Assessing Impact of Stewardship: The Why, When, and How of Interrupted Time Series

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COI & Disclosures

- Contracted research
  - Merck
- Investigator initiated research
  - AHRQ, CDC, Merck
- Other support
  - PCORI

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Learning Objectives

1. Define the importance of rigorous evaluation of antimicrobial stewardship interventions
2. Identify what research/quality improvement questions are best answered through interrupted time series
3. Identify different outcome types useful in evaluating stewardship efforts
4. Identify design elements that allow for development of a strong ITS study
5. Review fundamentals of statistical analysis for interrupted time series

Why Evaluate ASP Interventions?

- Demonstrate intervention effect
  - Defined, measurable outcome
- "Prove" effect was due to demonstration
  - Rule out alternate explanations

"Rigorous" evaluation of ASP

- Why "rigorous"?
  - Minimize bias and error
  - Maximize causal inference
- Support identification of best practice
- Maximal impact on patient care

What is ITS?

- A type of quasi-experimental study
  - Not observational or ecological
- Non-randomized, interventional
- Before and after studies
  - Multiple regularly spaced measurements before and after intervention
- Evaluate effect of an intervention implemented at group level
  - Antibiotic time out
  - Restriction policy
- Can include different design elements
  - With/without control groups
  - Staggered roll out

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When to use the ITS Design

- What is your research question?
  - Group/population level effect
    - Reduction in antibiotic use
    - Reduction in MDRO rates
    - Reduce *C. difficile* infection

When to use the ITS Design

- Population/patient setting characteristics
  - Consistent across time
  - Defined and enumerable
  - At-risk population

When to use the ITS Design

- Intervention characteristics
  - Group-level intervention
  - Not randomly assigned
  - Clear implementation date is known
  - Uniformly applied
  - Examples
    - New antibiotic restriction policy
    - Antibiotic time out
    - Provider education

When to use the ITS Design

- Outcome characteristics
  - Group/system level outcome
  - Measurable across units of time
  - Examples
    - Cost
    - Antibiotic orders
    - Infection/Colonization
    - Resistance

Designing Rigorous ITS Studies

Interrupted Time Series

- Example: Evaluation of antibiotic time out policy
  - Setting: Acute care hospital
  - Intervention: EHR alert to review systemic antibiotics after 72 hours
  - Outcome: CDI rate

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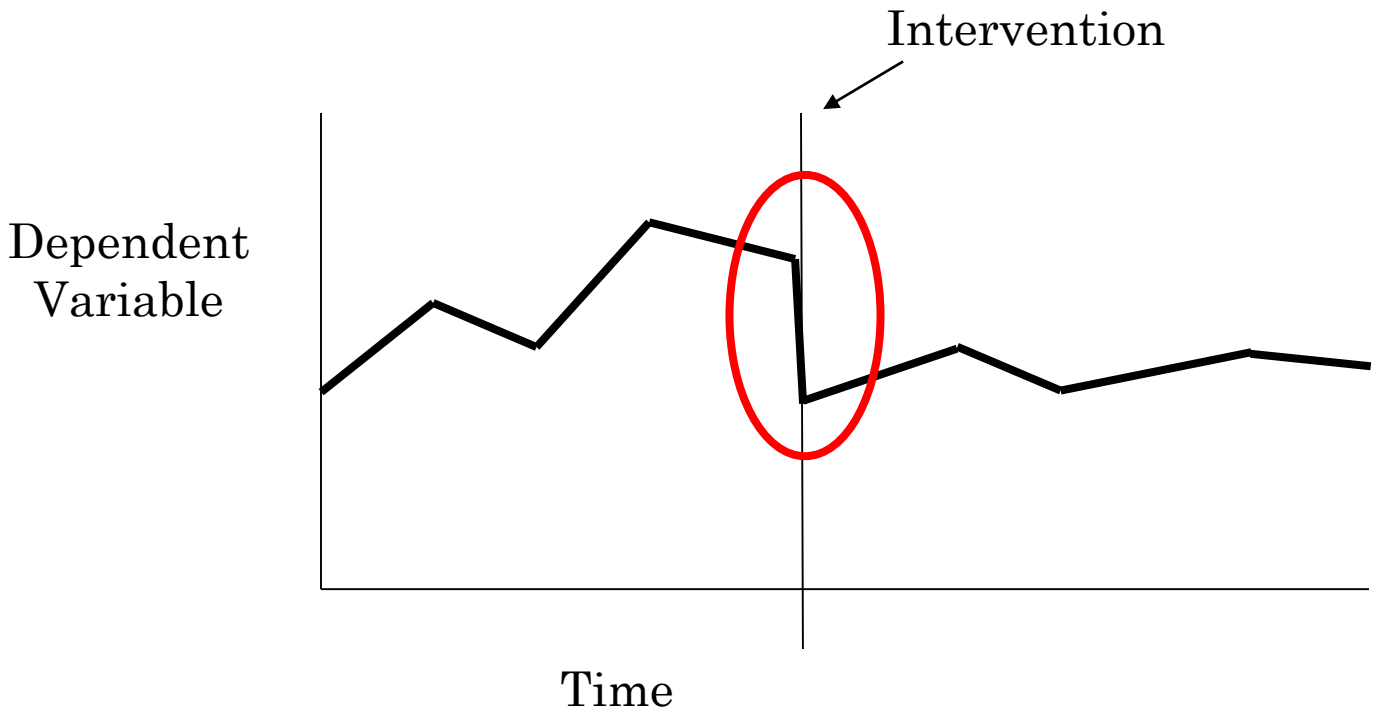
Interrupted Time Series

