Interrupted time series (ITS) analyses

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Introduction

In interrupted time series (ITS) studies data are collected at multiple time points before and after an intervention in order to detect whether or not the intervention had a significantly greater effect than any underlying secular trend (1). ITS studies may be acceptable for inclusion in EPOC systematic reviews if appropriately analysed or if re-analysed.

The preferred method to analyse ITS studies is a statistical comparison of time trends before and after the intervention (see Figure1). Time series analysis using ARIMA models is one way of analysing the data, but there are a number of statistical techniques that can be used depending on the characteristics of the data, the number of data points available and whether autocorrelation is present (3).

However, inappropriate analyses of time series data are consistently identified in original papers evaluating quality improvement strategies, which often have used a simple before-after comparison of the intervention effect at a single intervention site (2). Solely comparing the means before and after an intervention, without taking into account any secular trends, may result in overestimations (or underestimations) of the intervention effect (3).

If the data in the original paper are presented in tables or graphs, with at least three data points before and three data points after the intervention, and a clearly defined intervention point, re-analysis using segmented time series regression techniques (as described below) is a possibility. Re-analysis of data where the effects may be suspected to pertain to seasonality or to the normal decrease after an outbreak situation (see Appendix 1) must be approached with caution. If there are any doubts about the robustness of the analysis, a statistician should be consulted.

A depiction of the general elements of a segmented time-series regression analysis is presented in Figure 1 below. The analysis estimates the effect of the intervention whilst taking account of time trend and autocorrelation among the observations. Estimates for regression coefficients corresponding to two standardised effect sizes are obtained: a change in level (also called 'step change') and a change in trend before and after the intervention. According to Ramsay 2003, a change in level is defined as the difference between the observed level at the first intervention time point and that predicted by the pre-intervention time trend, and a change in trend is defined as the difference between post- and pre-intervention slopes. A negative change in level and slope would indicate a reduction in, for example, infection rates.

Figure 1
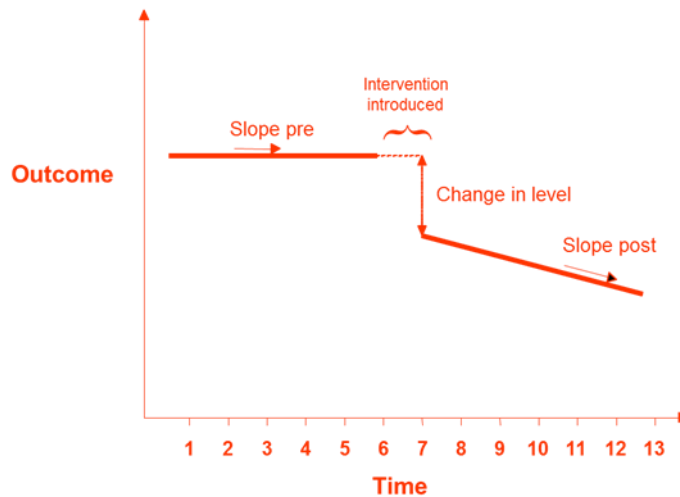
Retrieving data from printed ITS graphs

If an appropriate interrupted time series (ITS) analysis is not reported, but data are presented graphically, the data that are needed can be extracted by using one of many freely available programs for reading values from graphs, such as for example:
PlotDigitizer (http://plotdigitizer.sourceforge.net/),
xyExtract (http://xyextract-graph-digitizer.soft32.com/) or
Enguage (http://digitizer.sourceforge.net/).

Organising data

Example

Healthcare acquired infections are a big and costly problem. Methicillin-resistant Staphylococcus aureus (MRSA) is a bacterium responsible for several difficult-to-treat hospital acquired infections. In the UK, quarterly reporting of MRSA rates by hospital trusts is mandatory. One of the aims of the Healthcare Commissions Infection Inspection Programme, launched in June 2007, was to decrease the number of hospital acquired infections, including MRSA infections.

