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Reduction in outpatient antibiotic sales for pre-school children: interrupted time series analysis of weekly antibiotic sales data in Sweden 1992–2002

Liselotte Högberg[1,2,3]*, Thimothy Oke[4,5], Patricia Geli[1,3,4], Cecilia Stålsby Lundborg[4,5,6,7], Otto Cars[1,4] and Karl Ekdahl[1,2,3]

[1]Department of Epidemiology, Swedish Institute for Infectious Disease Control, Stockholm, Sweden; [2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [3]Stockholm Group for Epidemic Modelling (S-GEM), Sweden; [4]Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA), Stockholm, Sweden; [5]Division of International Health Care and Research (IHCAR), Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden; [6]Apoteket AB, Stockholm, Sweden; [7]Nordic School of Public Health, Göteborg, Sweden

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***Objectives*: The aim of this study was to use detailed weekly data on outpatient antibiotic sales for pre-school children in Sweden to test for the significance of trends during 1992–2002. We also report on the special features found in weekly antibiotic data, and how the interrupted time series (ITS) design can adjust for this.**

***Methods*: Weekly data on the total number of dispensed outpatient antibiotic prescriptions to pre-school children were studied, as well as the individual subgroups commonly used to treat respiratory tract infections in children: narrow-spectrum penicillins, broad-spectrum penicillins and macrolides. In parallel, monthly data of paracetamol sales of paediatric dosages were analysed to reflect trends in symptomatic treatment. An ITS model controlling for seasonality and autocorrelation was used to examine the datasets for significant level and trend shifts.**

***Results*: A significant increase in mean and change in level could be found in the total antibiotic data in 1997, also reflected in broad-spectrum penicillin data where a similar trend break occurred in 1996. For macrolides, a trend break with a decrease in mean was noted in 1996, but no trend breaks were found in narrow-spectrum penicillin data. In contrast to the general decreasing trends in antibiotic sales, the yearly over-the-counter sales of paracetamol in paediatric preparations increased during the same period, with no identified trend breaks.**

***Conclusions*: The overall decrease in antibiotic sales and increase in paediatric paracetamol sales might suggest that symptomatic treatment in the home has increased, as antibiotics are less commonly prescribed.**

Keywords: segmented regression analysis, community antibiotic prescribing, paracetamol, prescription rates

Introduction

Numerous studies have recognized use and misuse of antibiotics as an important driving force for selection and spread of antibiotic resistance.[1–3] As resistance is becoming a major public health threat, availability of high quality data on antibiotic use and development of appropriate analytic tools is important to facilitate trend analysis, intervention evaluations and further studies of the relationship between antibiotic use and resistance development.

Sweden is, from an international perspective, a country with low antibiotic use.[4] However, like many other countries the use

*Correspondence address. Department of Epidemiology, Swedish Institute for Infectious Disease Control, SE-171 82 Solna, Sweden. Tel: +46-8-457-23-84; Fax: +46-8-30-06-26; E-mail: liselotte.hogberg@smi.ki.se

increased throughout the 1980s, without any obvious medical reasons.[5] During 1986–93, there was an increase in antibiotic sales of ∼50%.[6] During the 1990s, the increase in outpatient antibiotic sales was curbed, with an especially prominent decrease among pre-school children (≤6 years of age), and their use of broad-spectrum penicillins and macrolides.[7] It has been suggested that this is not only a result of changed prescribing habits among physicians, but also the reduced tendency of parents of young children to seek medical care for common colds and uncomplicated respiratory tract infections.[8]

Despite the overall reduction in antibiotic sales for pre-school children in the 1990s, the trend did not continuously decline. Annual data describe how the decreasing trend was broken around 1998 when sales temporarily increased again.[6] The reason behind this temporary increase is not known, but the removal of patient fees in outpatient care for patients <20 years in 1998, followed by an increase in the attendance rate of children in outpatient clinics has been one hypothesis. It has, however, not been possible to establish if this temporary increase was part of a significant trend or not, since the annual data provide too few data points to enable a more detailed analysis. Data collected at more frequent intervals, such as monthly or weekly, could offer a complement to the annual data and enable time-series analysis of trend changes in drug sales. Even though these types of data are available in Sweden they have not been used previously to study trends in antibiotic use.

