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

SHEA Antimicrobial Stewardship Research Workshop 2017

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COI & Disclosures

- Contracted research
  - Merck
- Investigator initiated research
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- 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

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Why Evaluate ASP Interventions?

- Demonstrate intervention effect
  - Defined, measurable outcome
- "Prove" effect was due to intervention
  - 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

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

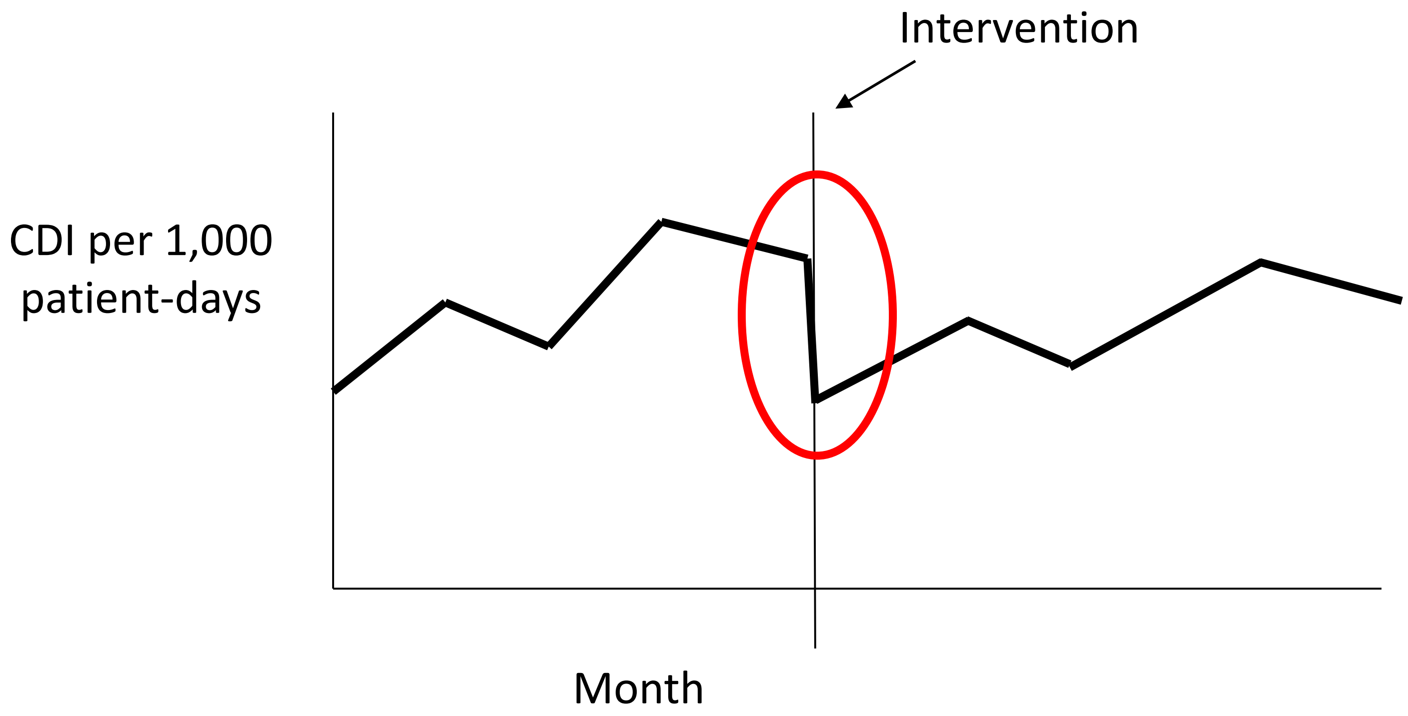
- Outcome characteristics
  - Group/system level outcome
  - Measurable across units of time
  - Examples
    - Cost
    - Antibiotic orders
    - Infection/Colonization
    - Resistance