1. This example data set consists of quarterly reported number of MRSA cases by all acute trusts in the UK, from April 2006 and up to June 2009. Figure 2 below is a graphical presentation of the time series data showing the total number of MRSA cases before and after the intervention. The vertical line indicates the time for the inspection. You wish to evaluate the effect of the Healthcare Commission's Infection Inspections on the MRSA rate. There are more than three data points before the intervention and more than three data points after the intervention, and a clearly defined intervention point, which means that a

time series analysis can be used. You want to know the direct effect of the intervention (at 3 months post intervention), but also the effects at 6, 12 and 24 months post intervention. So what do you do?

Figure 2
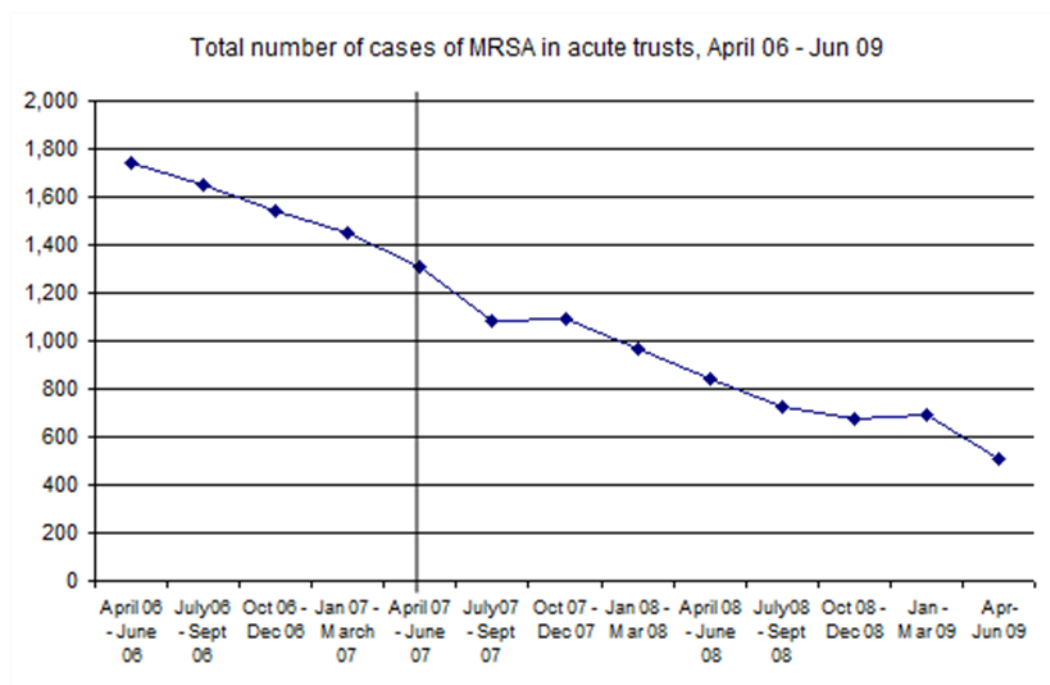
Data available from: Health Protection Agency (2009) MRSA bacteraemia: June 2009 [online] Available at: http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1233906819629 (Accessed: 01.07.13)

First, you extract the MRSA data from the graph by using one of the free software for reading values off graphs listed above.

Date	No of cases	Time periods
April 2006 – June 2006	1742	Pre intervention
July 2006 –September 2006	1651	Pre intervention
October 2006 –December 2006	1543	Pre intervention
January 2007 – March 2007	1447	Pre intervention
April 2007 – June 2007	**1306**	**Intervention starts in June**
July 2007 – September 2007	1083	3 months post intervention
October 2007 – December 2007	1092	6 months post intervention
January 2008 – March 2008	970	9 months post intervention
April 2008 – June 2008	839	12 months post intervention
July 2008 – September 2008	724	15 months post intervention
October 2008 – December 2008	678	18 months post intervention
January 2009 – March 2009	694	21 months post intervention
April 2009 – June 2009	509	24 months post intervention

Secondly, before performing a time series analysis you have to organise the data in a special way in the datasheet of your statistical program (in this example we have used SPSS):

2. Put your data into the first column of the datasheet and label it 'Outcomes' (see table below).

3. Add the time-points (from 1 to 13) to the second column and label it 'Time period'– in this example there are 13 time points- 6, 7, 9 and 13 represent the 3, 6, 12 and 24 months post intervention data points respectively (see table below), which are the time points that we are interested in.

