Interrupted time-series analysis to assess the impact of interventions

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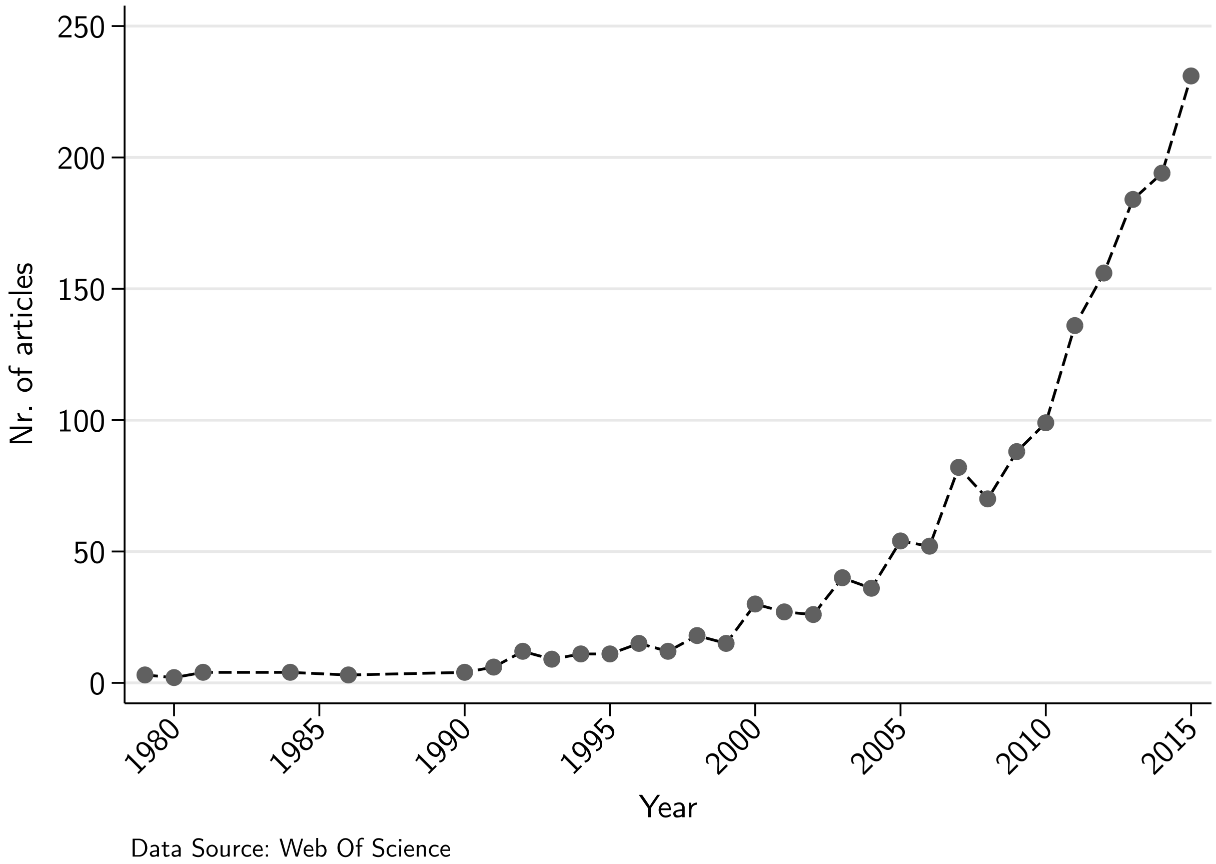
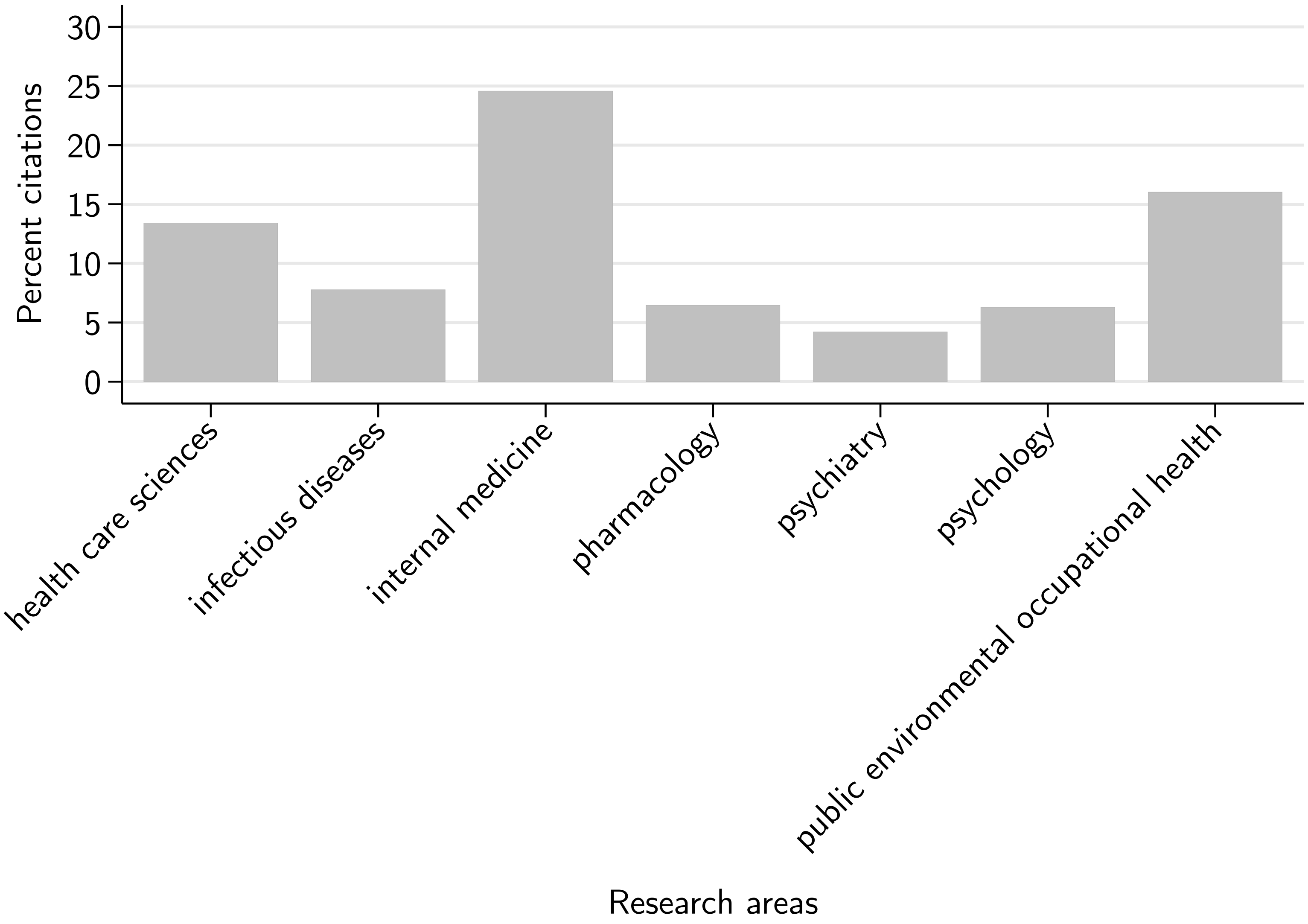
Outline