O_1 O_2 O_3 O_4 O_5  O_6 O_7 O_8 O_9 O_{10}

time



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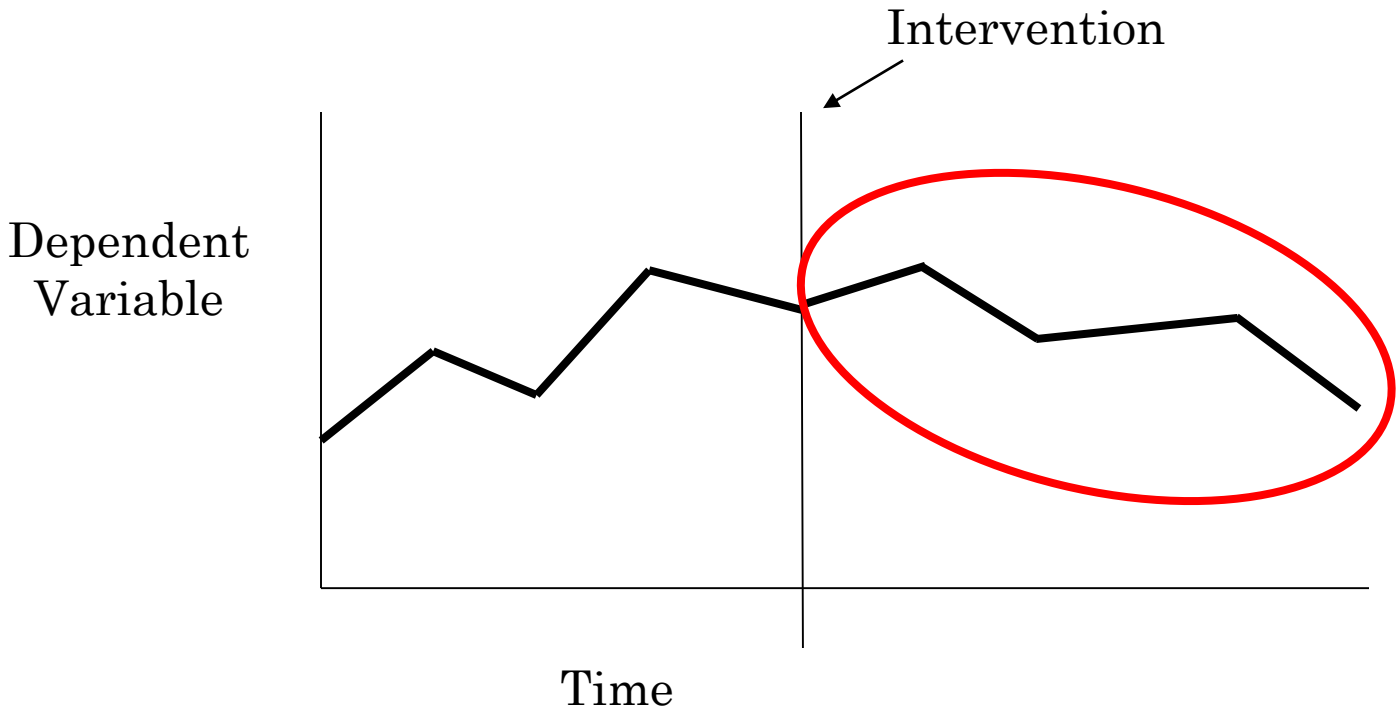
Interrupted Time Series

O_1 O_2 O_3 O_4 O_5  O_6 O_7 O_8 O_9 O_{10}

time



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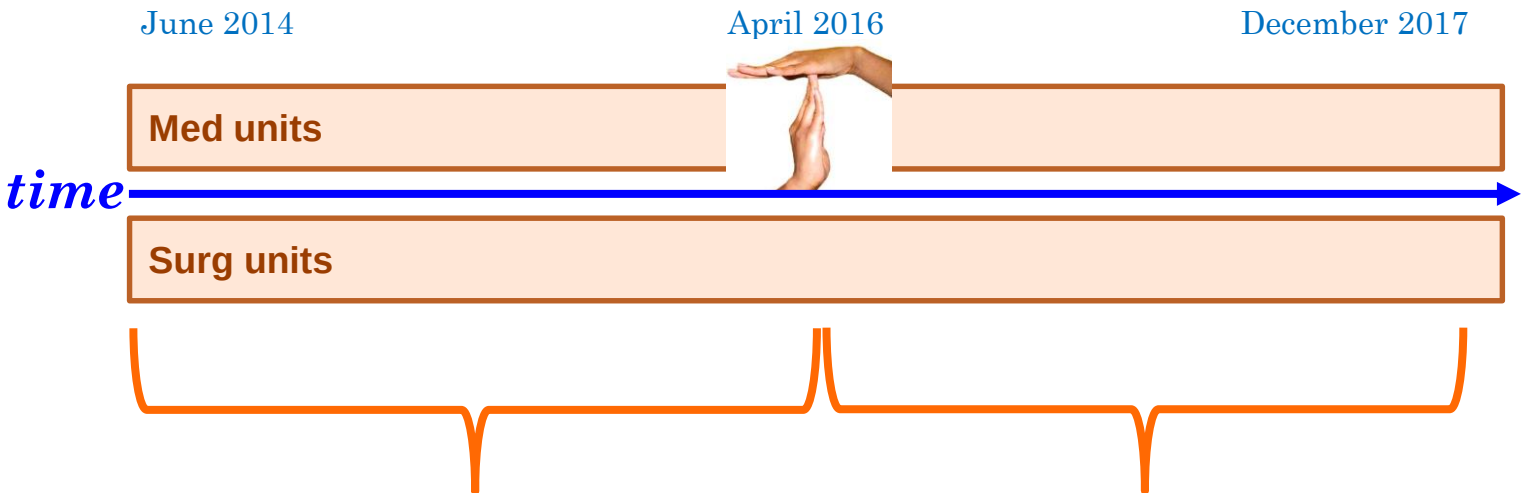
Advanced Design Features