4. Add the coding of the data to the third column and label it 'Phase'- put down '0' for all pre intervention data points and '1' for post intervention data points. In this example we have 5 pre intervention and 8 post intervention data points.

Outcomes	Time period	Phase	Interact	pre3	post3	pre6	post6	pre12	post12	pre24	post24
1742	1	0	0	1	0	1	0	1	0	1	0
1651	2	0	0	2	0	2	0	2	0	2	0
1543	3	0	0	3	0	3	0	3	0	3	0
1447	4	0	0	4	0	4	0	4	0	4	0
1306	5	0	0	5	0	5	0	5	0	5	0
1083	**6**	1	6	6	0	7	-1	9	-3	13	-7
1092	**7**	1	7	6	1	7	0	9	-2	13	-6
970	8	1	8	6	2	7	1	9	-1	13	-5
839	**9**	1	9	6	3	7	2	9	0	13	-4
724	10	1	10	6	4	7	3	9	1	13	-3
678	11	1	11	6	5	7	4	9	2	13	-2
694	12	1	12	6	6	7	5	9	3	13	-1
509	**13**	1	13	6	7	7	6	9	4	13	0

5. In the fourth column- 'Interact'-we put down '0' for all the pre-intervention data points, and let the post-intervention data points remain the same as the 'time periods' variable (6-13)- The point with the pre and post columns is to move the pre-slope line to the point of interest. The pre columns indicate what time point we are interested in.

The 5th column (the first pre column) indicates the first time-point of interest- i.e. it shows that focus of the analysis is now on the 6th time-point which in this case is equivalent with the 3 month level effect. The post columns move the focal point to the point of interest and the pre-slope line is extrapolated to this location (the last zero should always be placed at the focal point- in this case on the place for the first post intervention time point).

What Is being performed is that the data are being centred around the time point of interest e.g. if it is 6 monthly that is the 2nd post data-point or the 7th in the series hence why post6 has 0 at point 7.

In the subsequent columns the focal point will be moved from 3 months, to 6 months post-intervention, then to 12 months post intervention and lastly to 24 months post-intervention.

Therefore, in the next column 'pre6' we have the 1st to the 5th. The pre intervention time points as previously but instead of the 6th time point, we are now interested in the 7th time point (6 months post intervention) and thus the number 7 instead of number 6. In the column labelled 'post 6' the row of the 7th time point now holds the '0' and the sixth time-point holds (-1).

All the following pre and post columns follow the same pattern.

You will now have organised the data in an appropriate way for the analysis.

Analysing data (using SPSS/PASW Statistics)

1. Click on 'Analyse' and chose 'Forecasting' from the first drop down menu and 'Create models' from the second.

2. Put 'Outcome', i.e. the raw data, as the dependent variable, and 'Time periods, 'Phase' and 'Interact' as the independent variables in the analysis.

3. Choose 'ARIMA' from the methods drop down menu. Click on 'Criteria' and set the non-seasonal autoregressive (p) as 1. Click on 'continue'.

4. Click on 'Statistics' and tick box under 'Statistics for individual models' to present parameter estimates.

5. Click on 'Save' and tick box for 'Predicted values' to save predicted values to data file. Click on 'okay'.

6. Run the first part of the analysis. This will give you the difference between slopes (Interact) the pre slope (Time periods). The 'Phase' is in the first part of the model discarded, since it does not give anything of value for this type of analysis.