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

Interrupted Time Series



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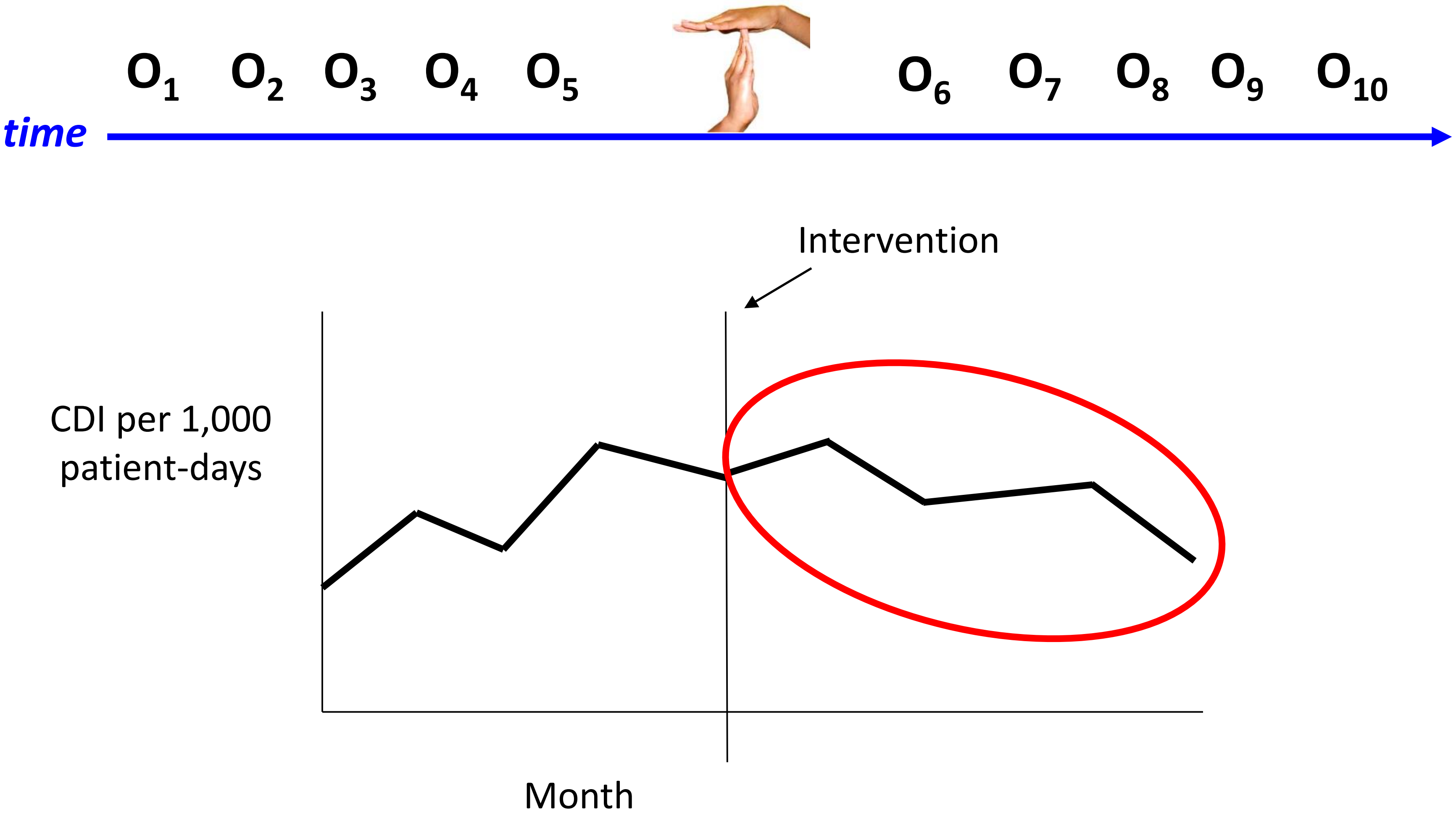
Interrupted Time Series