- Increase complexity of design framework
  - If pattern of outcome measurements over time conforms to the increasingly complex pattern, more evidence for causal inference
  - Increasingly unlikely that outside influencing factors, bias, confounders could have resulted in the observed pattern

Designs with control groups

Either of these designs could also be improved by adding a control…

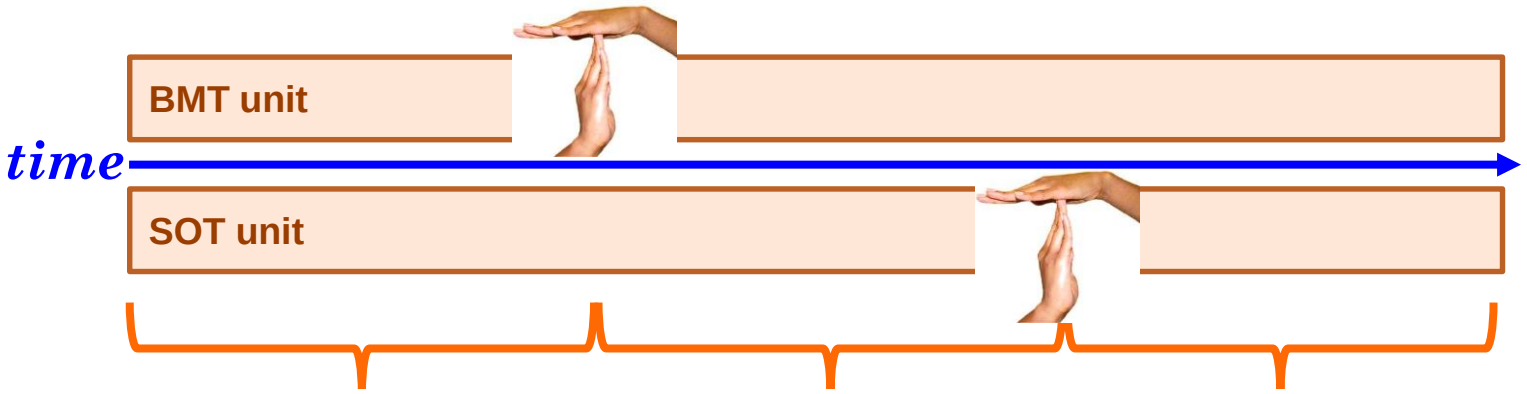


Designs with controls

- Control group selection
  - Affected by same external influences
  - Outcome in control group not affected by intervention implementation in "treatment" group
- "Control" variables
  - A.K.A.=Nonequivalent dependent variables
  - Alternate "outcome" variable that you expect not to change as a result of intervention
    - Example: hypoglycemia

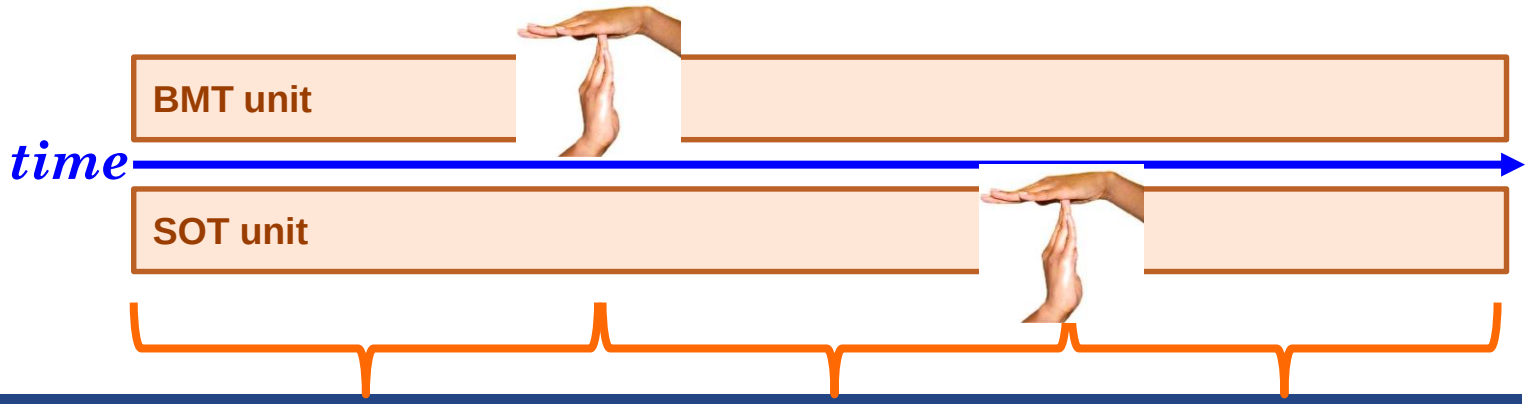
Staged Roll Out of Intervention

AKA Stepped wedge design



Staged Roll Out of Intervention

AKA Stepped wedge design



	CDI per 10,000 patient days		
	Pre-intervention	Post-intervention I	Post-intervention II
BMT unit	7.24	4.63	3.69
SOT unit	6.35	5.99	2.99