- Antibiotics Prescription: A motivational example
- Basic features
- Modelling the time-series
- One group and one intervention
- Two groups and one intervention
- Evaluating a policy on smoking
- Strengths and limitations

1634 articles over the last 35 years
80% over the last 10 years





Percent citations
30
25
20
15
10
5
0
health care sciences
infectious diseases
internal medicine
pharmacology
psychiatry
psychology
public environmental occupational health
Research areas

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What is it?

- A time series is a sequence of values of a particular measure taken at regularly spaced intervals over time.

- Interruption of a time series can be due to an experimental intervention, a policy change, or a real-world event.

- Routinely maintained records are commonly used sources of time series data.

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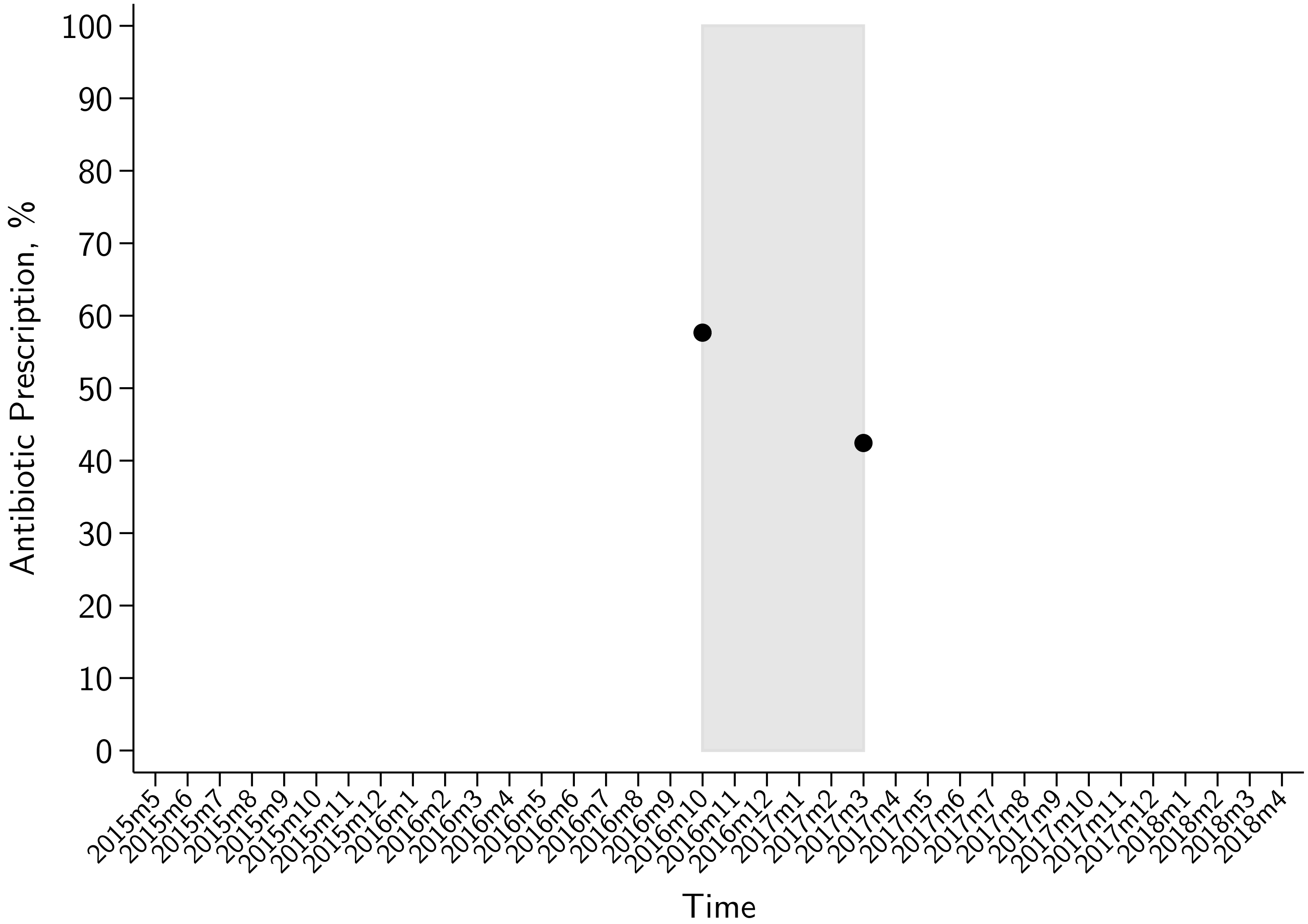
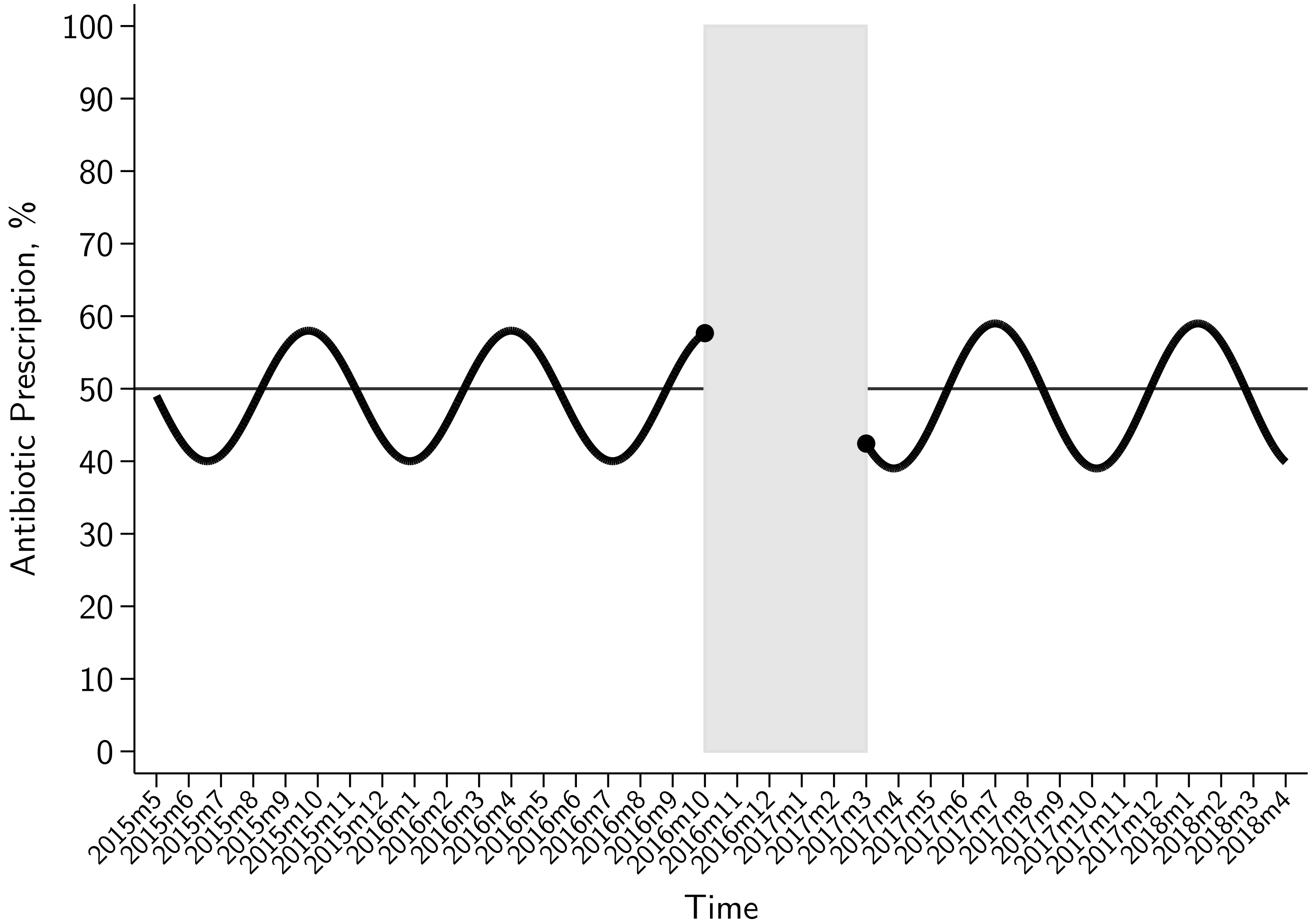
Design