The aim of this study was, therefore, to use weekly data on antibiotic sales between 1992–2002 for pre-school children, to examine the previously described temporary increasing trend in the late 1990s. In parallel, monthly data on sales of paracetamol in paediatric dosages were analysed as a measurement of trends in symptomatic treatment and morbidity due to respiratory tract infections during the same period. We also report on the special features found in weekly antibiotic data, and how the interrupted time series (ITS) design can adjust for this.

Materials and methods

Data sources

Antibiotic sales. In Sweden, antibiotics for human use can only be obtained by physician's prescription from pharmacies that all belong to the same state-owned company Apoteket AB (the National Corporation of Swedish Pharmacies). This corporation regularly collects and processes detailed and extensive information on drug dispensing in a national database. We obtained national data on the number of dispensed oral outpatient antibiotic prescriptions for systemic use to children aged 0–6 years from the database at Apoteket AB. Age classification was based on the year of birth of the patient until July 1998, when the method was changed to the use of the actual age, i.e. use of the full date of birth. Drugs were classified and arranged according to the Anatomical Therapeutic Chemical (ATC) system, as recommended by WHO.[9]

Until the end of 1995, data were built on a sample of every 25th dispensed prescription, but since 1996 all dispensed outpatient prescriptions in the country have been included in the database. As expected, data collected during the sample period showed greater inter-weekly variation compared with the total number available after 1996. Aggregated data from the sample period were validated by comparison with wholesale statistics from Apoteket AB during the same period, and estimates were considered accurate.

Prescriptions were registered on the week of dispensing, and weekly data recorded over the 574 consecutive weeks during January 1992–December 2002 were examined. Data on the total number of dispensed antibiotic prescriptions (the entire ATC group J01), as well as the individual ATC subgroups commonly used to treat respiratory tract infections in children—narrow-spectrum (β-lactamase sensitive) penicillins (J01 CE), broad-spectrum penicillins (penicillins with extended spectrum and combinations of penicillins including β-lactamase inhibitors: J01 CA and J01 CR) and macrolides (J01 FA)—were included in the study.

Data were recalculated to the number of prescriptions per 1000 inhabitants with demographic information from Statistics Sweden.[10] An age-specific denominator (the population between 0–6 years of age) was used to avoid bias introduced by demographic changes during the period, as an increasing number of births were noted during the 1990s. Data expressed as number of prescriptions were chosen in favour of defined-daily-dose to better reflect prescribing activity, and make data less sensitive to changes in dosage and length of treatment courses.

Paracetamol sales. Paracetamol is recommended as symptomatic treatment for upper respiratory tract infections in Sweden,[11] and was included in the study as a proxy measure of general morbidity and symptomatic treatment. Products containing paracetamol can only be purchased at pharmacies, where small packages for short-course treatment are over-the-counter (OTC) drugs available without prescription. We excluded paracetamol prescribed by physicians, since the indications for paracetamol use in these cases are mostly not symptomatic treatment of respiratory tract infections. Monthly OTC data have been collected since 1993, but as for antibiotics, data before 1996 were built on a sample of every 25th OTC sale. Since 1996 actual national sales numbers have been recorded.

We obtained national monthly data on the mg of paracetamol sold as preparations in paediatric dosages either as syrup, tablets or suppositories (containing 60, 125 and 250 mg of paracetamol). Data were recalculated to mg of paracetamol per 1000 inhabitants and calendar month, using the population between 0–6 years of age as denominator.

Statistical model specification and interpretation

We used an ITS design by segmented regression, a robust ITS technique that has previously been recommended for studying policy and educational interventions in medication use.[12,13] We included the fitting of linear segments to data extending back to 1992 to provide a historical review of the nature of previous shifts in trends.

A detailed analysis of the data was initially conducted to examine the structure of the time series. Patterns were visually explored, and descriptive statistics computed. The weekly number of outpatient antibiotics sales and monthly paracetamol sales revealed a strong seasonal variation. These seasonal components and their approximate time of occurrence were determined during the process and we hereby group the data into four seasons: winter (weeks 50–12), spring (weeks 13–24), summer (weeks 25–32) and autumn (weeks 33–49). Corresponding to this, the monthly paracetamol data were grouped as winter (December–February), spring (March–May), summer (June and July) and autumn (August–November). To control for the seasonality in data, dummy variables representing these seasons were added to the data set. Autumn was chosen as reference period, without loss of generality, since taking any other season would yield the same result.

