Interrupted Time Series Analysis

Michael Law, Ph.D.
The University of British Columbia
Vancouver, Canada

Objectives

- Learn about Interrupted Time Series Analysis
- Discuss the rationale for using the method
- Look at several examples
- Overview of data requirements

THREATS TO VALIDITY

What is an Observational Study

- Where the researcher does not control the intervention or factor being studied
- Selection mechanism can be potentially problematic, especially if it's choice-based
- Confounders and existing trends likely differ between groups

Threats to Validity

- History
- Maturation
- Instrumentation & Testing
- Statistical Regression
- Selection

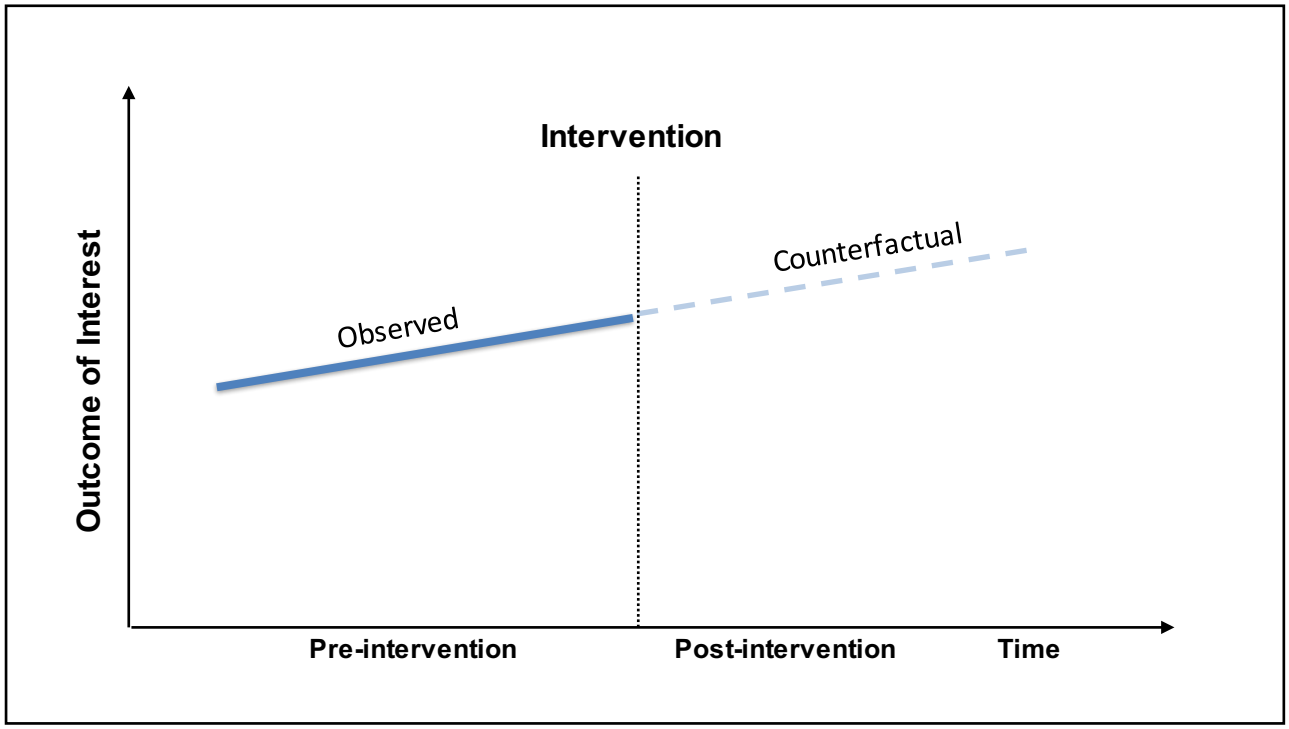
INTERRUPTED TIME SERIES

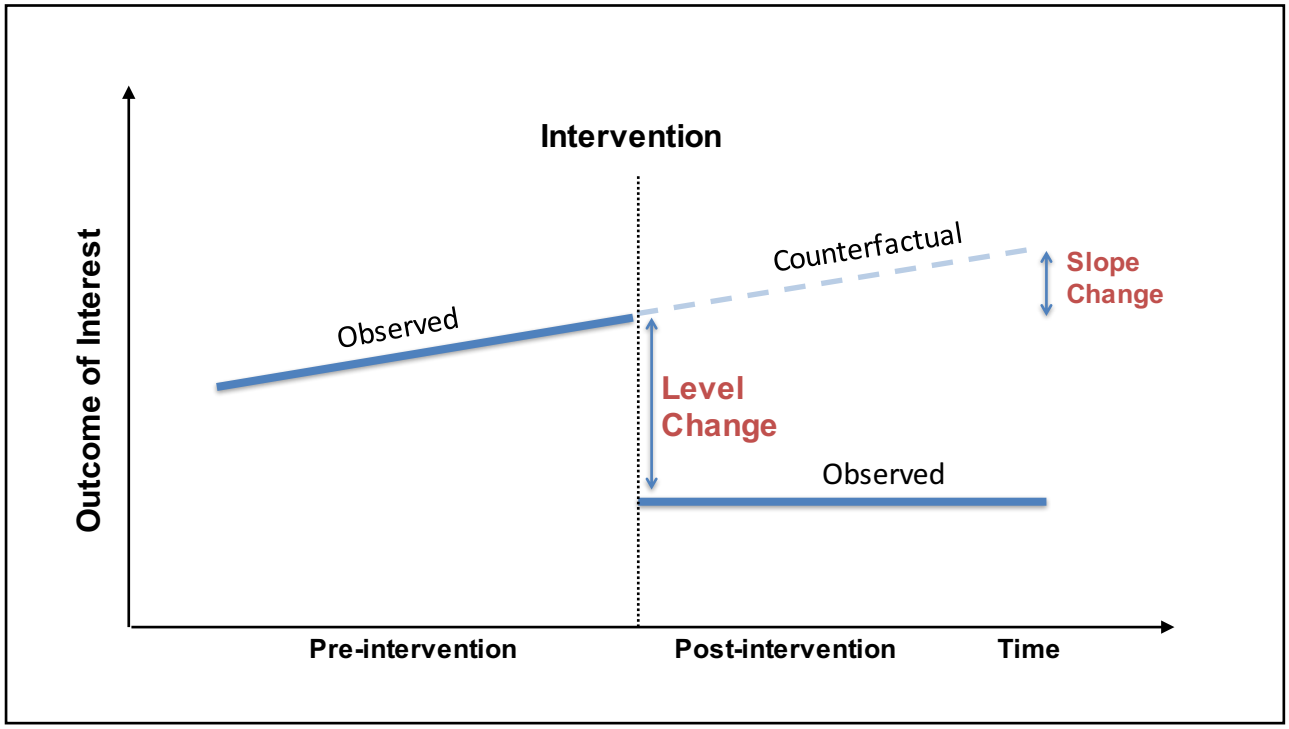
Single Group ITS

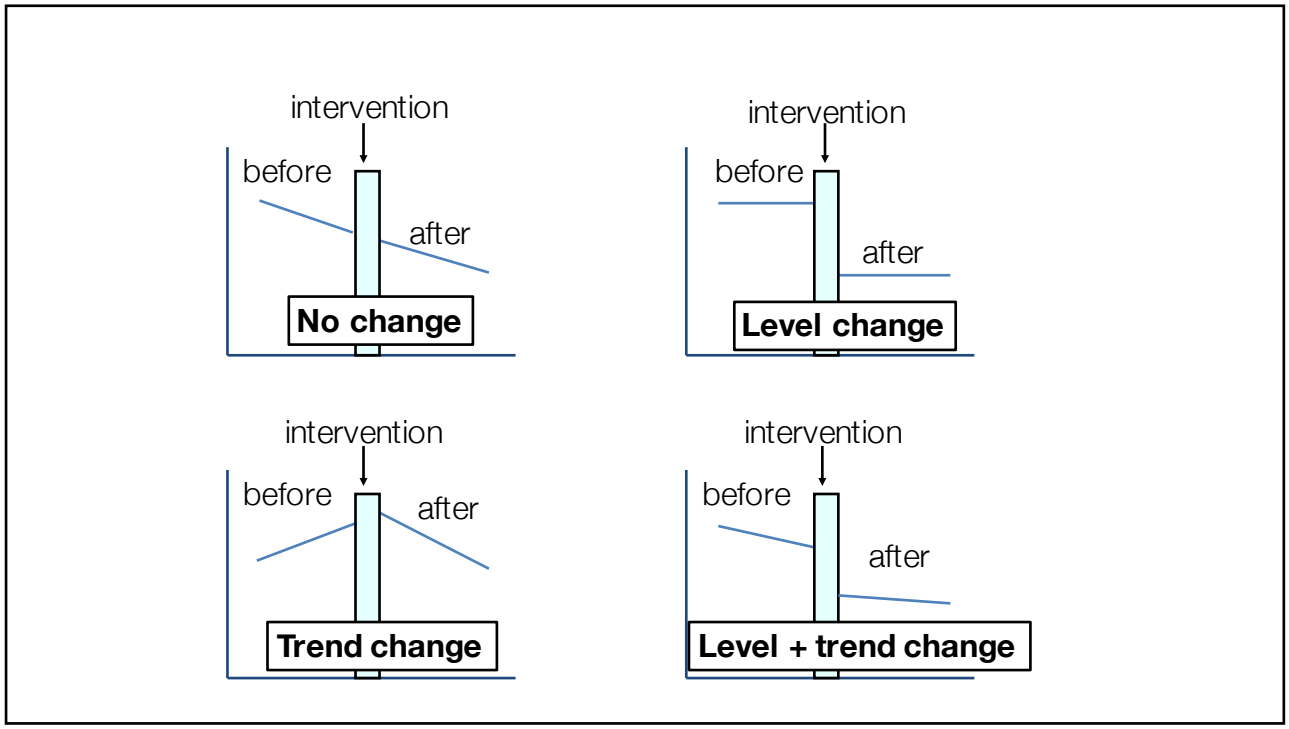
$O_1\ O_2\ O_3\ O_4\ O_5\ O_6\ O_7\ O_8\ X\ O_9\ O_{10}\ O_{11}\ O_{12}\ O_{13}\ O_{14}\ O_{15}\ O_{16}$