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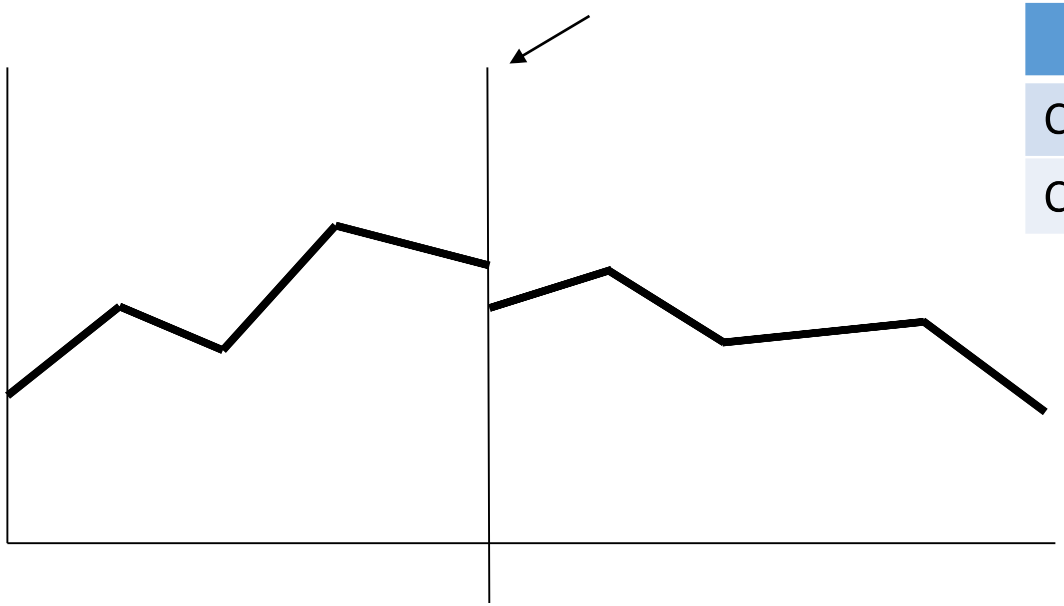
Interrupted Time Series

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

time



	Change in CDI (CI)
Change in Intercept	-2.03 (-3.45 – 0.76)
Change in Slope	-7.24 (-9.82 – -5.33)

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Do you believe this study…..

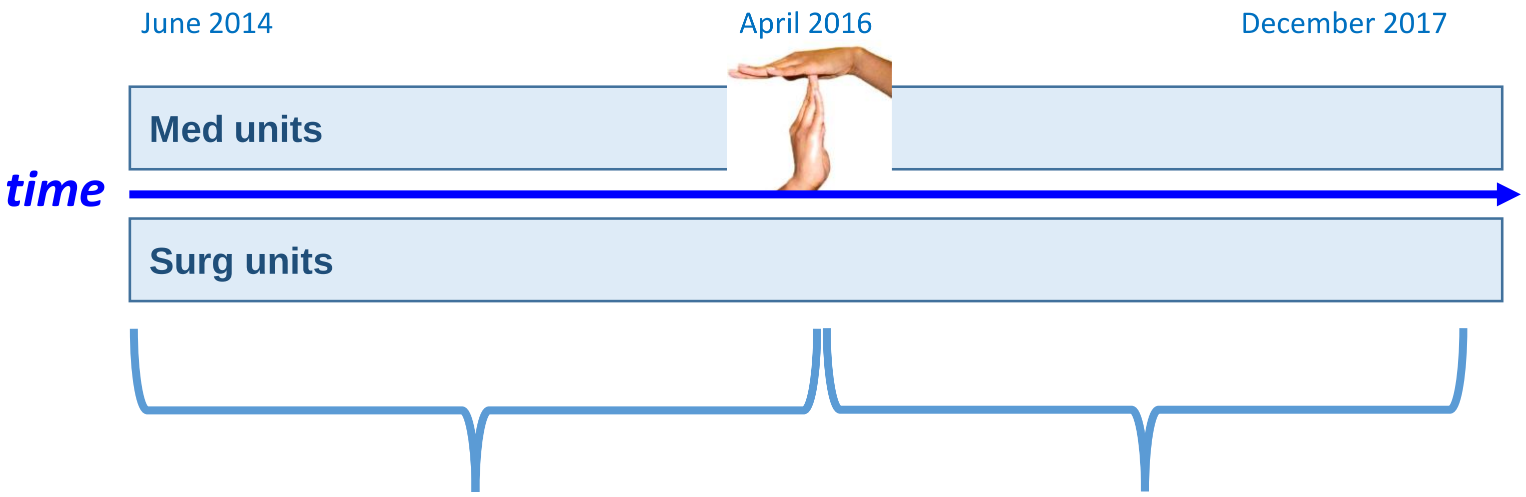
a. Demonstrates antibiotic time out is effective at reducing CDI
b. Is not a strong enough design to demonstrate time out effectiveness because it is not an RCT
c. Doesn’t provide adequate evidence to rule out other causes for CDI reduction
d. Can’t provide evidence for causation without a control group
e. Not sure what to make of this