 Note: in all subsequent analyses the data fits are identical it is only the way that the data are structured that has changed e.g. the slope is -108.042 in all models etc.

7. Now remove the 'Time periods' and 'Interact' (but keep 'Phase' in this, and in all the coming analyses) from the analysis and add instead 'pre3' and 'post3' as independent variables. Run the analysis. The coefficient for 'phase' gives you the level effect at 3 months post intervention (i.e. in this case the direct level effect since the data is quarterly reported).

8. Now remove 'pre3' and 'post3' and insert 'pre6' and 'post6' as independent variables. Run the analysis. The 'Phase' gives you the level effect at 6 months post intervention.

9. Now remove 'pre6' and 'post 6' and insert 'pre12' and 'post12' as independent variables. Run the analysis. The 'Phase' gives you the level effect at 12 months post intervention.

10. And lastly, remove 'pre12' and 'post12' and insert 'pre24' and 'post24'as independent variables. Run the analysis. The 'Phase' gives you the level effect at 24 months post intervention.

Interpreting the analysis

Time, phase and interact are all included in the regression.

- the coefficient for 'time' gives us the slope of the regression line pre-intervention
- the coefficient for 'phase' gives us the change in intercept
- the coefficient for 'interact' gives us the change in slope pre and post intervention

This is explained below:

If the coefficient for time is β_1, for phase is β_2 and for interact is β_3 then the regression model is:

Outcome= constant + $\beta_1$time + $\beta_2$phase + $\beta_3$interact

Therefore, **pre** intervention becomes:

Outcome = constant + $\beta_1$time

And **post** intervention becomes:

Outcome= constant + $\beta_1$time + β_2 + $\beta_3$interact = (constant + β_2) + (β_1 + β_3) time (as time and interact are the same post intervention)

Therefore, the difference in constant (intercept) pre and post intervention is β_2 and the difference in slope is β_3.

The complete results obtained from the time series analysis in the example are shown in Appendix 2 at the end of this resource.

What do your results tell you?
Skip the first three tables ('Model description', 'Model Fit' and 'Model Statistics'), and go the one labelled 'ARIMA Model Parameters'

The first part of the output in the time series analysis (see Figure 3) gives us the *coefficient for time periods* i.e. the *pre-slope (=the pre-intervention slope of the regression line)* which in this case is *-108.042*, and which is used in all the subsequent analyses of the different time points (to take into account the already existing trend in the data when calculating the intervention effects), The pre-slope tells us that before the intervention there was a decrease of 108 MRSA infections per quarter (P=0.000).

*The coefficient for 'phase' (-246.631) in the first part of the model **is discarded** in this type of analysis- it represents the point on the y-axis when projecting back the line for the post-slope to the y-axis (where x=0), which adds nothing of value for the analysis.

The coefficient for 'interact' (24.759) is the difference between the pre-slope and the post-slope, with P=0.145. When adding the pre-slope (-108.042) and the interact (24.759) we get the *post-slope* (-83.283), which also is used in all the next coming analyses of the following time-points.

Figure 3

ARIMA Model Parameters

					Estimate	SE	t	Sig.
Outcomes-Model_1	Outcomes	No Transformation	Constant		1861.860	46.317	40.199	.000
			AR	Lag 1	-.093	.368	-.254	.806
	Timeperiod	No Transformation	Numerator	Lag 0	-108.042	14.098	-7.664	.000
	Phase	No Transformation	Numerator	Lag 0	-246.631	79.607	-3.098	.015
	Interact	No Transformation	Numerator	Lag 0	24.759	15.337	1.614	.145

To get to the results that we are interested in- go to next table labelled *'ARIMA Model Parameters'*. Here the level effect (Phase), standard error and p-value and for the level effect are presented. 'Pre' (pre-slope) and 'Post' (post-slope) are the same in all analyses.
The 'Phase' is here the 3 month level effect =-98.067, a decrease of 98 cases per quarter (the direct intervention effect) (P=0.117).