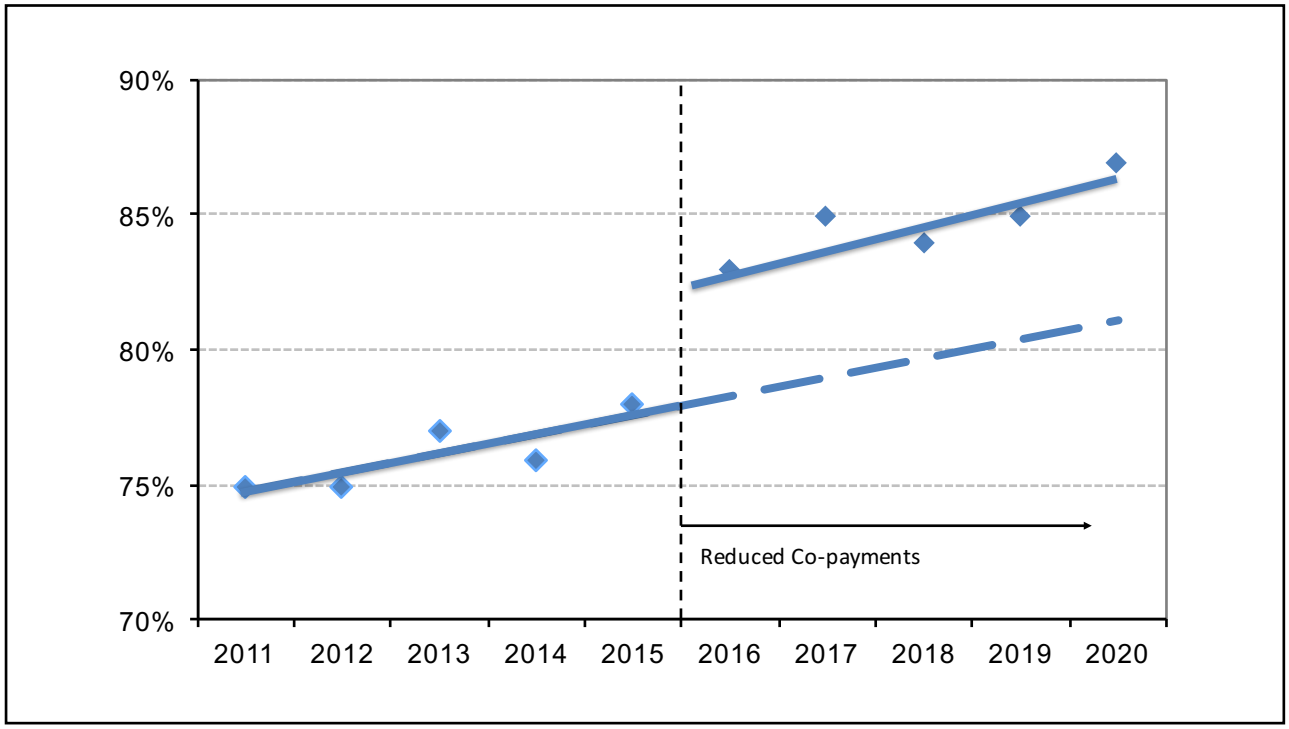
Interrupted Time Series

- Design
  - Compare longitudinal trends before and after the policy change
- Major Assumption
  - The existing level and trend in the outcome among those exposed to the intervention would have remained the same absent the intervention


Intervention
Outcome of Interest
Counterfactual
Observed
Pre-intervention
Post-intervention
Time


Intervention
Outcome of Interest
Counterfactual
Slope Change
Observed
Level Change
Observed
Pre-intervention
Post-intervention
Time


intervention
before
after
No change
intervention
before
after
Level change
intervention
before
after
Trend change
intervention
before
after
Level + trend change


90%
85%
80%
75%
70%
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
Reduced Co-payments

Common Time-Series Biases

1. History
   - Something aside from the policy affected the outcome and was implemented near the same time as the policy