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…



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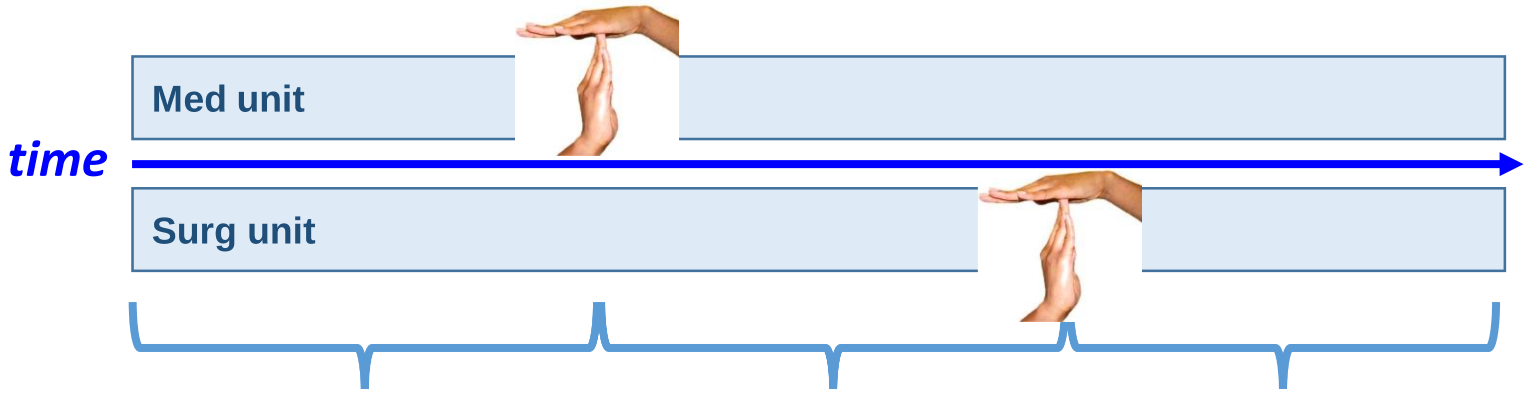
Designs with controls