Go to the next table labelled 'ARIMA Model Parameters'. The 'Phase' here is the 6 month level effect = -73.31, a decrease of 73 cases per quarter (P=0.292).

Go once again to the next table labelled 'ARIMA Model Parameters'. The 'Phase' here is the 12 month level effect = -23.799, a decrease of 24 cases per quarter (P=0.795).

Go again to the next table labelled 'ARIMA Model Parameters'. The 'Phase' is here the 24 month level effect = 75.209, an increase of 75 cases per quarter (P=0.616

Calculating confidence intervals

The results reported in the output from the analysis do not directly give us the confidence intervals around the estimated effects. But based on estimates of effects and the standard error (SE) of the estimates of effect we can calculate confidence intervals. The SE's are found in the same tables as the estimates of effect.

For the calculation of confidence intervals we need the two-tailed 2.5 percentile from the t-distribution with (the number of observations minus 5) degrees of freedom (df); in our example 13-5=8. This can easily be calculated in Excel using the formula tinv (0.05; 8) which equals 2.306. The confidence interval can now be calculated using the formula:

> Estimate of effect +/- tinv (0.05; df)*SE

Based on this formula we get:
3 months: Estimate of effect: -98.067; SE: 55.852; 95% CI: -226.86 to 30.73
6 months: Estimate of effect: -73.31; SE: 65.036; 95% CI: -223.28 to 76.66
12 months: Estimate of effect: -23.799; SE: 88.664; 95% CI: -228.26 to 180.66
24 months: Estimate of effect: 75.209; SE: 144.113; 95% CI: -257.12 to 407.53

Calculating percentages

In some instances relative effects are of more interest than absolute effects. For example, to facilitate the comparisons of different interventions the results must be standardized so that they are all on the same scale. In these cases relative effects can be calculated using the predicted values requested in step 5 above.

Each time the analysis was run a new variable was added to the dataset. The first variable is named Predicted_outcomes_Model_1, the second Predicted_outcomes_Model_1_A, the third Predicted_outcomes_Model_1_B, and so forth.

Switch to 'Data view' where you can see all the available data.

The relative 3 month effect can now be calculated based on the predicted value at three months post intervention (time period 6; Predicted_outcomes_Model_1 = 1116.99) and the 3 month level effect from above (98.067) as 100*(-98.067)/(1116.99 - (-98.067)) = -8.07%

In the same way we can calculate the relative 6 months effect as 100*(-73.31)/ (1035.28 - (-73.31)) = -6.61%.

The relative 12 months effects is 100*(-23.799)/ (863.73 - (-23.799)) = -2.68%

The relative 24 months effects is 100*(75.209)/ (525.27 - (-75.209)) = +16.71%

Interpreting the results and drawing conclusions

Beginning at 1742 MRSA cases in the second quarter of 2006 (the first quarter for which data are available for this analysis), the number of MRSA cases was decreasing by 108 MRSA infections per quarter prior to the intervention (at the end of the second quarter of 2007). When this trend is taken into account in the ITS analysis, it is uncertain what, if any impact the Healthcare Commissions external inspections had on MRSA infection rates. The point estimate suggests that the Healthcare Commissions external inspections may have had a short term effect (an additional reduction of 98 MRSA infections in the quarter immediately following the intervention). However, the confidence intervals around the effect estimates are wide and do not rule out the possibility of no effect or even an increase in the number of MRSA infections at 3, 6, 12 and 24 months.

If there were no other studies of the effects of external inspection on hospital acquired infections, and we were to assess the quality of this evidence using the GRADE approach (see the EPOC worksheets for preparing a summary of findings using GRADE), we would interpret this as very low quality evidence (a non-randomised study with important imprecision). We would conclude that the effect of external inspections on hospital acquired infections is uncertain.