Segmented regression of interrupted time series analysis

Segmented regression analysis of interrupted time series is based on a multiple linear regression model, where the trend of the dependent outcome variable, in this case antibiotic or paracetamol sales, is observed over time. The idea behind the model is to introduce one or more break points (level and trend shifts) as explanatory variables, allowing the linear model to break and change both intercept and slope in a manner that cannot be explained by random variation.[14]

We initially tested for a single shift in level and trend in 1998, when outpatient fees were removed for patients <20 years. If no significant result was found, we continued to look for other trend breaks in the data, allowing a maximum of two breaks. To detect the significant trend segments (divided by level and trend shifts) in the time series, a simple search algorithm was applied. The break points we wanted to test for were indicated in the regression equation by an explanatory dichotomous dummy variable (*DUM1*). The dichotomous dummy variable was built in such a way that the first 2 years were taken as reference years, i.e. 104 points of zeros, and ones were assigned to the last 9 years of the series for weekly antibiotic data. For the monthly paracetamol data, the first 24 points were used. A statistical significance *t*-test, $\alpha = 0.05$, was conducted for this dummy variable. If the *t*-test was non-significant, an incremental 1 year of zeros was successively added; i.e. the first 3 (then 4, 5 etc.) years were assigned zeros, and the last 8 (7, 6 etc.) years a value of 1. The search procedure for level and trend shifts was considered satisfactory as soon as the *t*-test was significant. If a significant level shift was found, a second level shift was searched for in the same fashion. A new explanatory variable (*DUM2*) was included, the two first years after the first trend break taken as reference years. A statistical significance *t*-test, $\alpha = 0.05$, was conducted for the new dummy variable. The full model, equation (1), is an extension of the segmented regression model previously described by Wagner *et al.*[12] with an addition of seasonal components to control for the strong seasonality in the dataset.

$$y_t = \beta_0 + \beta_1 * time_t + \beta_2 * DUM1_t + \beta_3 * timeafterDUM1_t + \beta_4 * DUM2_t + \beta_5 * timeafterDUM2_t + \beta_6 * WINtime_t + \beta_7 * SPRtime_t + \beta_8 * SUMtime_t + e_t \quad (1)$$

Here, y_t is the mean number of outpatient antibiotic or paracetamol sales per 1000 inhabitants in week or month t; *time* is a continuous variable indicating time in weeks or months at time t from the start of the observation period; $DUM1_t$ is an indicator for time t occurring before a given first level shift ($DUM1_t = 0$) or after the first level shift ($DUM1_t = 1$); $timeafterDUM1_t$ is a continuous variable counting the number of weeks or months after the first level shift at time t; $DUM2_t$ is an indicator for time t occurring before a given second level shift ($DUM2_t = 0$) or after the second level shift ($DUM2_t = 1$); $timeafterDUM2_t$ is a continuous variable counting the number of weeks or months after the second level shift at time t; *WINtime*, *SPRtime* and *SUMtime* are dummy variables for winter, spring and summer, respectively, with the value 1 for weeks falling in the given period and 0 when not.

β_0 estimates the baseline level of the outcome variable y_t as the weekly or monthly mean number of sales at time zero; β_1 estimates the change in weekly or monthly mean before the level shift (i.e. the baseline trend); β_2 estimates the first level change in mean from the end of the first segment; β_3 estimates the change in the trend after the first level shift compared with the baseline trend; β_4 estimates the second level change from the end of the second segment; β_5 estimates the change in the trend after the second level shift compared with the baseline trend; β_6 estimates the change during winter time compared with autumn; β_7 estimates the change during spring compared with autumn; and β_8 estimates the change in summer compared with autumn. The error term e_t at time t, represents a random variability not explained by the model.