2. Instrumentation
   - A change in measurement occurred near the same time as the policy

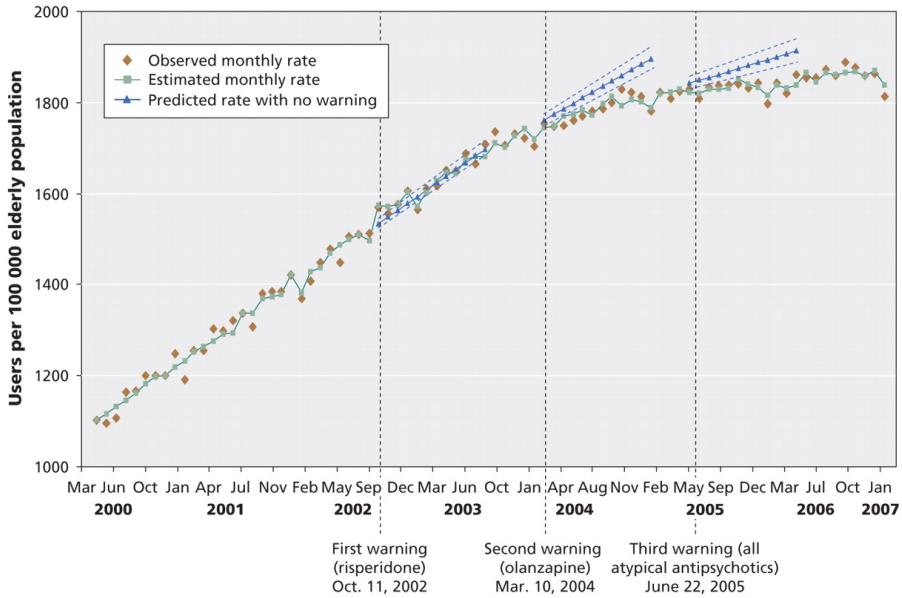
Problems with Interrupted Time Series

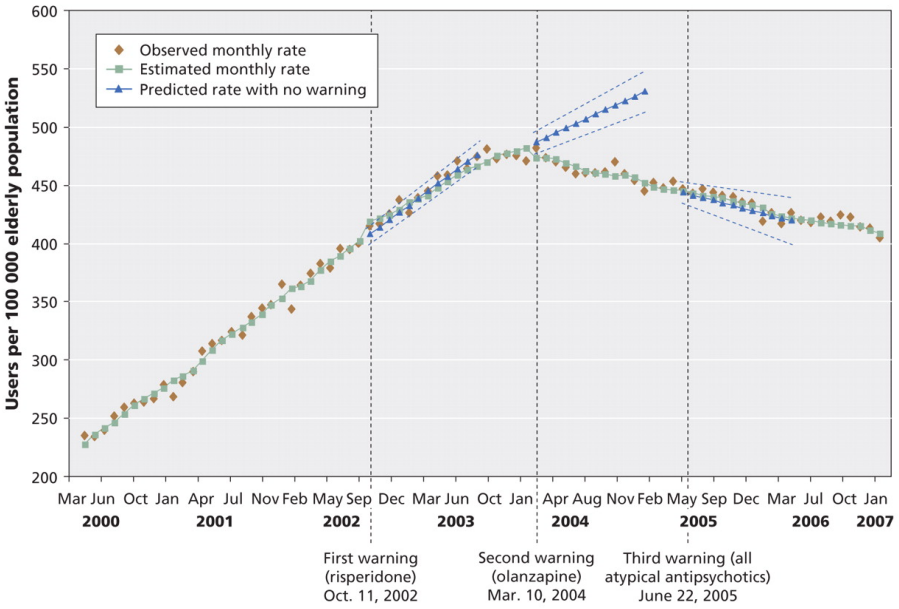
- Some potential issues:
  - Requires stable data, over longer time periods
  - Linear trend might not be realistic
  - Requires technical skill to properly fit from a statistical standpoint

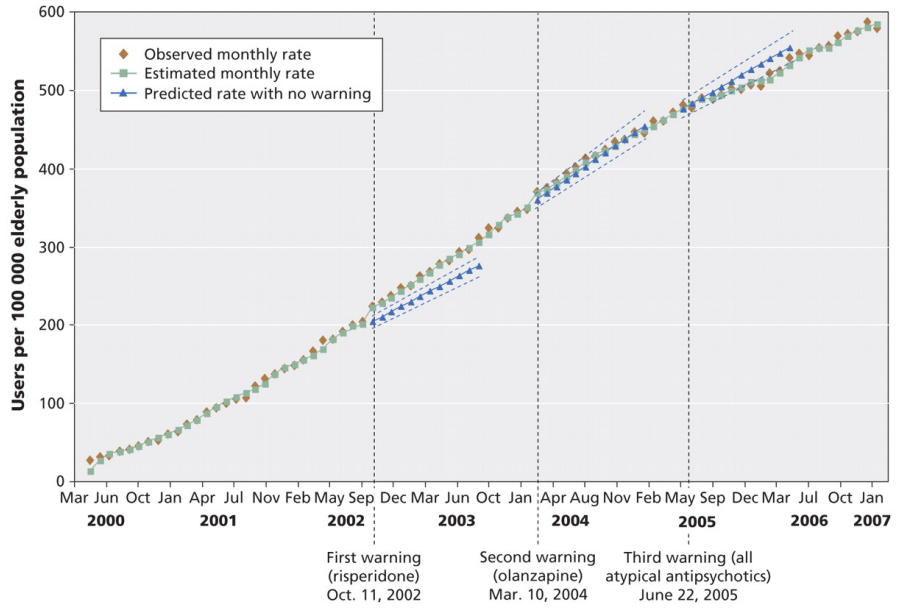
- The reward is protection from many threats to validity

Do warnings of serious adverse drug events impact utilization?

Valiyeva E et al. CMAJ 2008;179:438-446




Observed monthly rate
Estimated monthly rate
Predicted rate with no warning
Users per 100 000 elderly population
600
550
500
450
400
350
300
250
200
Mar Jun Oct Jan Apr Jul Nov Feb May Sep Dec Mar Jun Oct Jan Apr Aug Nov Feb May Sep Dec Mar Jul Oct Jan
2000 2001 2002 2003 2004 2005 2006 2007
First warning (risperidone) Oct. 11, 2002
Second warning (olanzapine) Mar. 10, 2004
Third warning (all atypical antipsychotics) June 22, 2005


Observed monthly rate
Estimated monthly rate
Predicted rate with no warning
Users per 100 000 elderly population
600
500
400
300
200
100
0
Mar Jun Oct Jan Apr Jul Nov Feb May Sep Dec Mar Jun Oct Jan Apr Aug Nov Feb May Sep Dec Mar Jul Oct Jan
2000 2001 2002 2003 2004 2005 2006 2007
First warning (risperidone) Oct. 11, 2002
Second warning (olanzapine) Mar. 10, 2004
Third warning (all atypical antipsychotics) June 22, 2005

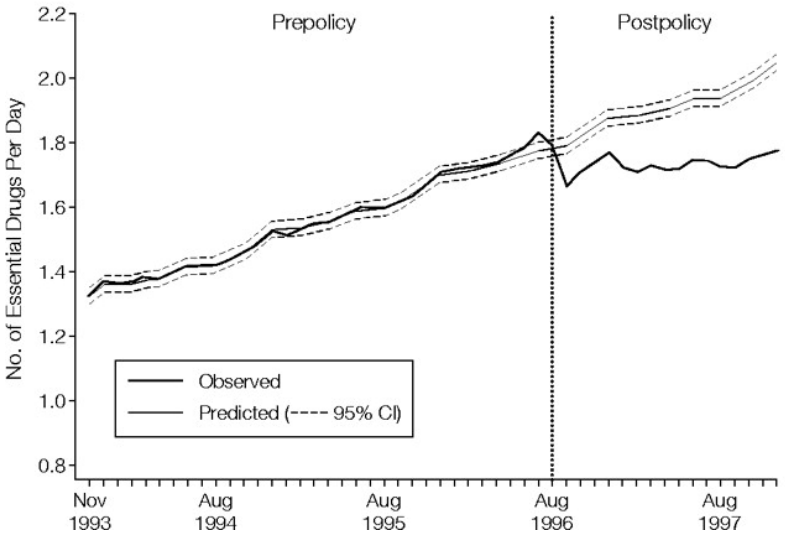
Do copayments reduce essential drug use?

Tamblyn R et al. JAMA
2001;285:421-429

Tamblyn et al. Study

- Drug cost increases have led to cutbacks in coverage by many jurisdictions
  - Introduction of co-payments in Quebec
- Question: What was the impact of these policies on drug use and cost?

Drug Co-Pays in Quebec



Source: Tamblyn et al. JAMA 2001;285:421-429.

Effect of Pay-for-performance

- Serumaga studied the impact of Pay-for-Performance incentives for GPs in the UK on hypertension control
- Government committed $2.8 Billion to achieve quality targets

Hypertension Indicators

Indicator	Number of Points
The practice can produce a register of patients with established hypertension	9
The percentage of patients with hypertension whose notes record smoking status at least once	10
The percentage of patients with hypertension who smoke, whose notes contain a record that smoking cessation advice has been offered at least once	10
The percentage of patients with hypertension in whom there is a record of the blood pressure in the previous 9 months	20
The percentage of patients with hypertension in whom the last blood pressure (measured in the previous 9 months) is 150/90 or less	56

Serumaga et al.