Frequently asked questions (FAQ)

- *When can a time series analysis be used - and with what type of data?*
  In principle time series analysis based on segmented regression analysis or ARIMA, as presented in this document, can be used for all types of numerical data (e.g. rates, counts, and means). These methods are based on the assumption of normal distributed error terms. When observed rates on which the time series analysis is based all are near 0% (less than 5-10%) or near 100% (more than 90-95%) the method described here might yield an expected value at time points of interest outside the range between 0% and 100%. The same also applies for low counts; that is counts near 0. If this occurs, alternative approaches based on Poisson regression or aggregate binomial regression can be used. You should seek advice from an experienced statistician in this case.

- *How do we handle 'care bundles' - a series of interventions implemented after each other (not having 3 data-points before and after each of the intervention - but well before the first and after the last intervention?*
  In order to handle 'care bundles' the series of 'care bundles' has to be treated as one intervention. As a consequence all observations for the period during which the series of interventions were implemented have to be discarded from the analysis. Additional observations (before or after the interventions are implemented) might also be discarded due to a transition period.

- *What is an autocorrelation? And should we always adjust for autocorrelation in time series regression?*
  The autocorrelation is a measure of the extent to which data collected close together in time are correlated with each other. The autocorrelation ranges between -1 and 1. A negative autocorrelation suggests that outcomes taken close together in time are likely to be dissimilar. For example, a high outcome is followed by a low outcome that is then

followed by a high outcome and so on. In contrast, a positive autocorrelation suggests that outcomes measured closed together in time are similar to each other. For example, a high income is followed by another high outcome. Ignoring autocorrelation can lead to spurious over-estimation of the statistical significance of effects.

By default time series regression should always adjust for the first-order auto-correlation (which looks at the correlation between two subsequent observations). First-order autocorrelations can be tested statistically by using the Durbin-Watson statistic (when performing a linear regression with the same specification as described here). If this statistic is not statistically significant one might, after consulting an experienced statistician, omit the adjustment for autocorrelation. If the time series is long it is possible that adjustment for higher-order autocorrelations (e.g. a second-order autocorrelation looks at the correlation between two observations with one observation in between) and moving averages (which mitigates large fluctuations in the data) might give a better fit and more accurate estimates of effect. Careful investigation of the autocorrelation and partial autocorrelation functions by an experienced statistician is needed before adjusting for higher-order autocorrelations.

If it is assessed that the analysis does not benefit from the adjustment of autocorrelation, this can be turned off by setting the non-seasonal autoregressive parameter to 0 in step 3 of the analysis, or alternatively by performing a linear regression with the same dependent and independent variables as defined in this document. This will give you the confidence intervals for the effects directly.

- *When should seasonality be taken into account? And how is it done?*
  Some outcomes can be expected to vary by month or season. In such cases it is appropriate to adjust for seasonality, but doing this requires that the outcome has been measured at least twice (preferably more times) before and after the intervention. Seasonality can be incorporated in two ways: (1) using dummy variables to define seasons and include those as adjustment factors in the analysis (2) model seasonality using autocorrelations (for example, the observed value in March is correlated to the observed value in March the previous year). Both methods can be used within the framework described in this document. An experienced statistician should be consulted before adjusting for seasonality.

- *How many observations do we need to perform a time series regression or ARIMA analysis?*
  As is the case with all types of statistical analysis the more data the better. The method outlined in this document is based on the so called ARIMA and time series regression techniques. If only a few observations are available (less than 10) the analysis should be based on time series regression without adjustment for autocorrelation; this can be done by setting the non-seasonal autoregressive parameter to 0 in step 3 of the analysis, or alternatively by performing a linear regression with the same dependent and independent variables as defined in this document.

If you have any queries regarding ITS analyses or the specific content of this resource for EPOC review authors, please send your query to:
gerd.flodgren@dph.ox.ac.uk
Jan.Oddgard-jensen@kunnskapssenteret.no

Asking questions about anything that you may find unclear, will help us improve this resource.