In a general linear regression model, the random error term e for each time point t is assumed to be independent and identically normally distributed, but in this model the random term might be correlated and not independent of the antibiotic sales the previous week, hence autocorrelated. In the presence of autocorrelation, standard errors for parameter estimates become inconsistent. This means that their standard errors are underestimated, which may lead to an overestimated significance level. The Durbin–Watson statistic to test for serial autocorrelation was performed in equation (1).[15] All estimated models suggested autocorrelated residuals. An analysis of the sample partial autocorrelation function of deseasonalized data,[16] showed that a correction for this serial autocorrelation by a lag of 3 weeks was the most suitable. The regressions were therefore performed with Newey–West standard errors,[17] with a lag of 3 weeks, hence possible level and trend shifts are expected to be correctly significant. Since monthly data were used for paracetamol a lag of one was used in this dataset.

Data were analysed using Stata release 8.

Results

General trends

During 1992–2002, the annual number of dispensed outpatient oral antibiotic prescriptions to pre-school children was reduced by 34%. The proportional reduction in individual antibiotic subgroups was especially prominent for macrolides (Table 1). The annual prescription trends during the period are presented in Figure 1. Approx. 50% of the increase seen in the total annual data in 1998 and 1999 consisted of antibiotic subgroups not belonging to the subgroups included in this study (antibiotics commonly used for treatment of respiratory tract infections).

In contrast to the overall decrease in antibiotic sales, the yearly OTC paracetamol sales in paediatric preparations increased by 25% during 1993–2002.

The weekly antibiotic sales and monthly paracetamol sales revealed a similar seasonal pattern (Figures 2 and 3). Sales were highest during winter, decreasing during spring, lowest in summer and increased in the autumn for every year of the entire observation period. A distinct reduction in antibiotic sales could be noted in the weeks around Christmas and New Year in each individual year. The underestimation of spring sales due to

Table 1. Annual total number of dispensed oral antibiotic prescriptions to pre-school children per 1000 inhabitants, during 1992–2002

	1992	2002	Change (%)
All antibiotics (J01)	1159	764	−34*
Narrow-spectrum penicillins (J01 CE)	553	395	−29*
Broad-spectrum penicillins (J01 CA + J01 CR)	280	181	−35*
Macrolides (J01 FA)	190	46	−76*

*Runs test for randomness significant at $P < 0.01$.

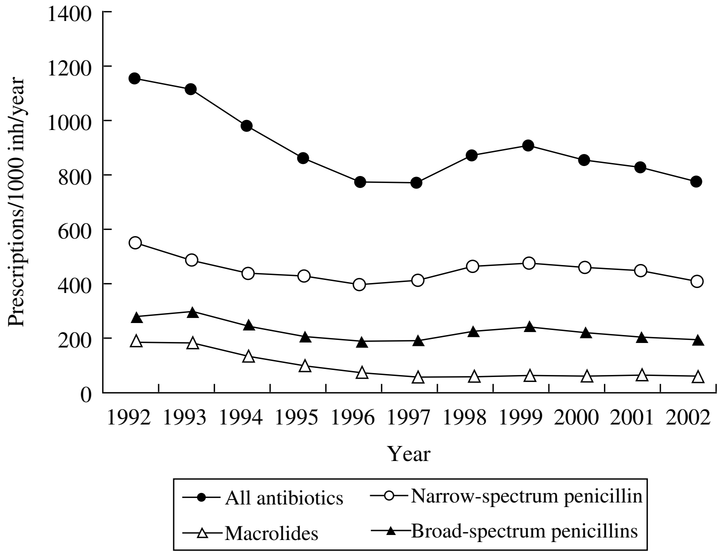

Figure 1. Annual number of dispensed oral antibiotic prescriptions to pre-school children/1000 inhabitants/year 1992–2002.

the crude age calculation may be seen in the data during 1992–98 in Figure 2.

Interrupted time series analysis

Table 2 contains parameter estimates from the segmented regression model. A worked example of their interpretation is provided below.