- Studies impact of the scheme on hypertension
  - 5 targets were specific to hypertension
- Collects data at 48 time points before, and 36 time points after the intervention
  - Health improvement network database (358 practices, > 470K patients)
  - Studied care, intermediate and clinical outcomes

$$O_1\ O_2 \ldots O_{47}\ O_{48}\ X\ O_{49}\ O_{50} \ldots O_{83}\ O_{84}$$

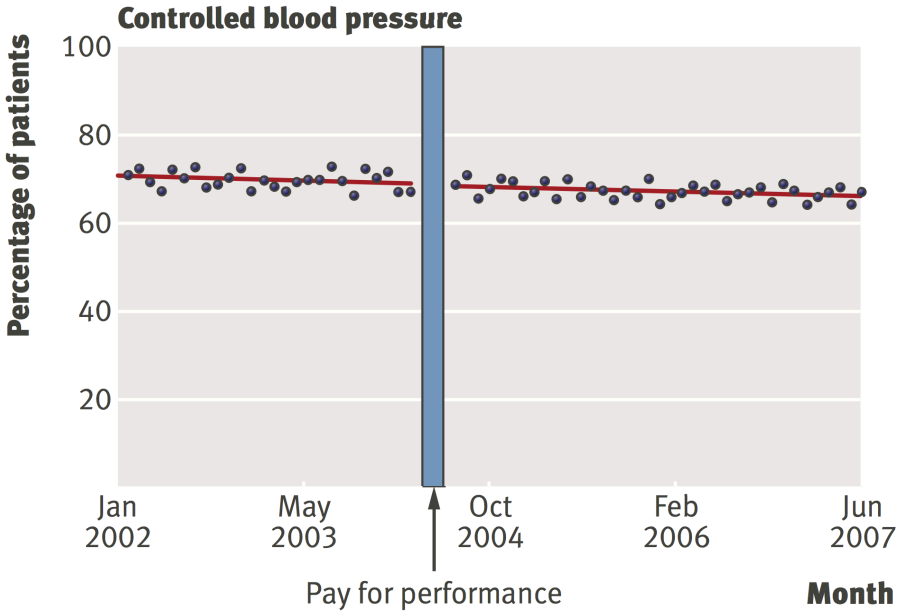
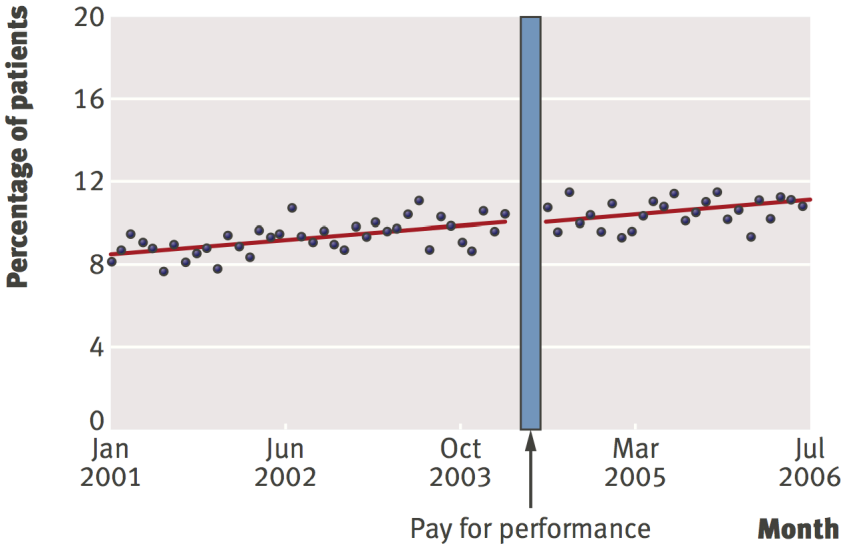


Fig 4 | Effect of pay for performance on hypertension related adverse outcomes (myocardial infarction, stroke, renal failure, heart failure) or on all cause mortality in United Kingdom



ITS WITH A CONTROL GROUP

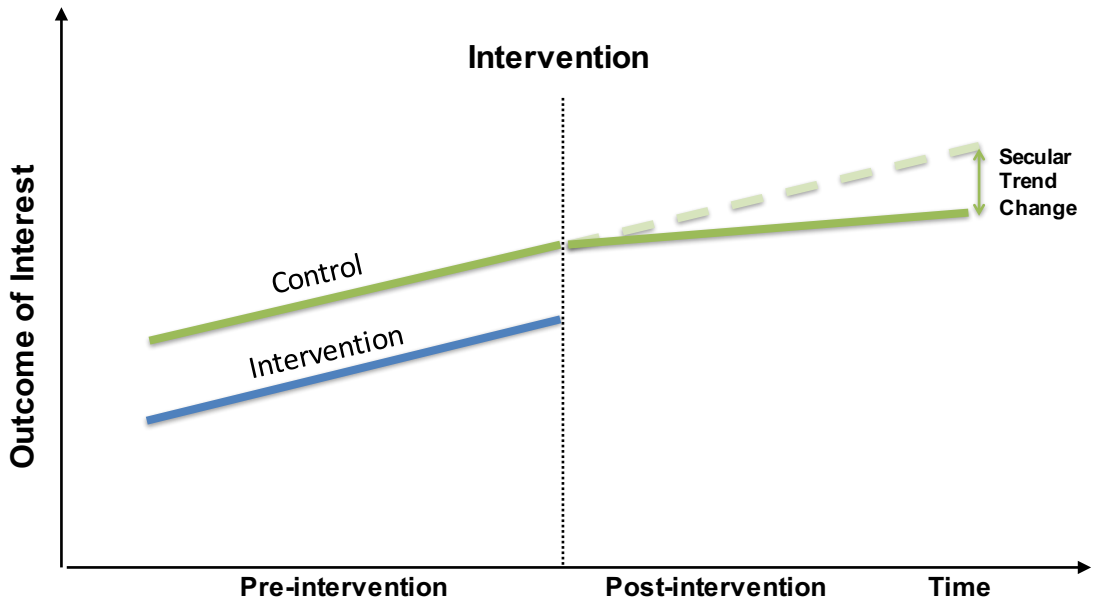
ITS with a Control Group

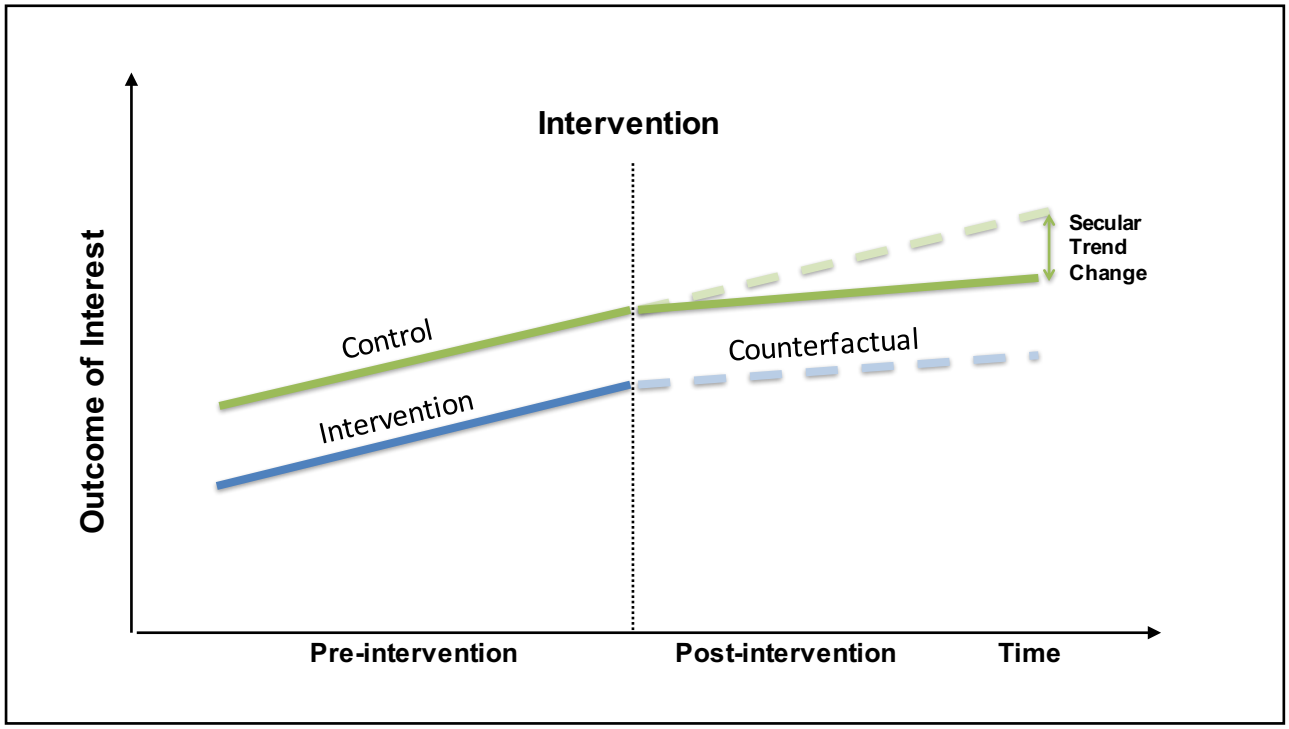
$$O_1\ O_2\ O_3\ O_4\ O_5\ O_6\ O_7\ O_8\ X\ O_9\ O_{10}\ O_{11}\ O_{12}\ O_{13}\ O_{14}\ O_{15}\ O_{16}$$