References

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2. Shojania KG, Grimshaw JM. Evidence-based quality improvement: the state of the Science. Health Affairs 2005; 24: 138-50.

3. Eccles M, Grimshaw J, Campbell M, C Ramsay. Research designs for studies evaluating the effectiveness of change and improvement strategies. Quality Safety Health Care 2003; 12: 47-52.

Appendix 1
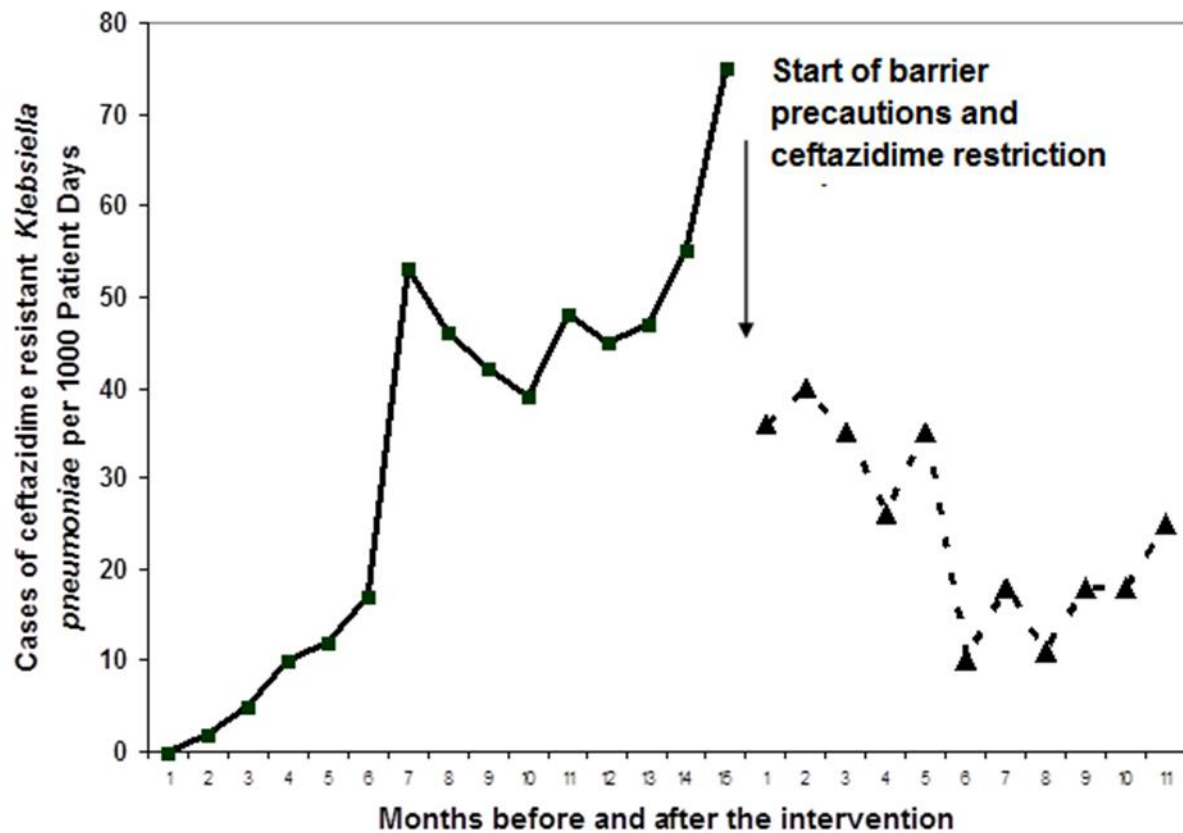
Meyer KS, Urban C, Eagan JA, Berger BJ, Rahal JJ. Nosocomial outbreak of Klebsiella infection resistant to late-generation cephalosporins. Annals of Internal Medicine 1993; 119: 353-8.

Appendix 2

See 21a SPSS time series analysis.