Antibiotic sales

We initially tested for a trend break in 1998, the year where an increase in annual sales could be noted and outpatient fees for patients <20 years were removed. No significant trend break could be found at this point in any of the datasets. When fitting linear segments to data extending back to 1992, a significant increase in mean and change in level could be found in total antibiotic data in 1997, also reflected in the broad-spectrum penicillin data where a similar trend break occurred in 1996. For macrolides, a trend-break with a decrease in mean and change in level was noted in 1996. No trend breaks could be identified for narrow-spectrum penicillins, the most commonly prescribed antibiotic for respiratory tract infections. This group mainly consist of phenoxymethyl-penicillins (penicillin V), the recommended drug of choice for uncomplicated respiratory tract infections. As no trend breaks could be identified, a continuously decreasing baseline trend was fitted to the data. Figure 2 illustrates how the segments fit to the data.

Paracetamol sales

We examined paracetamol sales data with the same methodology as antibiotics sales data, but no significant breaks could be identified. A baseline trend with a continuous increase of 703 mg of paracetamol per 1000 inhabitants and month was present in the paracetamol time series, and a single regression line illustrating this baseline trend has therefore been fitted to the paracetamol data in Figure 3.

Interpreting parameter estimates

We interpret the results in Table 2 by looking at total antibiotic sales. The estimated baseline level $\hat{\beta}_0 = 23.163$ indicates the average weekly sales per 1000 inhabitants in autumn 1992. The estimated baseline trend $\hat{\beta}_1 = -0.031$ is the average weekly change in the number of sales compared with the previous week. Thus we could note a constant slight decrease in sales until week 32 of 1997 (the first segment). Immediately after that period, there was an increase in mean, estimated as $\hat{\beta}_2 = 4.086$, compared with the last point in the baseline segment. The estimated change in trend of $\hat{\beta}_3 = 0.021$ between the autumn of 1997 and the end of the time series, gave us a new slope of $\hat{\beta}_1 + \hat{\beta}_3 = -0.01$ during the second segment. As β_4 and β_5 were not significant in any of our time series, they are not reported and were removed from the final equation.

The estimates of the seasonal components were $\hat{\beta}_6 = 3.501, \hat{\beta}_7 = -1.405$ and $\hat{\beta}_8 = -7.857$, for winter, spring and summer, respectively, compared with average weekly sales in autumn. This suggests that winter had the highest sales level and summer the lowest. Interpretation of parameter estimates for the remaining antibiotic groups follows the same reasoning. For illustration purposes, we chose, in some cases, to report parameter estimates that were not statistically significant.

Discussion

The availability of extensive retrospective data on drug sales in Sweden provides unique opportunities for detailed studies of trends in antibiotic sales by time series analysis. We have explored the time series of outpatient antibiotic sales for pre-school children during the 574 consecutive weeks during 1992–2002, by applying a segmented regression model. We also applied the same model on monthly data of sales of paracetamol in paediatric preparations during 1993–2002 to reflect trends in symptomatic treatment during the same period.

No significant effects on antibiotic sales could be seen after the removal of patient fees for patients <20 years in 1998. Instead, a significant increase in mean was found for total antibiotic sales