- 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

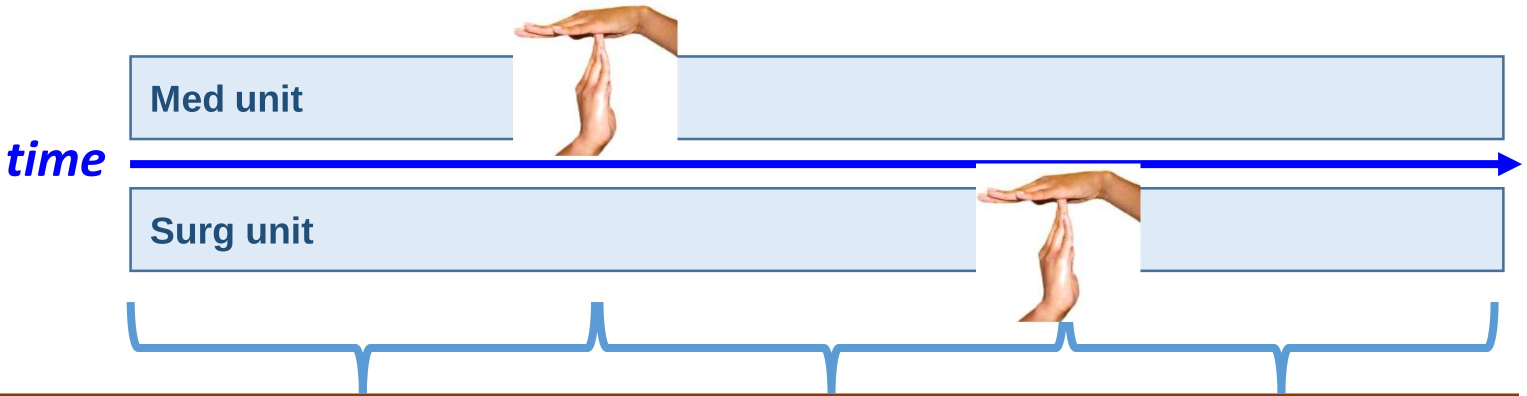
Staged Roll Out of Intervention

AKA Stepped wedge design



Staged Roll Out of Intervention

AKA Stepped wedge design



	ΔCDI per 10,000 patient days		
	Pre-intervention	Post-intervention I	Post-intervention II
Med unit	7.24	4.63	3.69
Surg unit	6.35	5.99	2.99

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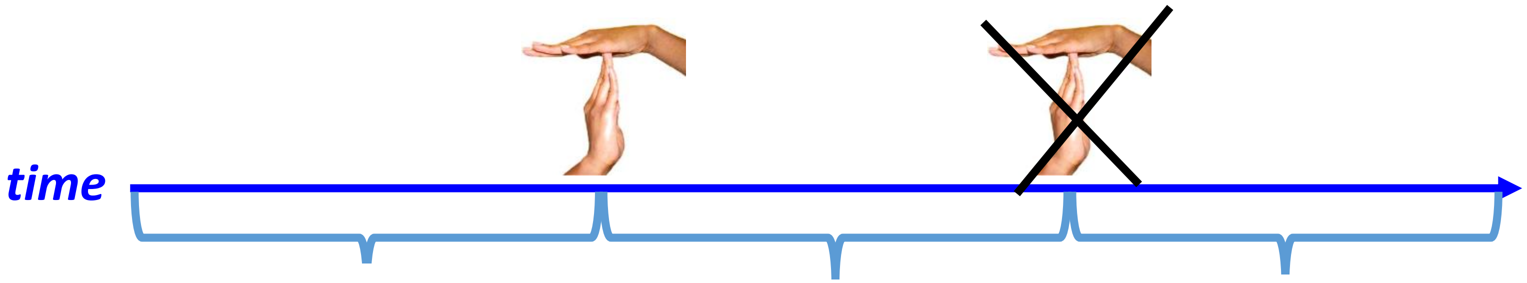
Removed Intervention



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

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Analyzing ITS Studies

- Need to account for correlation that arises from clustering or secular trends
  - Avoid biased statistical tests
- Want to retain advantages of ITS study design

Regression Approaches for ITS

- Marginal models (GEE)
  - Best for correlation structures that are not overly complex
- Mixed effects/random effects models
  - Allows for more complicated, hierarchical clustering
- Auto Regressive Integrated Moving Average
  - Allows for complicated correlation structure, secular trends

Regression

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

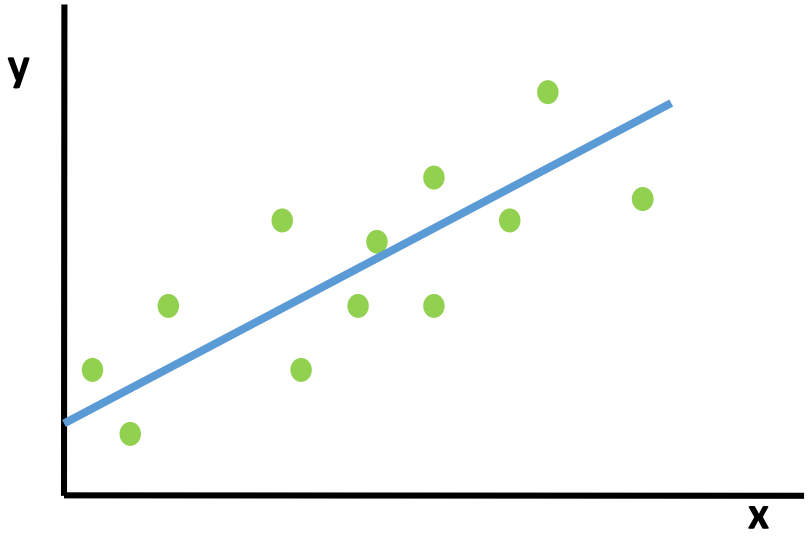
Dependent/Outcome Variable

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

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Segmented Regression for ITS