- Quasi-experimental design (absence of randomization)
- Longitudinal effects of interventions
- If the intervention had an impact, the hypothesis is that observations after intervention will be different from those before intervention.
- Unit of analysis can be a person or a group of persons

One measure before and after intervention



Multiple measures before and after intervention



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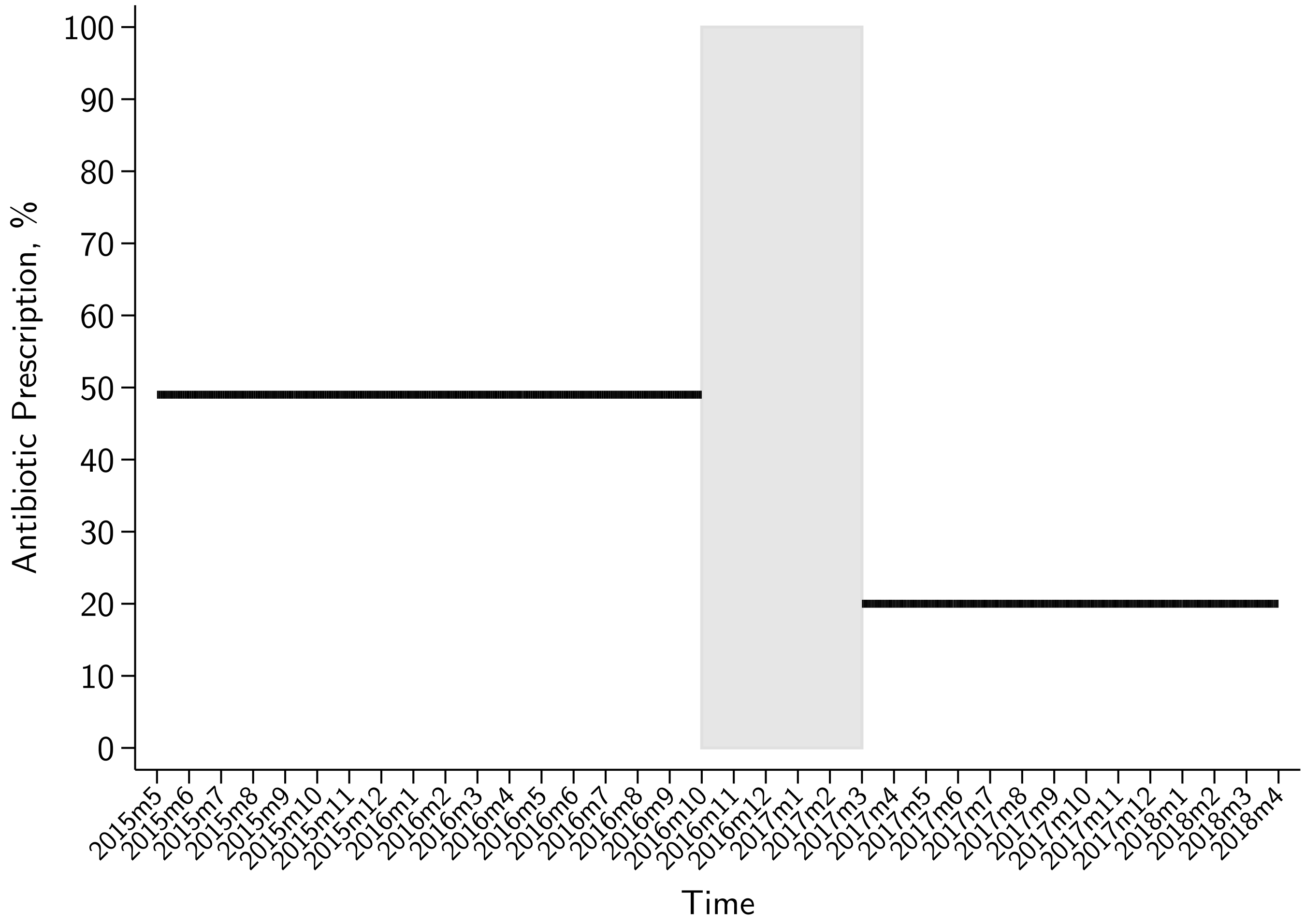
Different dimension of the effect

- Type of change (level, trend, variability)
- Immediacy (immediate, delayed)
- Duration (permanent, temporary)