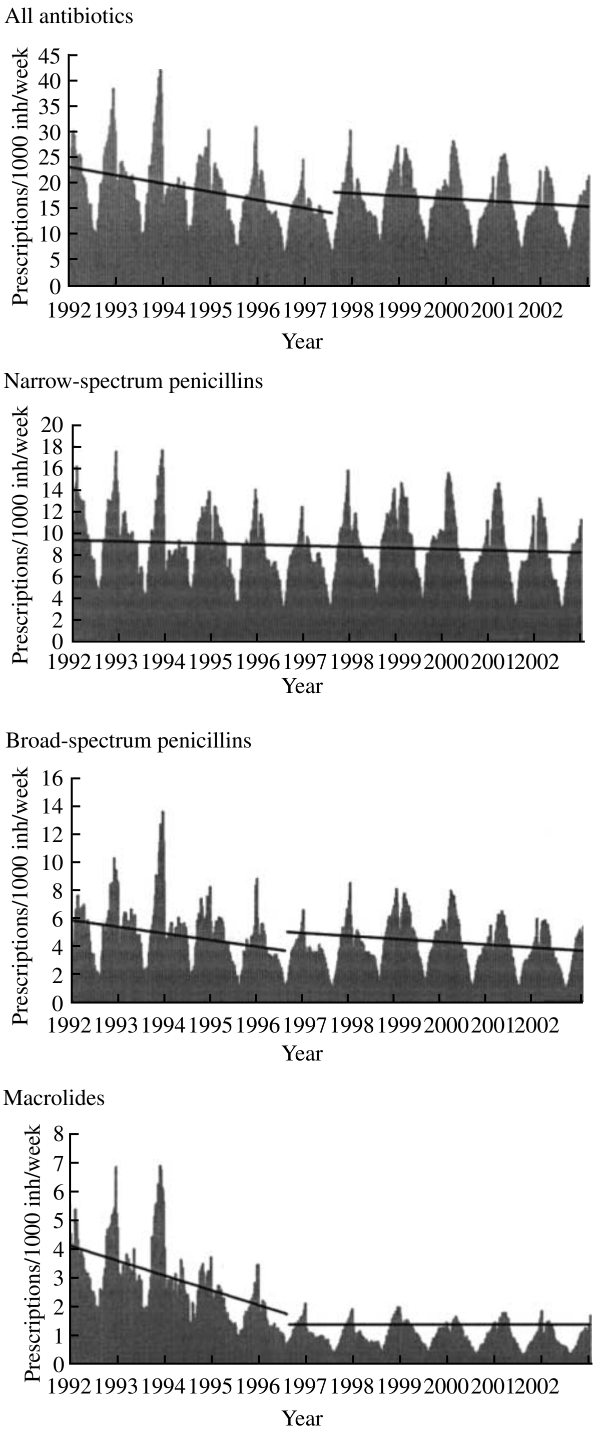

Figure 2. Segmented trend-lines for the mean number of dispensed oral antibiotic prescriptions to pre-school children/1000 inhabitants during autumns for all analysed antibiotic groups. Regression lines (black lines) illustrate mean weekly number of prescriptions during autumn period over weekly antibiotic sales (solid grey bars).

and broad-spectrum penicillins in 1997 and 1996, respectively, indicating that the increase seen in annual data in 1998 was a result of a process starting at least the year before fees were removed. Even though changes in patient fees could have reinforced this process, additional explanations are needed for this increase. Furthermore, an increase in antibiotic use due to increased healthcare utilization of young children would probably also have been clearly visible in narrow-spectrum penicillins sales, as this is the first choice for treatment of uncomplicated upper respiratory tract infections in outpatient care, and the most commonly prescribed antibiotic for pre-school children.

We included paracetamol sales as a proxy measure for symptomatic treatment of upper respiratory infections. Although there is no documented relationship between paracetamol use and upper respiratory tract infections, symptomatic relief in the form of paracetamol is recommended to parents of children with upper respiratory tract infections.[11] We therefore interpret the increasing trend in paediatric paracetamol use as an indication of increased symptomatic treatment at home. In recent years, patients have been discouraged from consulting a doctor with uncomplicated upper respiratory tract infections (URTIs), and treatment guidelines have changed to not recommending treatment to patients aged >2 years with uncomplicated otitis media.[18] A change in consultation threshold has been suggested as an explanation for the decrease in antibiotic use seen in Britain,[19,20] and a decrease in consultations due to acute otitis media and acute bronchitis in children has also been described in Australia.[21] We lack good continuous measures of infectious disease morbidity or health-seeking behaviour for Swedish children, but there are no other indications that child morbidity has undergone any major changes corresponding to the prominent reduction in antibiotic use during the decennium. In separate years, the infectious disease burden might vary due to the magnitude of influenza and epidemics of respiratory syncytial virus, but our observation period was too long to be affected by isolated events in individual years.

There are probably a number of explanations for the decline in antibiotic sales during the study period. The work towards a reduction in unnecessary antibiotic use has been intense and multifaceted in Sweden. In 1994, the Swedish Strategic Programme for Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA) was initiated to serve as a coordinating body for these activities. The organization has launched a series of initiatives drawing attention to the problem of antibiotic resistance, to increase awareness among healthcare workers and the general public on the need to reduce inappropriate antibiotic use to minimize the risk of development of resistance. One of the initial targets of the organization was to reduce unnecessary use of broad-spectrum penicillins and macrolides in children. In addition, the media has played an important role in raising awareness on the consequences and risks of inappropriate antibiotic use. The growing problems with penicillin-resistant pneumococci seen in southern Sweden and in Iceland in the early 1990s, extensively covered in the media especially during the beginning of the observation period, stressed the importance of prudent antibiotic use both among prescribers and the public.