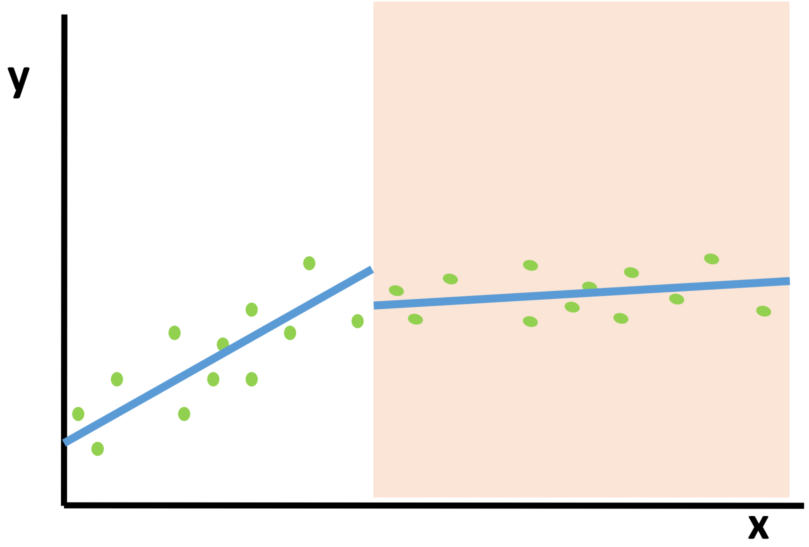
$$Y_t = \beta_0 + \beta_1(\text{time}_t) + \beta_2(\text{intervention}_t) + \beta_3(\text{time after intervention}_t) + e_t$$