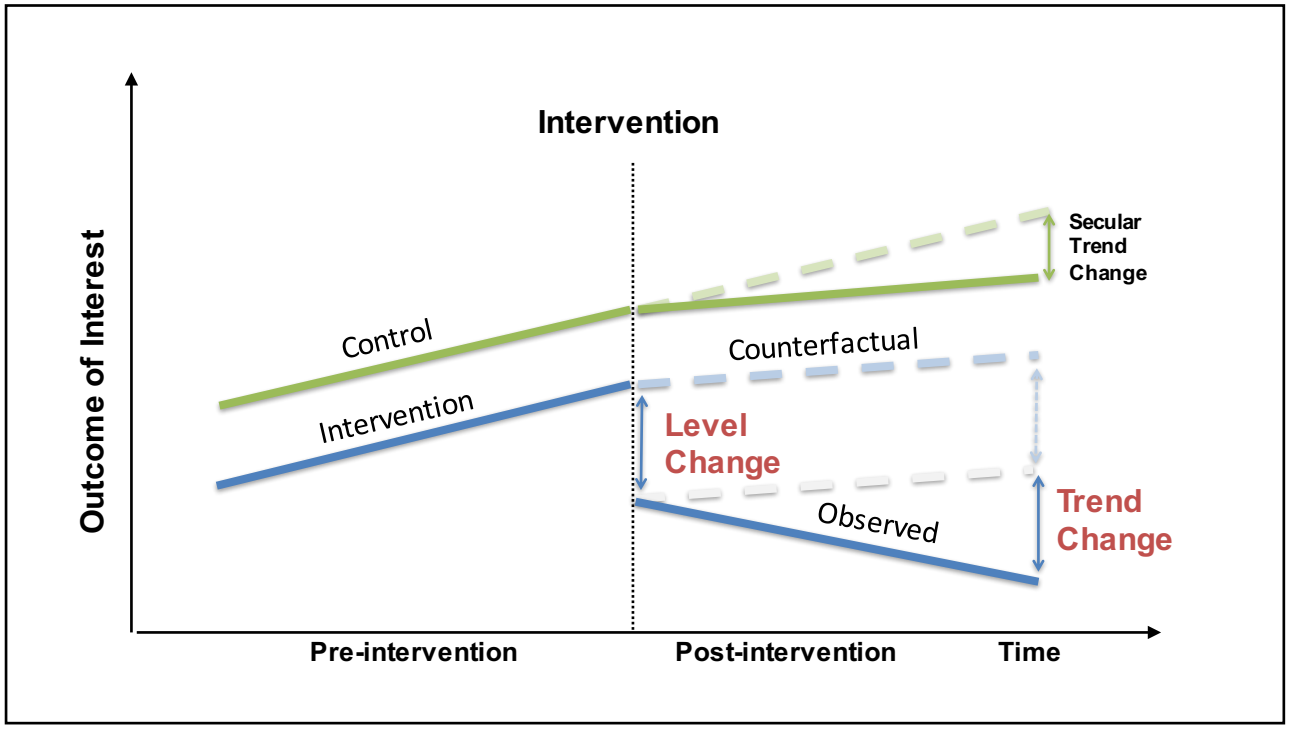
$$O_1\ O_2\ O_3\ O_4\ O_5\ O_6\ O_7\ O_8 \qquad O_9\ O_{10}\ O_{11}\ O_{12}\ O_{13}\ O_{14}\ O_{15}\ O_{16}$$

Interrupted Time Series with Control

- Design
  - Compare longitudinal trends before and after the policy change between the intervention and control group
- Major Assumption
  - The existing level and trend in the outcome among those exposed to the intervention would have changed identically to the control group absent the intervention




Intervention
Outcome of Interest
Secular
Trend
Change
Control
Counterfactual
Intervention
Pre-intervention
Post-intervention
Time


Intervention
Outcome of Interest
Secular
Trend
Change
Control
Counterfactual
Intervention
Level
Change
Observed
Trend
Change
Pre-intervention
Post-intervention
Time

The Control Series

- Counterfactual becomes the observed change in the control group
- Control group adds further legitimacy by limiting possible history threats
- Can be an unaffected group, another jurisdiction, etc.
  - Does not have to have the same pre trend (although a similar trend is more convincing)
  - Also does not have to be balanced

Potential Biases

1. Selection—History
   - Something aside from the intervention affected the outcome and was implemented near the same time as the intervention

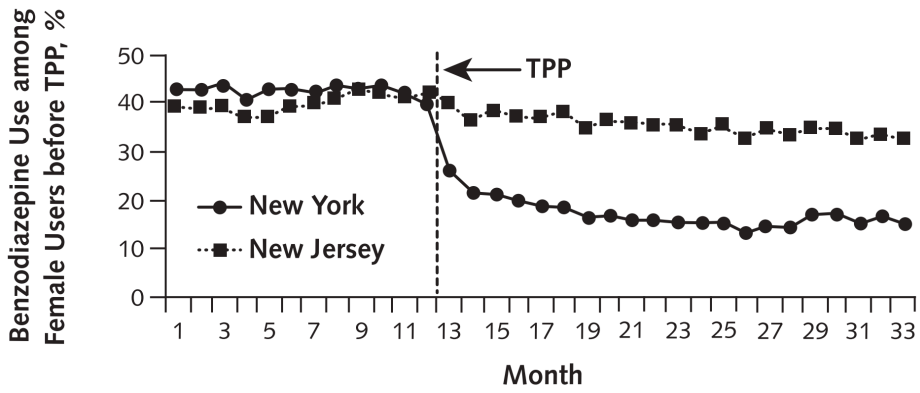
2. Selection—Instrumentation
   - A change in measurement for one group occurred near the same time as the intervention