The pattern of macrolide sales differed from the trends in the other studied antibiotic groups. The sales decreased steeply at the beginning of our study period, and have thereafter continued in very low numbers, seemingly unaffected during the general increase in sales around 1997. Inappropriate prescription of macrolides was one of the initial targets for STRAMA, and macrolide treatment of upper respiratory infections is today a second treatment choice, only recommended for upper respiratory tract infections if the patient is allergic to penicillins. In addition

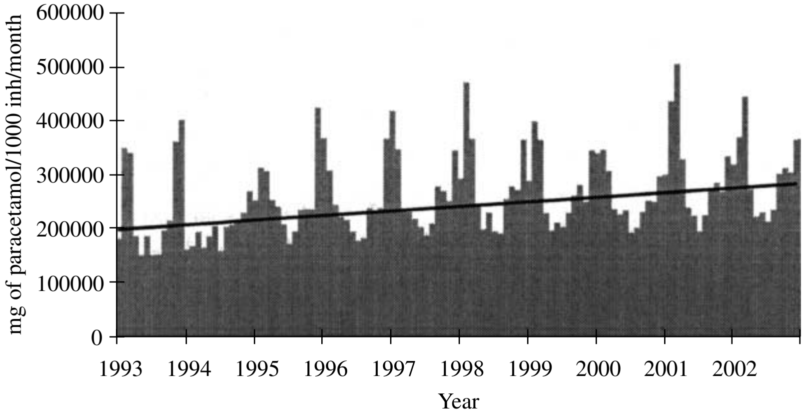

Figure 3. Segmented trend-line for mean autumn sales of paracetamol in paediatric dosages. Regression line (black line) illustrates mean monthly mg of paracetamol/1000 inhabitants during autumn period over monthly paediatric paracetamol sales (solid grey bars).

Table 2. Parameter estimates from the segmented regression model predicting the mean weekly number of dispensed oral antibiotic prescriptions to pre-school children per 1000 inhabitants, accounting for level and trend shifts

Antibiotics	Coefficient (prescriptions/1000 inhabitants/week)	95% confidence interval		*P* value	Newey–West standard error
		lower limit	upper limit		
All antibiotics (J01)					
intercept, β_0	23.163	20.396	25.930	0.000	1.409
baseline trend, β_1	−0.031	−0.042	−0.021	0.000	0.005
level shift from 1997, β_2	4.086	1.946	6.227	0.000	1.089
trend shift from 1997, β_3	0.021	0.007	0.035	0.003	0.007
winter seasonal, β_6	3.501	1.774	5.228	0.000	0.879
spring seasonal, β_7	−1.405	−3.026	0.217	0.089*	0.826
summer seasonal, β_8	−7.857	−9.356	−6.358	0.000	0.763
Narrow-spectrum penicillins (J01 CE)					
intercept, β_0	9.371	8.402	10.340	0.000	0.493
baseline trend, β_1	−0.002	−0.004	−0.003	0.023	0.001
winter seasonal, β_6	2.143	1.273	3.015	0.000	0.443
spring seasonal, β_7	−0.636	−1.442	0.169	0.121*	0.410
summer seasonal, β_8	−4.134	−4.819	−3.450	0.000	0.349
Broad-spectrum penicillins (J01 CA and J01 CR)					
intercept, β_0	5.764	4.840	6.689	0.000	0.470
baseline trend, β_1	−0.009	−0.119	−0.005	0.000	0.002
level shift from 1996, β_2	1.317	0.602	2.032	0.000	0.364
trend shift from 1996, β_3	0.005	0.000	0.009	0.043	0.002
winter seasonal, β_6	1.130	0.561	1.700	0.000	0.290
spring seasonal, β_7	−0.015	−0.691	0.386	0.579*	0.274
summer seasonal, β_8	−2.266	−2.768	−1.763	0.000	0.259
Macrolides (J01 FA)					
intercept, β_0	4.157	3.630	4.684	0.000	0.268
baseline trend, β_1	−0.010	−0.013	−0.008	0.000	0.001
level shift from 1996, β_2	−0.356	−0.620	−0.922	0.008	0.134
trend shift from 1996,β_3	0.010	0.008	0.012	0.000	0.001
winter seasonal, β_6	0.146	−0.110	0.040	0.263*	0.130
spring seasonal, β_7	−0.409	−0.663	−0.155	0.002	0.129
summer seasonal, β_8	−0.918	−1.185	−0.650	0.000	0.136
Paracetamol in paediatric preparations					
intercept, β_0	194460.3[a]	168032.2	220888.4	0.000	13342.1
baseline trend, β_1	703.47[a]	375.52	1031.41	0.000	165.56
winter seasonal, β_6	91305.6[a]	65234.3	117376.8	0.000	13161.9
spring seasonal, β_7	−17205.25[a]	−35844.4	1433.9	0.070*	9409.9
summer seasonal, β_8	−43230.9[a]	−56695.1	−29766.8	0.000	6797.3