Pre-Intervention Slope

Post-Intervention Change in Slope

Pre-Intervention Intercept

Post-Intervention Change in Intercept



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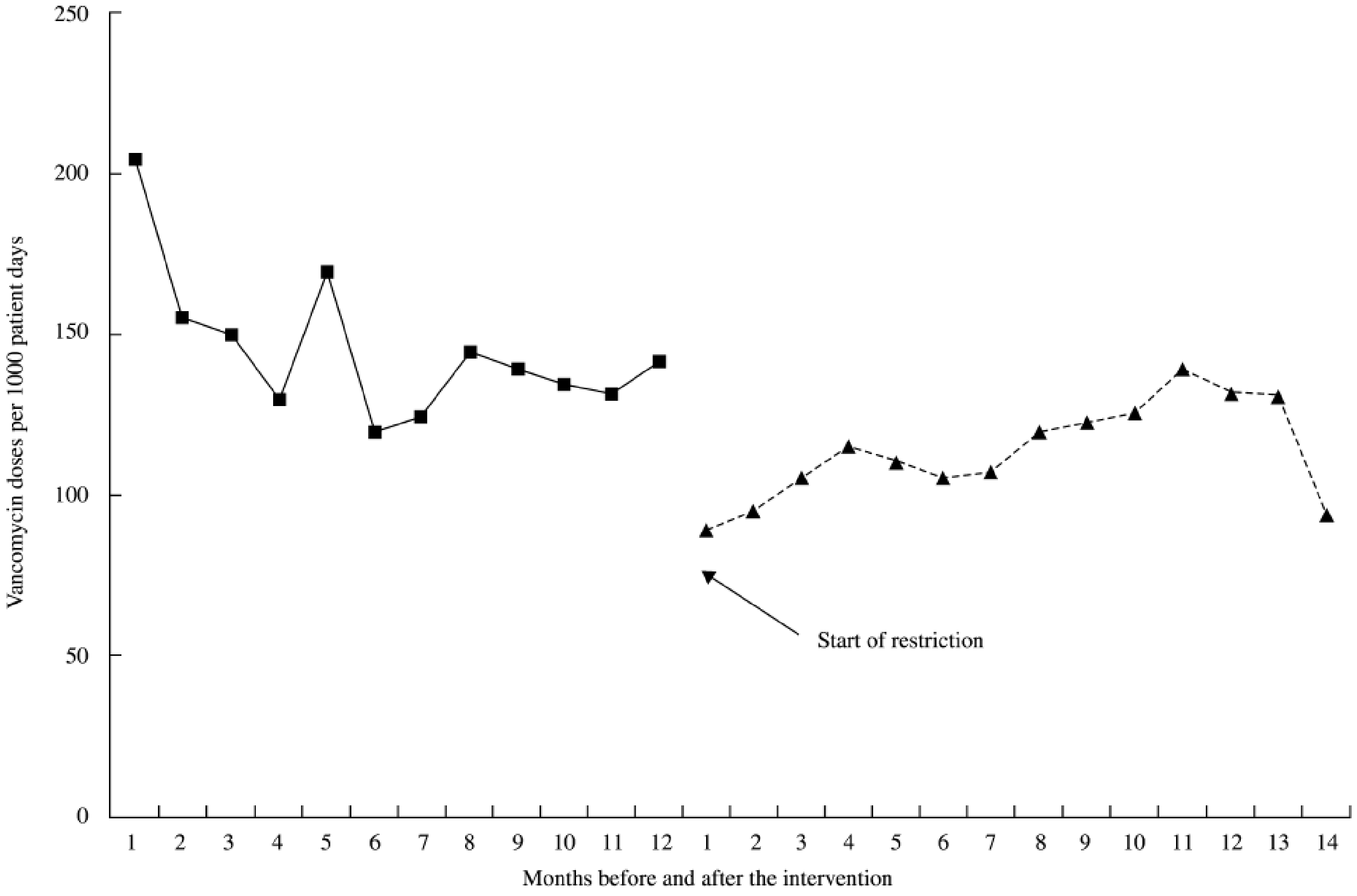
Analyzing ITS