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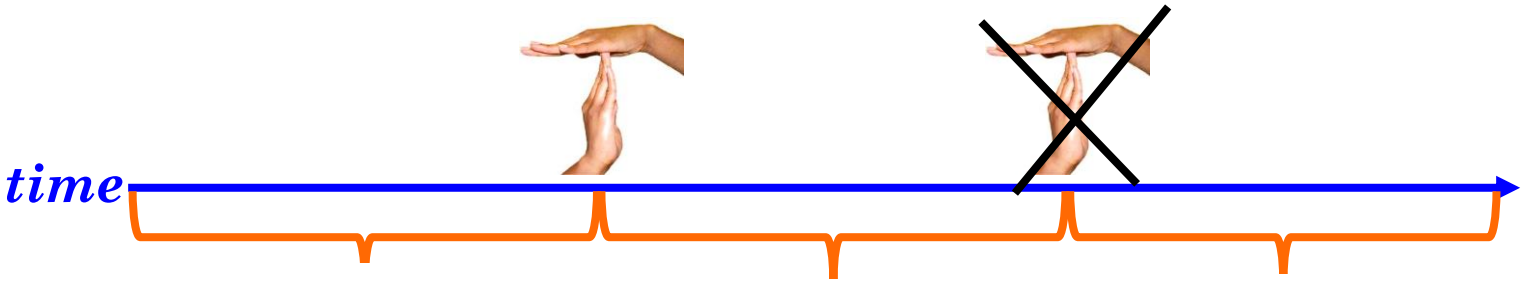
Removed Intervention



Strengths of ITS Design

- Evidence against pre-existing trends and regression to the mean
- Demonstrates immediate and sustained effects
- Easy to visualize intervention effect
- Multiple outcomes can be assessed
  - Process measures, patient outcomes

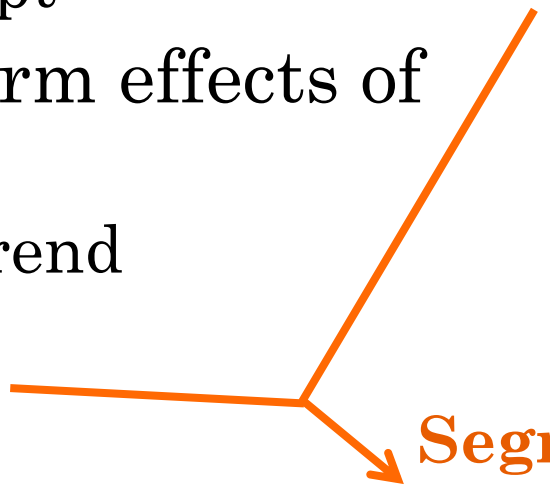
Weakness of ITS Design

- Often requires longer periods of baseline and follow-up data
  - Particularly for rare outcomes and small populations
- Changes over time can introduce bias
- Validity of outcome measurements may change over time

Statistical Analysis for ITS

Interrupted Time Series

- Most powerful sub-group of quasi-studies
- Can detect immediate effects of intervention
  - Change in intercept
- Can detect long-term effects of interventions
  - Change in slope/trend



Segmented Regression

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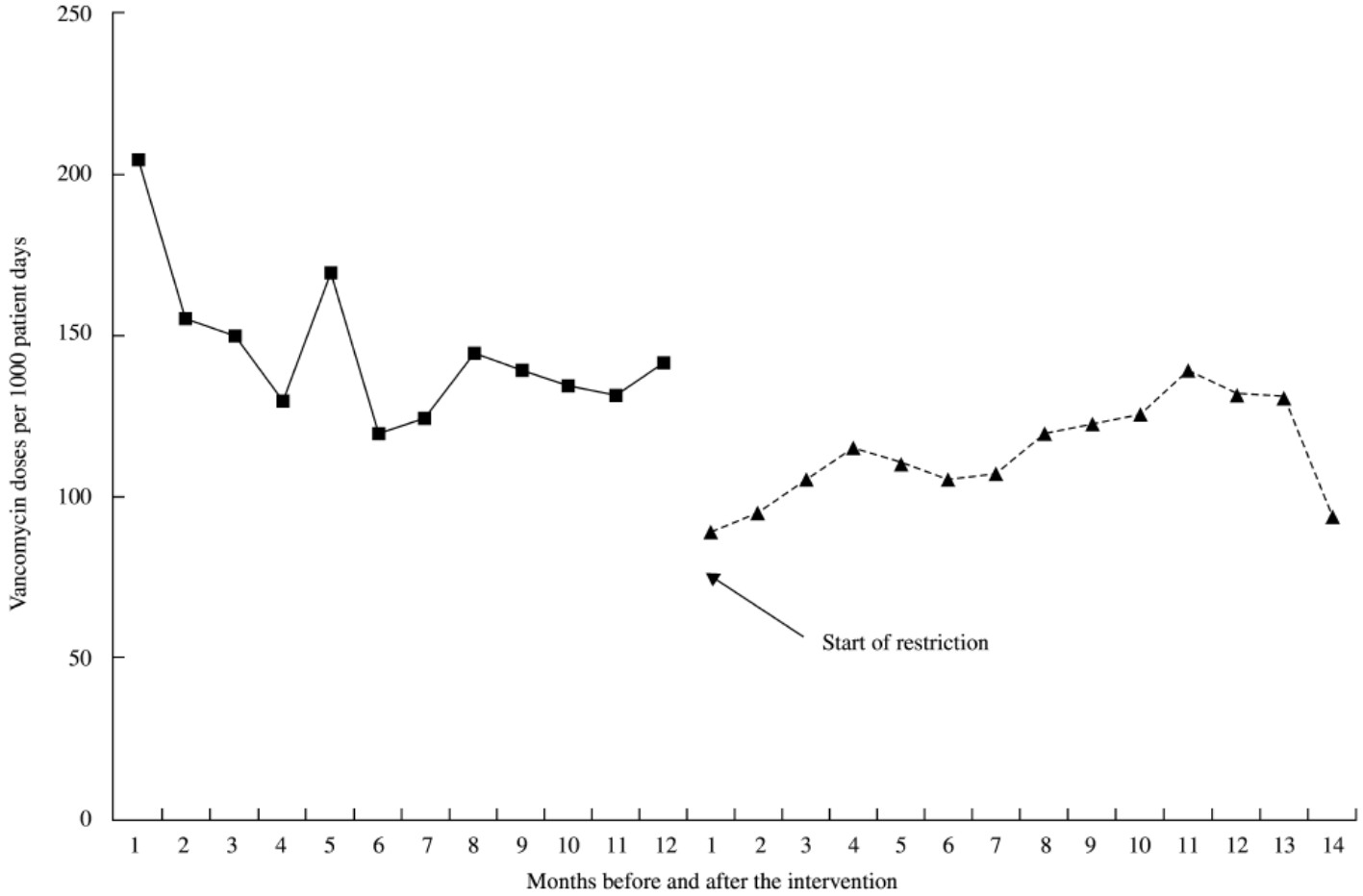
Analyzing ITS Studies