*Parameter estimate not significant at 5% confidence interval.
[a]Units for coefficient are mg/1000 inhabitants/month.

to this, immunization against pertussis was introduced in Sweden in 1996, further reducing the need for macrolide treatment and contributing to keeping the trend in macrolide use stable.

In addition to testing for the effect of removal of outpatient fees in 1998, we explored retrospectively the time series for significant level and trend shifts for a historical review of sales trends since 1992. It might be tempting to link individual interventions introduced at the time of the identified break points, but retrospective conclusions should be avoided for several reasons. First, the lack of a control group makes isolation of confounding events that might influence data difficult. Second, a vast number of activities to promote prudent antibiotic use have taken place during the period, which makes isolation of individual interventions difficult, not least since we lack knowledge on how the interventions interact with each other and the lag time from implementation to expected effect.

In all studied antibiotic groups, the weekly antibiotic sales data showed a very strong seasonal pattern, basically reflecting the previously described seasonal pattern of respiratory tract infections in Swedish pre-school children.[22] The sales of antibiotics were reduced in the weeks surrounding Christmas and New Year in all studied antibiotic groups. The holiday implies a decreased access to prescribers, but might also contribute to a reduction in exposure to respiratory tract pathogens, since many children stay home from group day-care in these weeks. Similar but more temporary patterns of decreased sales could be noted in other specific weeks where school holidays took place.

Since antibiotics and paracetamol can only be obtained from the state-owned pharmacies in Sweden, and sales data from all pharmacies are collected in a central database, the data used in our analysis are unique with regard to the high quality and total national population coverage. The availability of data collected at frequent intervals, such as month or week, also provides opportunities for detailed analysis of drug sales. However, two changes in data compilation, with the potential to threaten the internal validity, have occurred during the observation period. Data collected during the period when a sample was used (before 1996) showed stronger variations between weeks, but otherwise expressed no differences compared with the total data coverage. A more systematic error in the data was introduced by the two different ways of classifying age during our observation period. Until July 1998, age was only calculated on the year of birth of the patient, resulting in a pattern where spring sales were underestimated compared with autumn, since many 6-year-olds were wrongly labelled as 7 years before their actual birthday. This pattern disappeared after 1998 when the criteria for age definition changed to being based on the full date of birth and the actual age, and spring sales were thereafter higher compared with autumn. The identified trend break for broad-spectrum penicillins and total antibiotic sales were close to this point in time, but no effect was seen in narrow-spectrum antibiotics, a group that made up ~50% of all antibiotics dispensed to pre-school children. If the artefact from age classification change affected the analysis, it would probably be noticed in all antibiotic groups.

Since detailed time series data on antibiotic sales are easily available in Sweden, time series analysis offers an additional tool for studies of antibiotic use. Our study demonstrates that segmented regression of time series analysis can be useful when studying trends in antibiotic use, if seasonality is appropriately controlled for. In conclusion, our results confirm that the work towards more prudent outpatient antibiotic use in children in Sweden has been successful. The fact that, in a country where antibiotic use is considered low, further reductions can be achieved sends an important message.

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