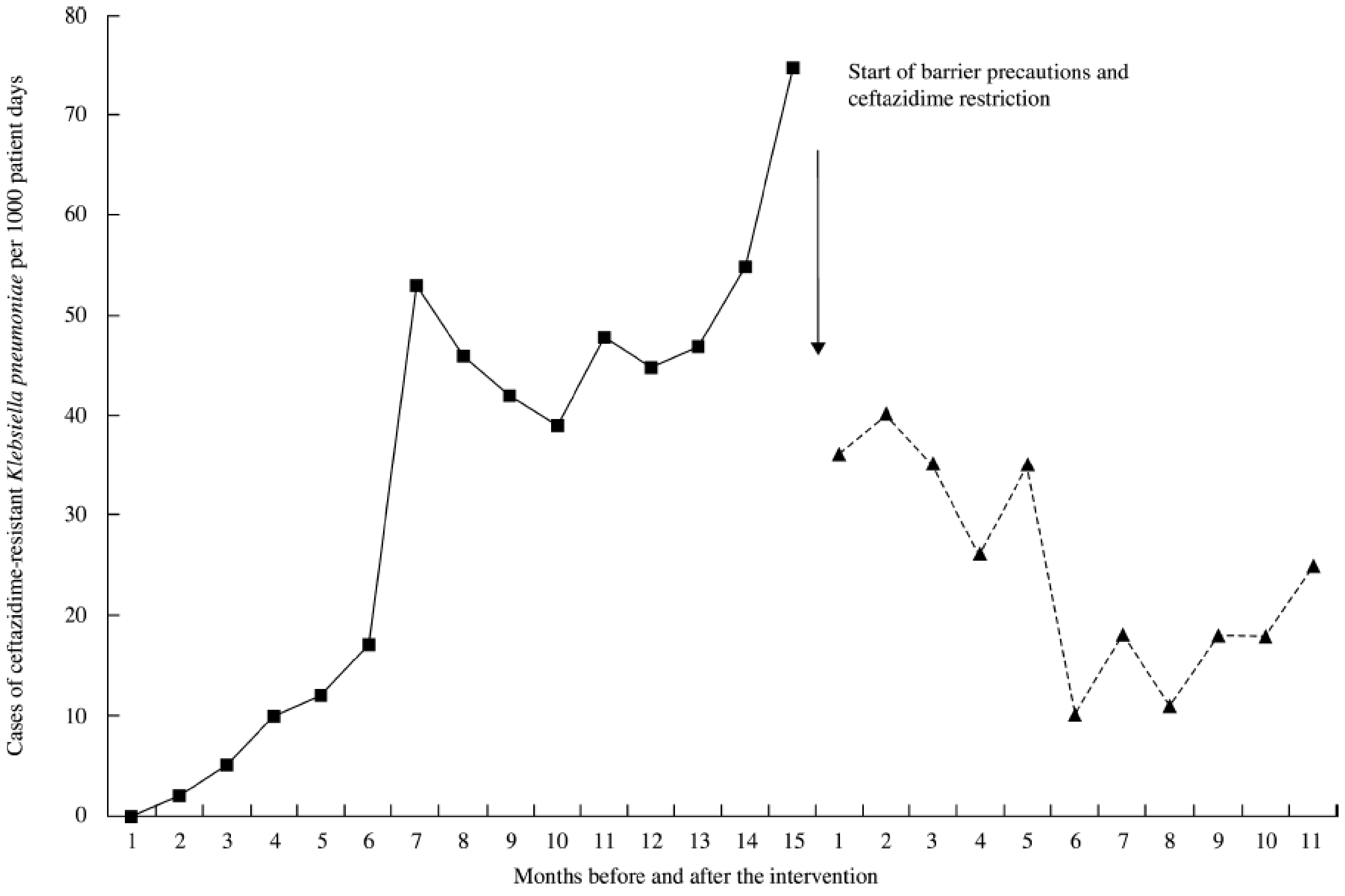
- Why can't we summarize the pre-intervention and post-intervention data and compare (i.e., compare two means)?
  - Reduces the study to a single pretest-postest design
  - Intervention effects can be over- or under-estimated



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



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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Segmented Regression for ITS

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

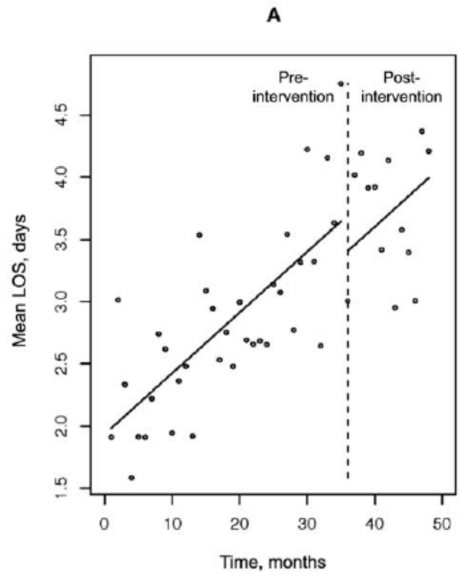

Figure 2. Interrupted time-series data regarding length of hospital stay (LOS) simulated from a segmented linear regression model with a change in slope (before vs. after the intervention), fit with a nonsegmented linear regression model that cannot estimate a change in slope *(A)* and a segmented linear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

Shardell et al. *Clin Infect Dis* 2007

Summary

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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- Wagner AK, Soumerai SB, Zhang F and Ross-Degnan D (2002). "Segmented regression analysis of interrupted time series studies in medication use research." J Clin Pharm Ther 27(4): 299-309.
- Quasi-experimental study design series (12 papers) in J Clin Epidemiol 89(2017).

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References & Resources

Intermediate/Advanced References to assist with design and analysis:

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- McLeod AI, Vingilis ER. Power computations in time series analyses for traffic safety interventions. Accid Anal Prev. May 2008;40(3):1244-1248.

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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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