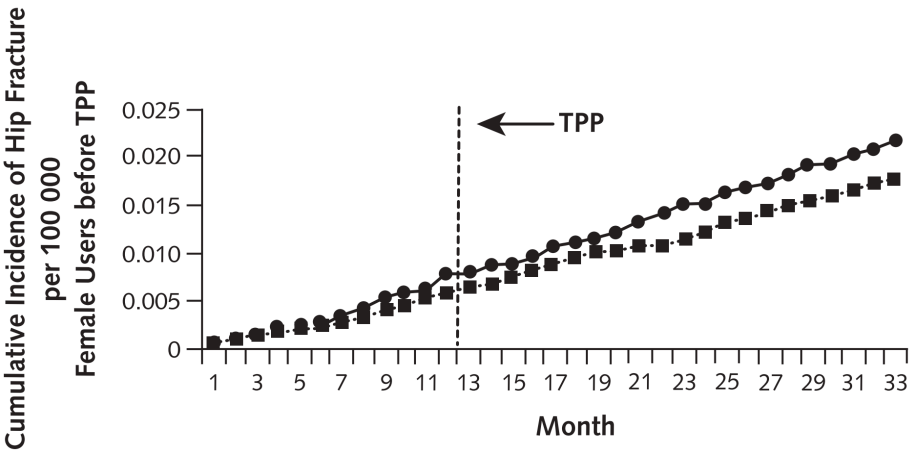
Impact of Restricting Benzodiazepines

- Existing studies showed an association between benzodiazepine use and hip fractures
- As a result, many states restricted their use in the elderly, and they were excluded from Medicare Part D
- Authors studied a "triplicate" policy in NY on incidence of hip fractures
  - New Jersey was used as a control series

Table 1. **Age, Sex, and Eligibility Categories of Medicaid Enrollees in 1988 in New York and New Jersey**

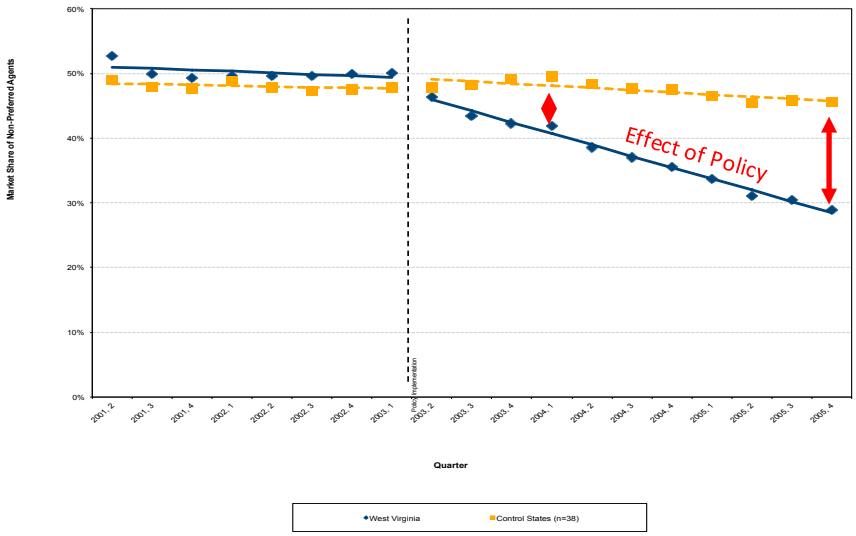
Characteristic	New York	New Jersey
Sample, *n*	51 529	42 029
Age on 1 January 1988, %		
65–74 years	49.2	60.4
75–84 years	35.7	28.8
≥85 years	15.2	10.8
Female sex, %	77.3	77.2
Eligibility category as of June 1988, %		
Aid to the Permanently and Totally Disabled	8.2	24.9
Old Age Assistance	91.8	75.1


Benzodiazepine Use among Female Users before TPP, %
50
40
30
20
10
0
TPP
New York
New Jersey
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33
Month


Cumulative Incidence of Hip Fracture per 100 000 Female Users before TPP
0.025
0.020
0.015
0.010
0.005
0
TPP
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33
Month

Impact of Prior Authorization

- In the US, many State Medicaid programs require enrollees to get "prior authorization" before receiving particular medicines
- What is the impact on the use of those drugs?
  - I examined a policy in West Virginia that restricted the use of some particular atypical antipsychotics



Source: Law et al. Psychiatric Services.

Does eliminating and reducing copayments increase drug use?

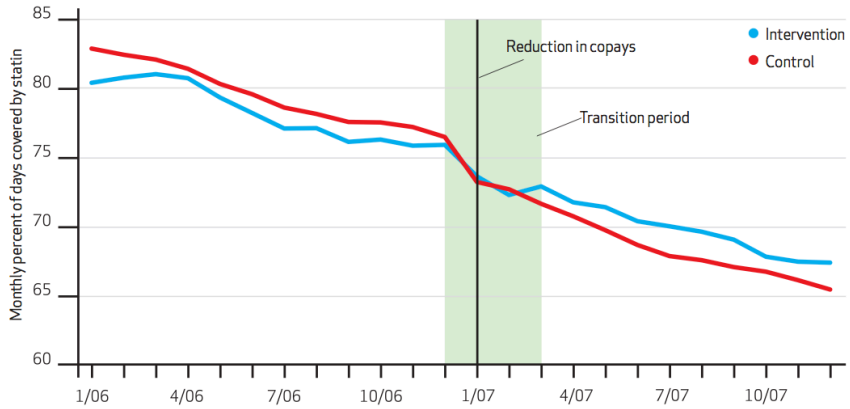
Choudhry N et al. Health Affairs
2010; 11: 1995-2001

Pitney Bowes Drug Program

- Reduction in copayments at Pitney Bowes
  - Eliminated co-payments for statins for patients with vascular disease or diabetes
  - Lowered co-payments for clopidogrel
- Studied longitudinal changes in the proportion of days covered by filled prescriptions in the year

EXHIBIT 2

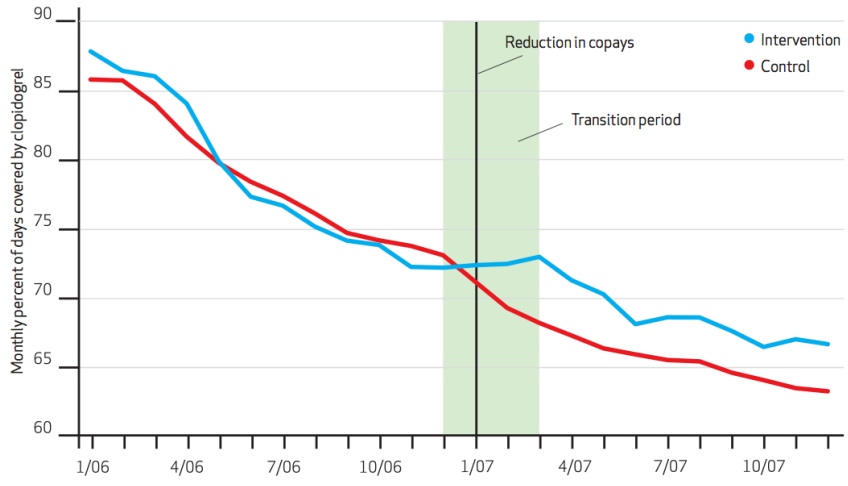
Changes In Monthly Statin Adherence In The Reduced-Copayment Cohort Compared With Control



SOURCE Authors' analyses. **NOTES** The blue and red lines represent crude monthly adherence rates for the cohort for whom copayments were reduced and for controls, respectively.

EXHIBIT 4

Changes In Monthly Clopidogrel Adherence In The Reduced-Copayment Cohort Compared With Control