Scenario 1



Antibiotic Prescription, %
100
90
80
70
60
50
40
30
20
10
0
2015m5
2015m6
2015m7
2015m8
2015m9
2015m10
2015m11
2015m12
2016m1
2016m2
2016m3
2016m4
2016m5
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2017m1
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2017m6
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2017m11
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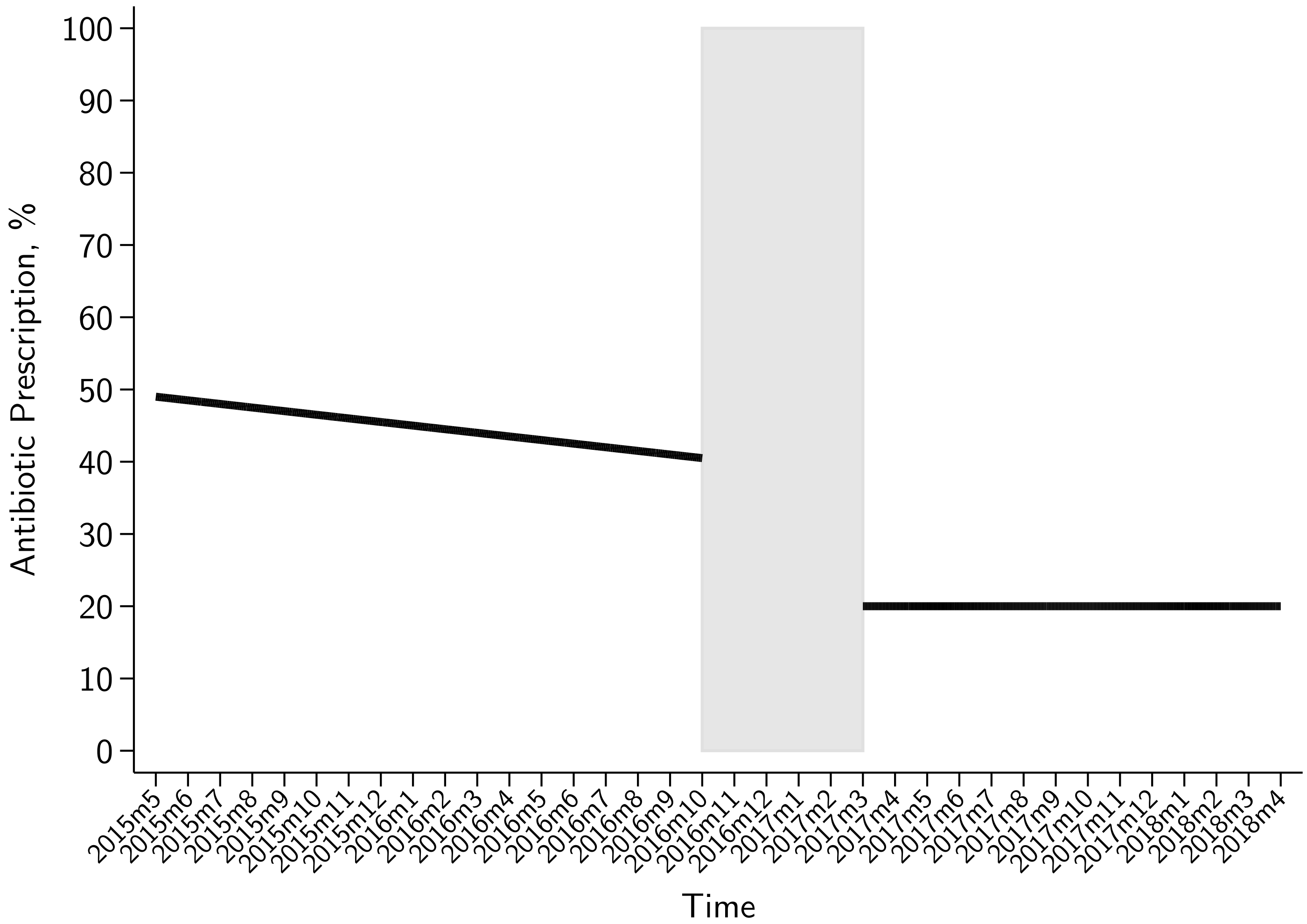
2018m1