- Want to retain advantages of ITS study design
  - Generally 10-20 recommended for analysis
    - 3 observations each, before and after intervention is absolute minimum to be called ITS
  - Regularly spaced time intervals
- Need to account for correlation and secular trends

Analyzing ITS

- Why can't we summarize the pre-intervention and post-intervention data and compare (i.e., compare two means)?
  - Reduces the study to a single pretest-postest design
  - Intervention effects can be over- or under-estimated



Change (post-intervention minus pre-intervention) in vancomycin doses per 1000 patient days		*P* value
Change in mean	Decrease by 31 doses	<0.001
Change in level	Decrease by 23 doses	0.05
Change in slope	Increase by 6 doses	<0.001

Figure 3. An example of an interrupted time series in which the effect of the interventions is overestimated by analysis of mean data before and after the intervention.[10]

Ramsay et al. JAC (2003) 52: 764-771

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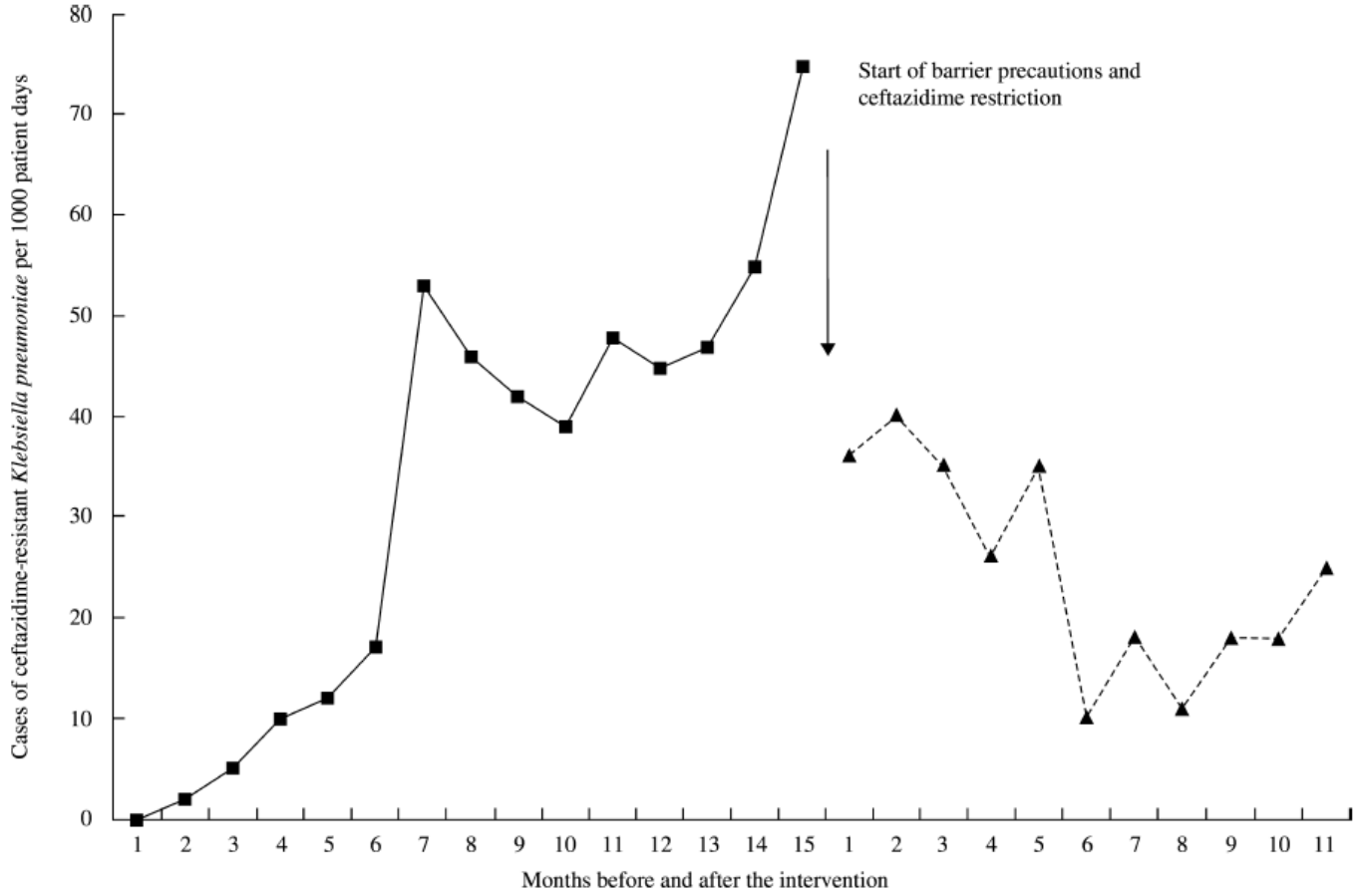

