estimated underlying trend (coefficient β_1) for cefepime was decreasing by -0.047 (95%CI $-0.086, -0.009$) DDD/100 bed-days per month and was significant in 3 hospitals (group A, $p < 0.01$) (Fig. 2,3). Cefepime withdrawal was associated with a significant increase in level of use (β_2) of piperacilline/tazobactam and imipenem/cilastatine in respectively 1 and 5 hospitals from group A.

After the withdrawal, the average estimated trend (β_3) was greatest for piperacilline /tazobactam ($+0.043$ DDD/100 bed-days per month; 95% CI $-0.001, 0.089$) and was significant in 4 hospitals from group A ($p < 0.05$). The hospital without drug shortage showed no significant change in the trend and the level of use. The hypothesis of seasonality was rejected in all hospitals.



$$Y_t = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{event}_t + \beta_3 \times \text{time after event}_t + e_t$$

Fig. 1 Graphic illustration of segmented regression analysis of interrupted time series data.

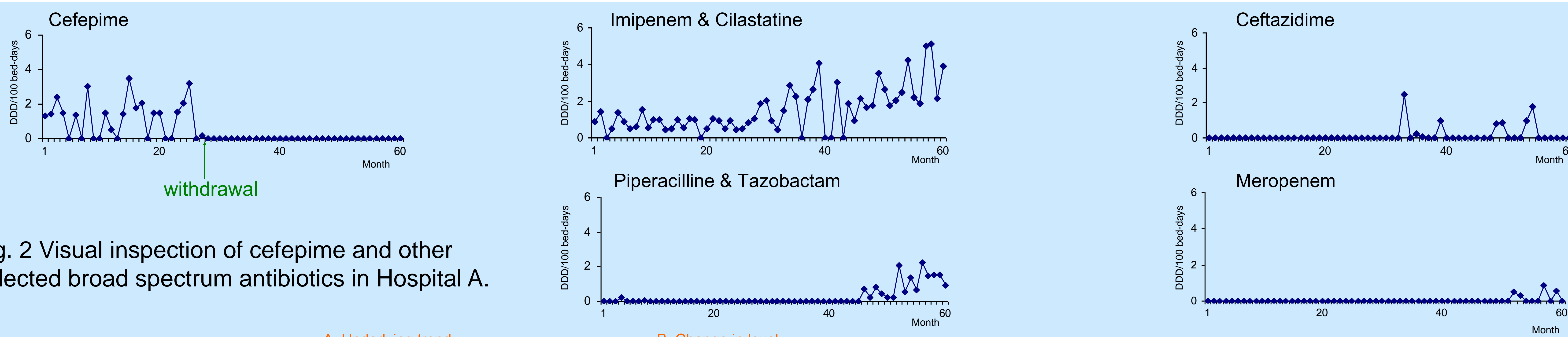


Fig. 2 Visual inspection of cefepime and other selected broad spectrum antibiotics in Hospital A.

Fig. 3 Parameter estimates and p values from the segmented regression models predicting monthly DDD/100 bed-days per hospital over time for the underlying trend (A), the change in level (B) and the change in trend (C).

A. Underlying trend			B. Change in level			C. Change in trend					
Cefepime			Imipenem & Cilastatine			Piperacilline & Tazobactam			Piperacilline & Tazobactam		
Hospital	Coefficient β_1	p Value	Hospital	Coefficient β_2	p Value	Coefficient β_2	p Value	Hospital	Coefficient β_3	p Value	
A	-0.0049275	0.850	A	0.2827179	0.479	0.00426159	0.300	A	0.546144	0.000	
B	-0.0473721	0.000	B	-0.1250277	0.400	-1.591833	0.000	B	0.0962737	0.000	
C	-0.1544024	0.099	C	1.861201	0.000	-0.1753089	0.681	C	-0.0013912	0.964	
D	-0.0000699	0.986	D	0.316672	0.182	0.2262886	0.016	D	-0.0038368	0.395	
E	-0.1309812	0.000	E	1.265777	0.006	-1.069847	0.037	E	0.156795	0.000	
F	-0.0048357	0.952	F	3.369909	0.000	-1.260862	0.099	F	0.1046336	0.027	
G	-0.047456	0.348	G	0.5631727	0.034	0.116857	0.519	G	-0.0390074	0.000	
H	-0.0453755	0.212	H	1.138991	0.025	0.1666248	0.427	H	-0.0204324	0.141	
I	-0.0147802	0.001	I	-0.51518	0.049	-0.0317878	0.791	I	0.0110235	0.216	
J	-0.0336172	0.487	J	0.0634558	0.236	0.08244287	0.125	J	0.1067304	0.136	

Conclusions

The decreased use of cefepime already observed before its withdrawal from the market could be explained by pre-existing difficulty in drug supply. The withdrawal of cefepime resulted in change in level for piperacilline/tazobactam and imipenem/cilastatine. Moreover, an increase in trend was found for piperacilline/tazobactam thereafter. As these changes generally occur at the price of lower bacterial susceptibility, a manufacturers' commitment to avoid shortages in the supply of their products would be important. As perspectives, we will measure the impact of the changes in cost and sensitivity rates of these antibiotics.