2018m2
2018m3
2018m4
Time

Scenario 2



Antibiotic Prescription, %
100
90
80
70
60
50
40
30
20
10
0
2015m5
2015m6
2015m7
2015m8
2015m9
2015m10
2015m11
2015m12
2016m1
2016m2
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2017m1
2017m2
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2017m5
2017m6
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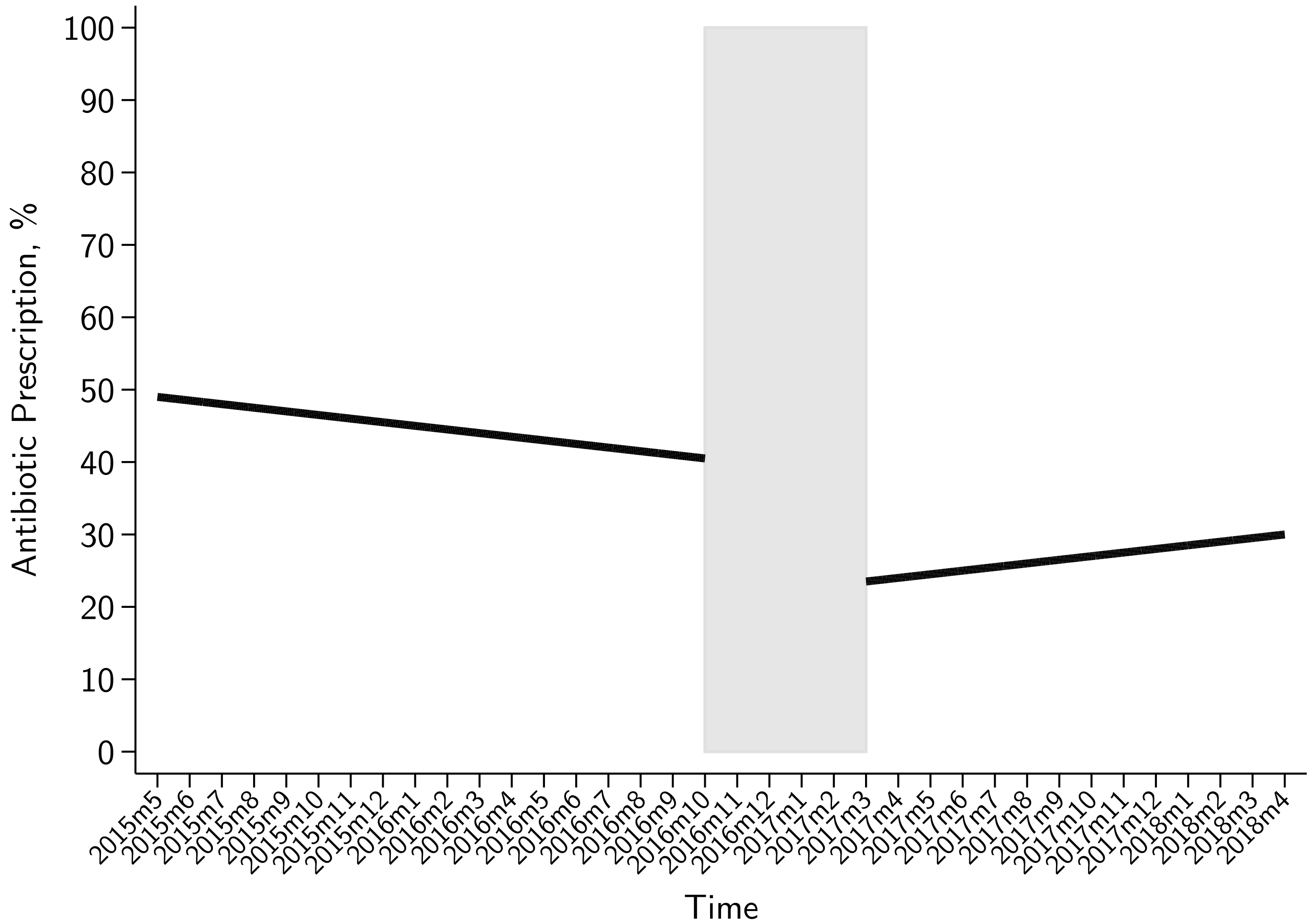
2017m11
2017m12
2018m1
2018m2
2018m3
2018m4
Time