Change (post-intervention minus pre-intervention) in cases of ceftazidime resistant *Klebsiella pneumoniae* per 1000 patient days		*P* value
Change in mean	Decrease by 11.7 cases	0.1
Change in level	Decrease by 38.6 cases	<0.001
Change in slope	Decrease by 6.7 cases	<0.001

Figure 4. An example of an interrupted time series in which the effect of the interventions is underestimated by analysis of mean data before and after the intervention.[33]

Ramsay et al. JAC (2003) 52: 764-771

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Analyzing ITS

- Why can't we use our 'standard' regression models?
  - Need to model change in mean outcome and change in trend in outcome
  - Data are not independent--correlated
- What if we use 'standard' regression models anyway?
  - Parameter estimates are not biased
  - SD of parameter estimates are biased
    - Biased statistical test
    - Generally, interventions effects will appear statistically significant when they are not

ARIMA Models

- Auto Regressive Integrated Moving Average
  - Analyzes and forecasts equally spaced univariate time series data, including intervention or ITS data
  - Models both parameters of interest and correlation structure
    - Account for variability over time, seasonal trends, etc.

ARIMA Models

- ARIMA Family (SAS: PROC ARIMA)
  - Includes subsets that include
    - ARMA: auto regressive and moving average
    - Autoregressive
      - SAS PROC ARIMA
      - PROC AUTOREG
- Highly recommend working with a statistician
  - Modeling process is complex
  - To follow is an overview

ARIMA Models

- Model Components
  - Deterministic
    - Parameters of our time series
  - Stochastic ("noise" component)
    - Unsystematic
      - Random "shocks"
    - Systematic
      - Responsible for autocorrelation
      - Major goal is to identify/model structure
        - Leaves only unsystematic portion
        - Can then calculate unbiased estimates of SD

Analyzing ITS

- How do we model the deterministic component? (i.e., how do we set up our model parameters?)
- Segmented Regression
  - Model parameters are entered in such a fashion that allows for changes in mean outcome levels (intercepts) and trends in outcome (slopes)
  - Can be used with various statistical models (not limited to ARIMA)

Regression

$$Y = \beta_0 + \beta_1(x_1) + e$$

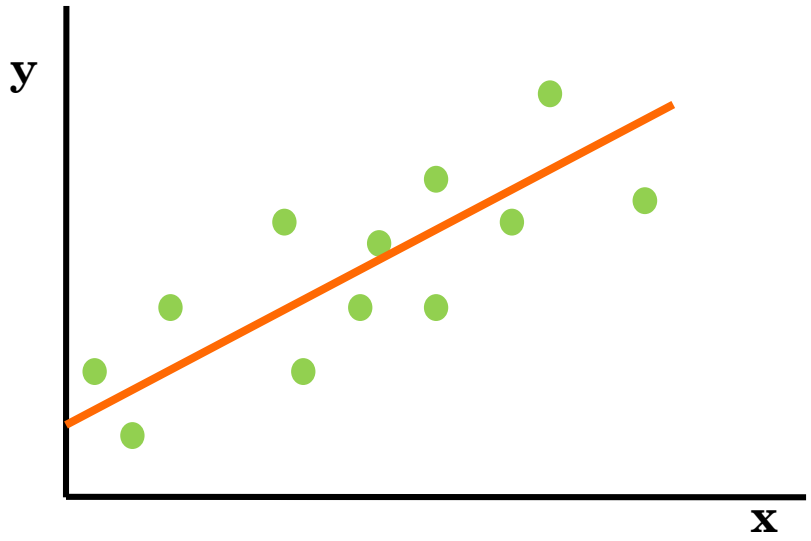
Dependent/Outcome Variable

Intercept

Slope

Independent/Predictor Variable

Error



Segmented Regression for ITS

$$Y_t = \beta_0 + \beta_1(\text{time}_t) + \beta_2(\text{intervention}_t) + \beta_3(\text{time after intervention}_t) + e_t$$

Time	Continuous variable; time since study start
Intervention	0 = Pre-intervention period 1 = Post-intervention period
Time after Intervention	Continuous variable; time since intervention