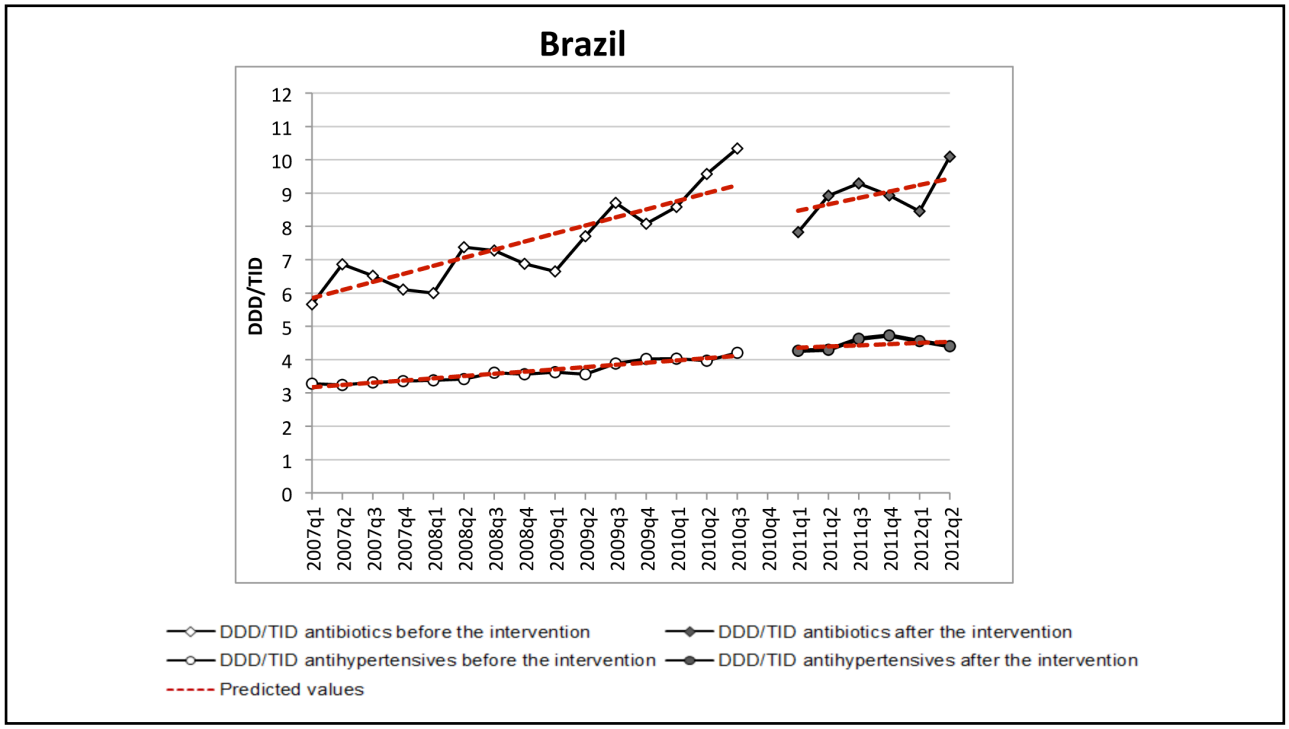
SOURCE Authors' analyses. **NOTES** The blue and red lines represent crude monthly adherence rates for the cohort for whom copayments reduced and controls, respectively.

How does enforcing prescription laws for antibiotics impact use?

Santa-Ana-Tellez et al. PLOS One
2013

Antibiotic Restrictions

- OTC dispensing of antibiotics is common
  - Can lead to resistance due to inappropriate use
- Studied longitudinal changes in defined daily doses after Brazil and Mexico started enforcing laws about their use



Group Work

- We will form groups of 3-4 people
- Please come up with a:
  - Policy intervention from your country
  - Some ideas about data sources
- Make this into a research question
  - For example: "What was the impact of _____ on _____?"

CONDUCTING AN ITS STUDY

Overview of steps

1. Determine time periods
2. Select analytic cohorts
3. Determine outcomes of interest
4. Setup data
5. Visually inspect the data
6. Perform preliminary analysis
7. Check for and address autocorrelation
8. Run the final model
9. Plot the results
10. Predict relative and absolute effects

Basic data setup

Time	Level	Trend	Outcome
1	0	0	4
2	0	0	5
…			
10	0	0	3
11	0	0	4
12	0	0	5
13	1	1	5
14	1	2	3
15	1	3	4
…			
23	1	11	6
24	1	12	5

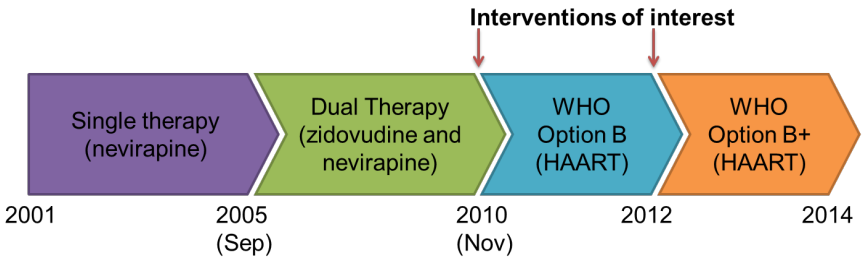
ABIMPAYE M, KIRK CM, IYER HS, GUPTA N, REMERA E, MUGWANEZA P, LAW MR

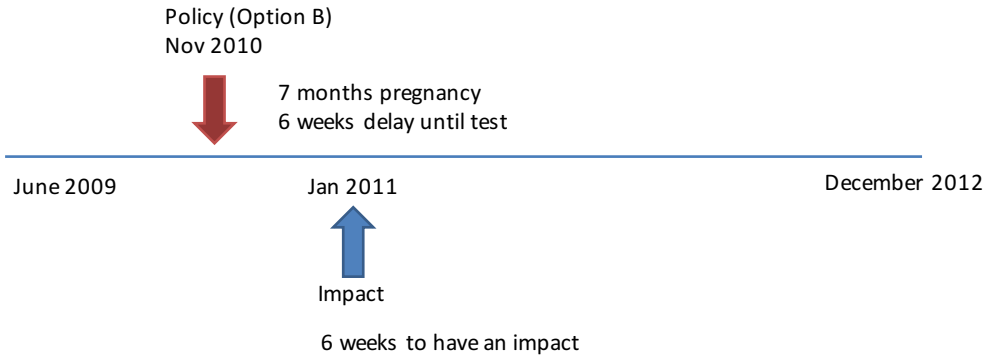
THE IMPACT OF "OPTION B" ON HIV TRANSMISSION FROM MOTHER TO CHILD IN RWANDA: AN INTERRUPTED TIME SERIES ANALYSIS

2016 (UNDER REVIEW).

Abimpaye et al. Study

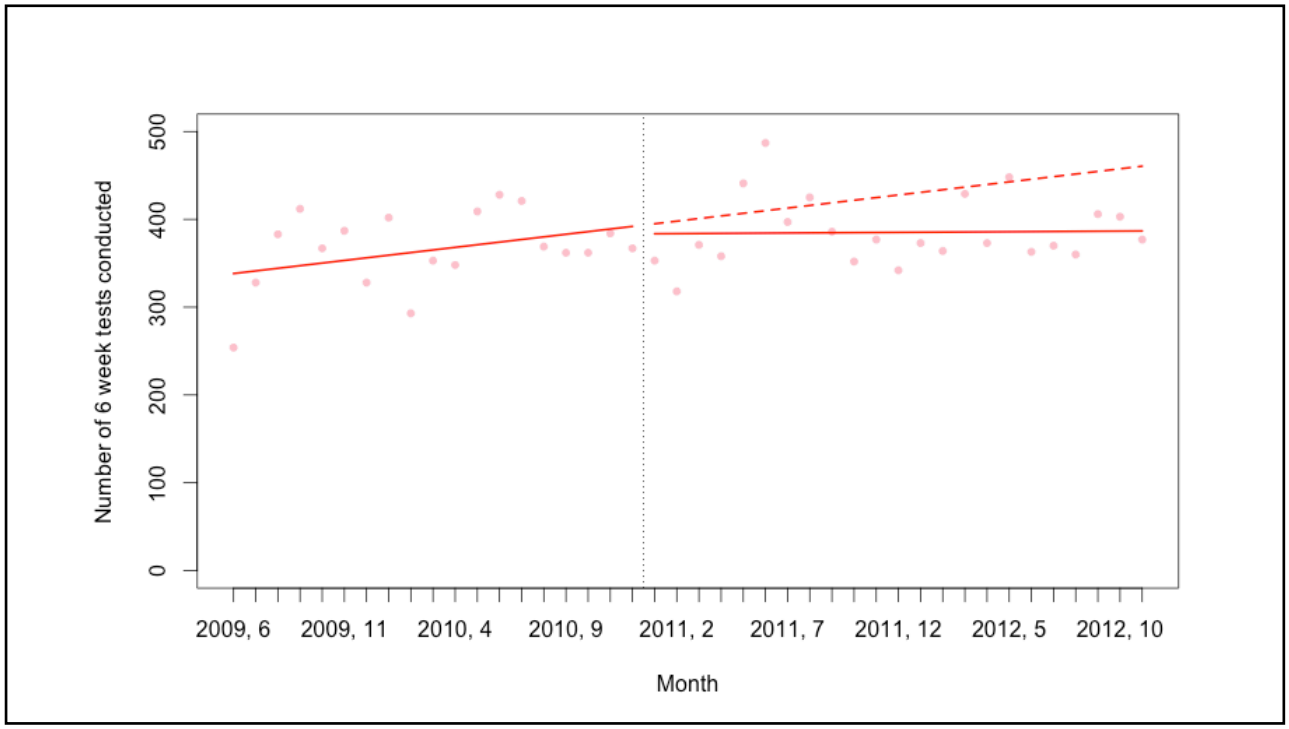
- WHO has recommended that countries adopt option B+
- Issue: costly, little real world evidence
- Question: What was the impact of this policy on mother to infant HIV transmission?