Scenario 3



Antibiotic Prescription, %
0
10
20
30
40
50
60
70
80
90
100
2015m5
2015m6
2015m7
2015m8
2015m9
2015m10
2015m11
2015m12
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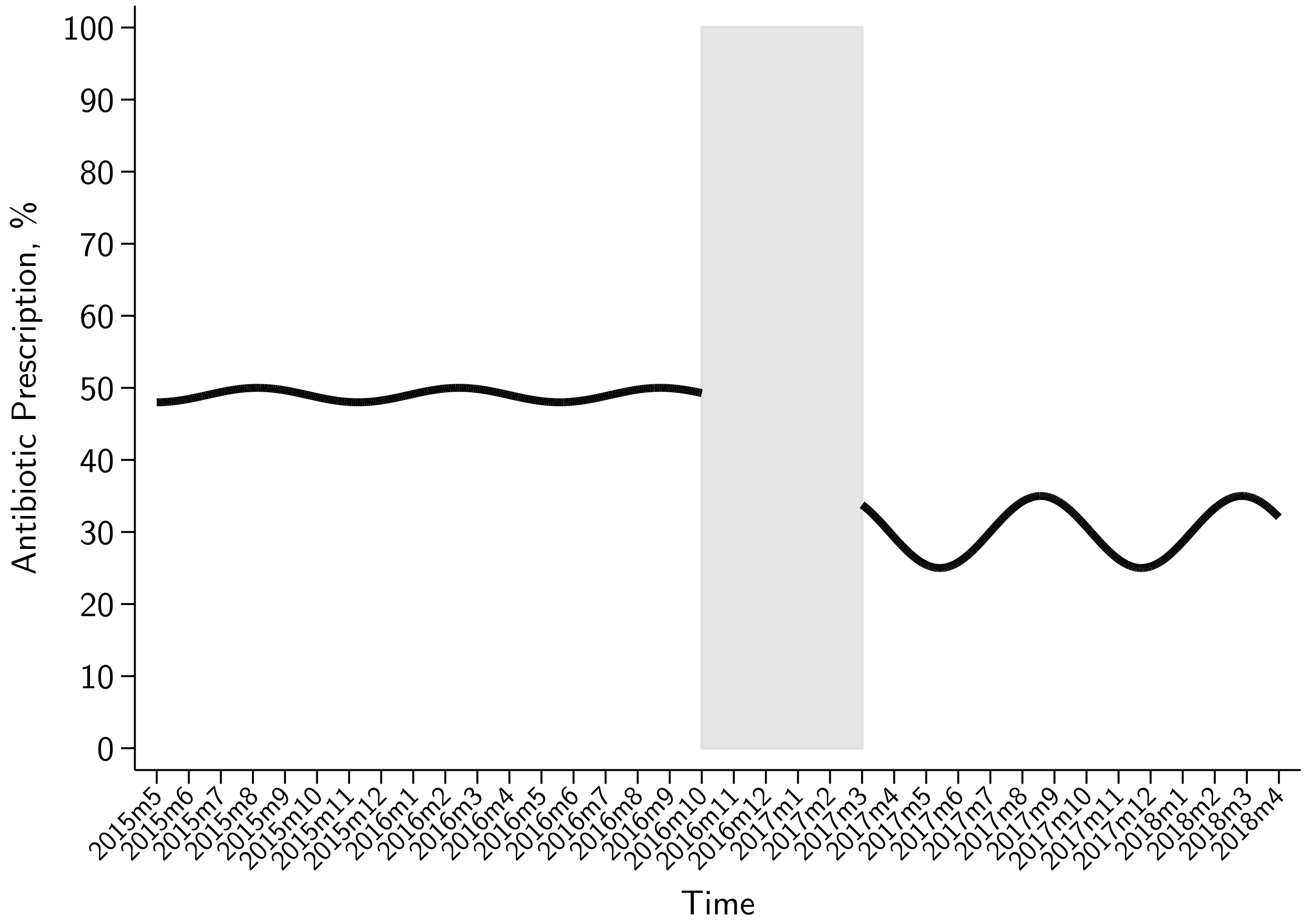
2017m12
2018m1
2018m2
2018m3
2018m4
Time