Segmented Regression for ITS

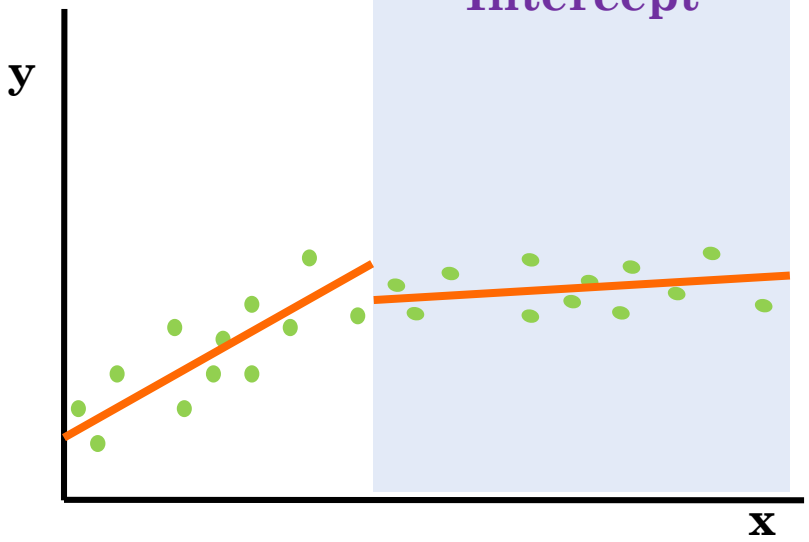
$$Y_t = \beta_0 + \beta_1(\text{time}_t) + \beta_2(\text{intervention}_t) + \beta_3(\text{time after intervention}_t) + e_t$$

Pre-Intervention Intercept

Pre-Intervention Slope

Post-Intervention Change in Intercept

Post-Intervention Change in Slope



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Segmented Regression for ITS

$$Y_t = \beta_0 + \beta_1(\text{time}_t) + \beta_2(\text{intervention}_t) + e_t$$

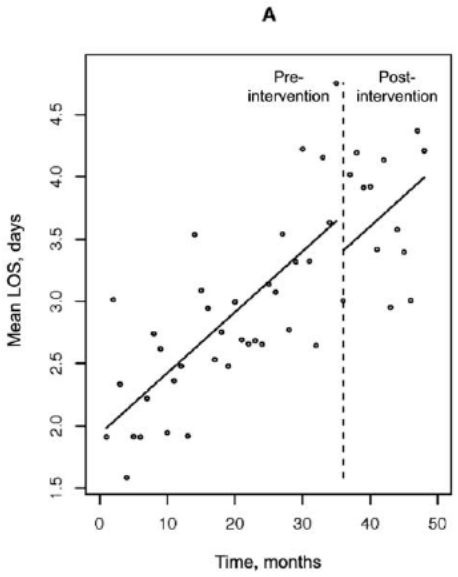


Figure 2. Interrupted time-series data regarding length of hospital stay (LOS) simulated from a segmented linear regression model with a change in slope (before vs. after the intervention), fit with a nonsegmented linear regression model that cannot estimate a change in slope *(A)* and a segmented linear regression model that can estimate a change in slope *(B)*. The intervention was implemented at month 36.

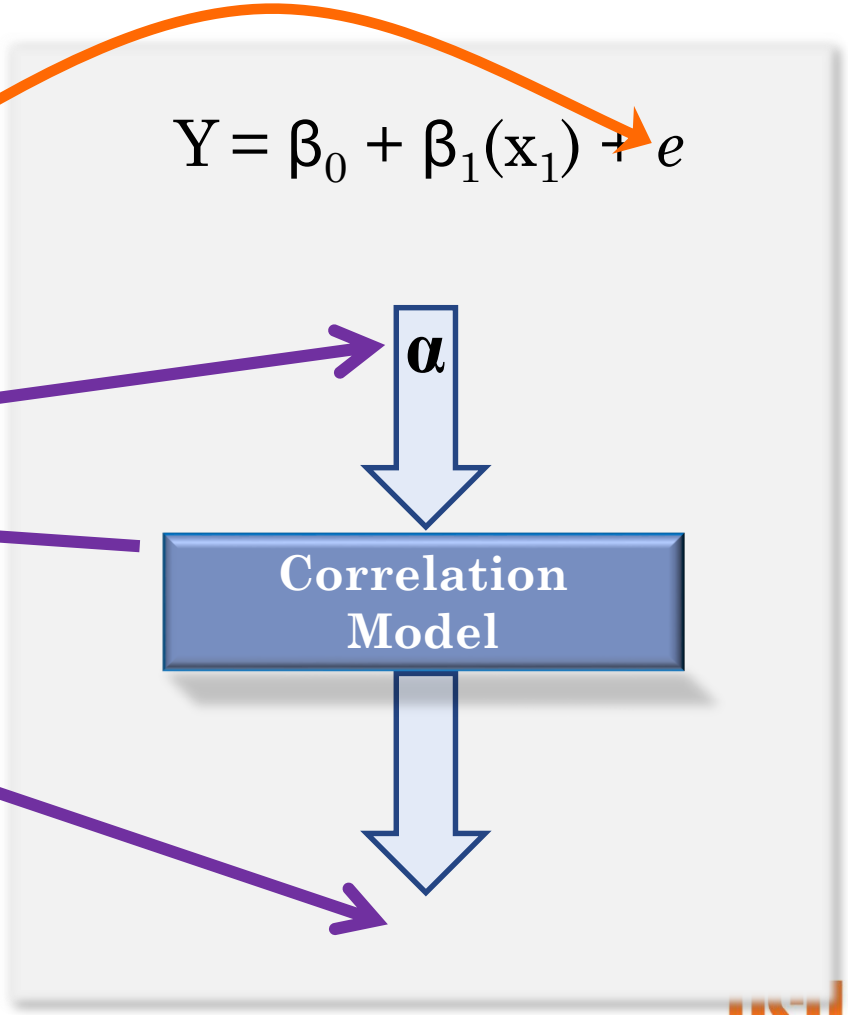
Shardell et al. *Clin Infect Dis* 2007

ARIMA Models

- Model Components
  - ~~Deterministic~~
    - ~~Parameters of our time series~~
  - Stochastic ("noise" component)
    - Unsystematic
      - Random "shocks"
    - Systematic
      - Responsible for autocorrelation
      - Major goal is to identify/model structure
        - Leaves only unsystematic portion
        - Can then calculate unbiased estimates of SD