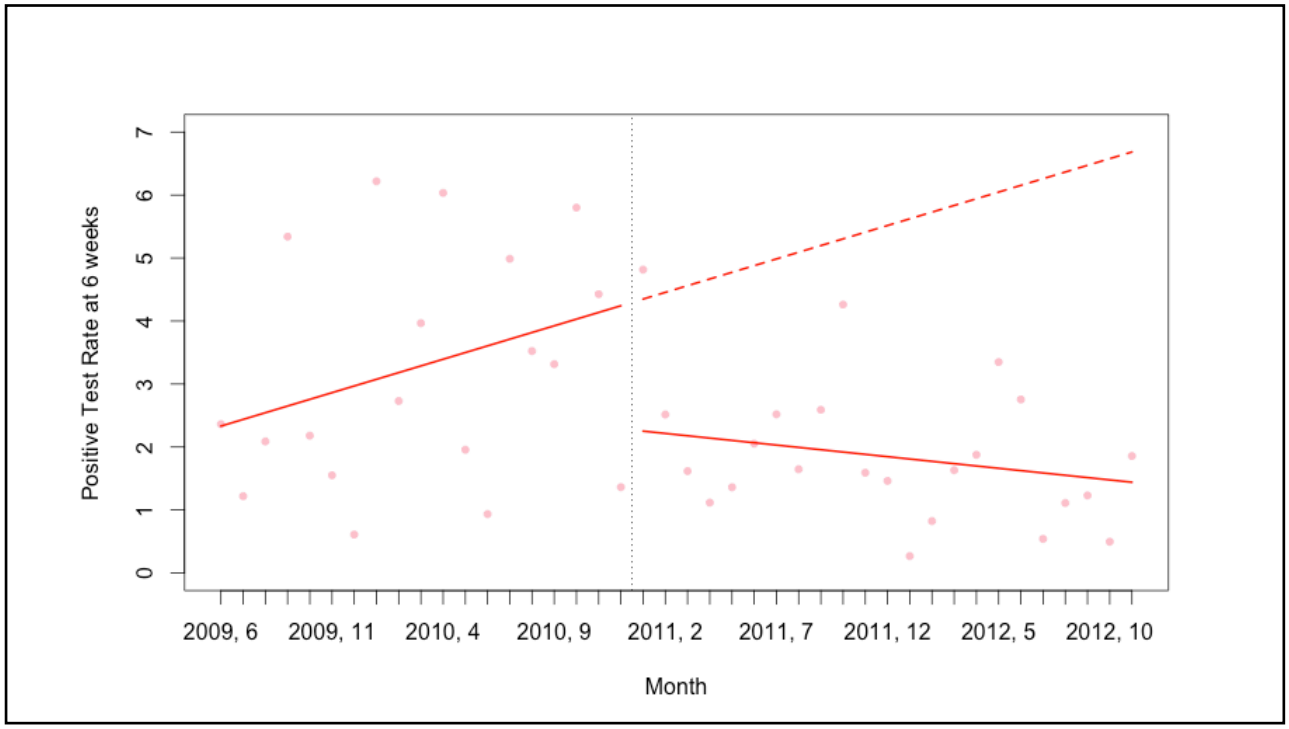


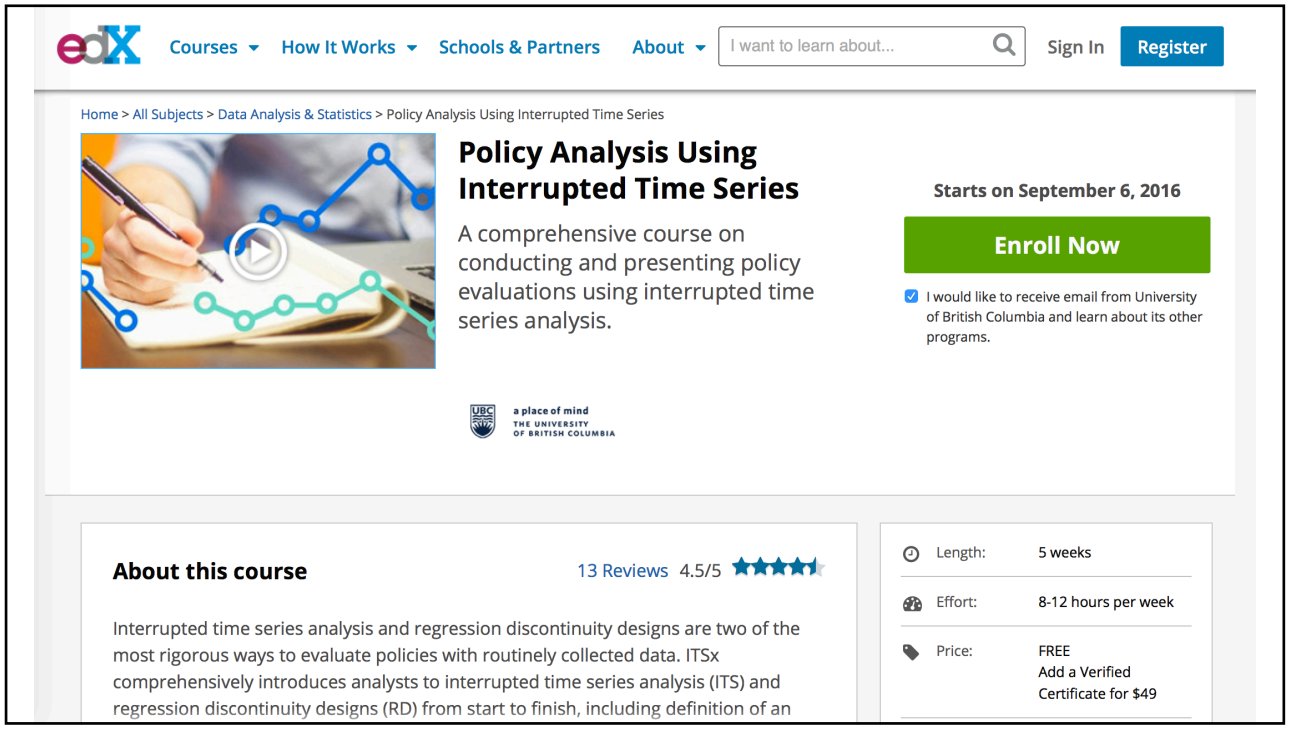


Data Sources

- TRACNET data from 2009 to 2012
- Outcomes
  1. Number of 6-week HIV tests conducted
  2. Rate of HIV transmission per 100 6-week tests


Number of 6 week tests conducted
0
100
200
300
400
500
2009, 6
2009, 11
2010, 4
2010, 9
2011, 2
2011, 7
2011, 12
2012, 5
2012, 10
Month


Positive Test Rate at 6 weeks
0
1
2
3
4
5
6
7
2009, 6
2009, 11
2010, 4
2010, 9
2011, 2
2011, 7
2011, 12
2012, 5
2012, 10
Month



Thank You!

Michael Law
michael.law@ubc.ca
@myclaw