ARIMA Models

- "Typical" regression
  - Error component
    - Independent
- Stochastic component
  - Correlated Errors
    - Systematic
      - Responsible for correlation
    - Unsystematic



ARIMA Models

- How do we model the structure of the stochastic systematic component? (i.e., the autocorrelation structure)
  - Three types of functions; user-defined
    - Autoregressive
      - Past observations can be used to predict the current observation
    - Differencing
      - E.g., subtraction of one observation from the previous observation
      - Helps to make the data "independent" of time
        - Required for ARIMA
    - Moving Average
      - Aka running average or rolling average
      - Used to smooth out short-term fluctuations and identify longer-term trends

Building ARIMA Models

I. Model the correlation structure (stochastic or noise component)
   1. Identification stage
      - Defines the autoregressive, differencing, and moving average functions
   2. Estimation stage
      - Estimate model parameters
   3. Diagnostic stage
      - Generate diagnostic statistics to judge model fit
   4. If diagnostics indicate inadequate model, repeat steps 1-2

II. Model and test the intervention (the deterministic component; segmented regression)
   - Level of complexity dependent on the study design and the nature of expected effect of the intervention

Notes on ARIMA Modeling

- For outcome data that are approximately normally distributed
- Count data
  - Rates
    - Approximately normally distributed if based on large numbers
  - Generalized ARMA models
    - E.g. Poisson regression
    - Available in R
- Models can be made more complex
  - Control groups
  - Account for lagged intervention effects
  - Etc….

Practical Tips For Conducting an ITS Study

Conducting a ITS Study

- What is the intervention
  - Does it contain multiple components?
  - Does fidelity vary over time?
  - Is a lagged effect anticipated?

Conducting an ITS Study

- Define study population
- Evaluate baseline data
  - How far back can you collect baseline data?
    - Consider other policies, interventions, institutional changes
    - Longer pre-intervention period is preferrable
- Expected impact
  - Appropriate unit of time
  - Appropriate duration of study

Conducting an ITS Study

- Consider other influences on outcome
  - Drug shortages, seasonality, etc.
- If possible study multiple outcomes
  - Often difficult to identify change in event rates of interest in our field
  - Increase likelihood of documenting interventional impact
    - Process/intermediate measures

Conducting ITS Studies

- Can incorporate higher-level design features
  - Control group
  - Removed treatment
  - Staged roll out

Conducting an ITS Study

- Data collection
  - Be systematic
    - Need equally space time intervals
  - Collect descriptive data—establish generalizability
  - Consider other mitigating factors
    - Outbreaks
    - Changes in formulary, drug shortages, etc.
  - Enumerate your denominator
    - Average number of antibiotics ordered per patient
    - Percent of patients treated according to guidelines
    - Average quantity of alcohol-based hand rub used in a unit (consider # HCWs)

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Conducting an ITS Study

- Data management
  - Data structure
    - Plan ahead
  - Consider granularity
    - Ability to collapse data into different time units
    - Ability to stratify outcome data (e.g., antibiotics)

Conducting an ITS Study

- Data analysis
  - Make a plan *a priori*
  - Intervention
    - Date(s)
    - Phases?
    - Staggered roll out?
  - Number observations before/after intervention
  - Graphical representations of data are useful
    - Plotting the average/predicted effects

ITS Summary

- Useful for studying system/group level effects of intervention
  - Immediate and gradual effects assessed through segmented regression
- Analysis methods require adjustment for correlation structure
- Advanced design features strengthen ability to make causal inference
- Design and implementation requires some planning
  - Most difficult aspect is planning study duration

References & Resources

Useful Background on ITS:

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- Shadish WR, Cook TD and Campbell DT (2001). Experimental and quasi-experimental designs for generalized causal inference. Boston, Houghton Mifflin.
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References & Resources

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References & Resources

ITS Examples in the literature:

1. Taggart LR et al. "Differential outcome of an antimicrobial stewardship audit and feedback program in two intensive care units: a controlled interrupted time series study." BMC Infect Dis. 2015 Oct 29;15:480.
   - Controlled ITS, with non-dependent outcome
2. Standiford et al. "Antimicrobial Stewardship at a Large Tertiary Care Academic Medical Center: Cost Analysis Before, During, and After a 7-Year Program." Infect Control Hosp Epidemiol. 2012 Apr 33 (4): 338-45.
   - ITS with removed intervention
3. Elligsen et al. "Audit and Feedback to Reduce Broad-Spectrum Antibiotic Use among Intensive Care Unit Patients A Controlled Interrupted Time Series Analysis." Infect Control Hosp Epidemiol. 2012 Apr 33 (4): 354-61.
   - ITS with control
4. Palmay et al. "Hospital-wide Rollout of Antimicrobial Stewardship: A Stepped-Wedge Randomized Trial." Clin Infect Dis. 59(6): 867-874.
   - Staged-roll out of intervention

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