Scenario 4


Antibiotic Prescription, %
0
10
20
30
40
50
60
70
80
90
100
2015m5 2015m6 2015m7 2015m8 2015m9 2015m10 2015m11 2015m12 2016m1 2016m2 2016m3 2016m4 2016m5 2016m6 2016m7 2016m8 2016m9 2016m10 2016m11 2016m12 2017m1 2017m2 2017m3 2017m4 2017m5 2017m6 2017m7 2017m8 2017m9 2017m10 2017m11 2017m12 2018m1 2018m2 2018m3 2018m4
Time

Regression approach

- Interrupted time-series encompasses a wide range of modelling approaches.

- It can be done using popular regression models for different types of outcome data (linear, quantile, logistic, poisson, multilevel).

- The main quantitative predictor is time.

- Values of the time series are likely to be correlated (autocorrelation). Failing to take into account correlation may lead to biased inference.

Outcome is a flexible function of time

$$g(\mu|t) = f(t)$$

μ expected value (mean, proportion, rate) of an outcome

g link function between μ and the linear predictor $f(t)$

Splines of time

Piecewise polynomials of time t that depend on n interventional times t_k and the degree j

$$t_{kj+} = I(t > t_k)(x - t_k)^j$$

$$k = 1, 2, \ldots, n$$

$$t_1 < t_2 < \cdots < t_n$$

$j = 0$ constant

$j = 1$ linear

$j = 2$ quadratic

$j = 3$ cubic

One group and one intervention

Consider one intervention at time k

$$g(\mu|t) = \beta_0 + \beta_1 t + \beta_2 I(t > k)(t-k)^0 + \beta_3 I(t > k)(t-k)^1$$

$$g(\mu|t) = \beta_0 + \beta_1 t + \beta_2 t_{10+} + \beta_3 t_{11+}$$

Common notation used in ITS defines $x = t_{10+}$ and $xt = t_{11+}$

$$g(\mu|t) = \beta_0 + \beta_1 t + \beta_2 x + \beta_3 xt$$

$$g(\mu|t) = \beta_0 + \beta_1 t + \beta_2 x + \beta_3 xt$$

β_0 is the outcome at time 0

β_1 is the pre-intervention linear trend

β_2 is the post-intervention change in mean outcome

β_3 is the post-intervention change in linear trend

A note on how time is handled

- **Stata** and **SAS** provides dates measured as the number of days since 01jan1960.

- **SPSS** provides dates and datetimes measured as the number of seconds since 14oct1582.

- **R** stores dates as days since 01jan1970.

Make sure you are familiar with date and time functions in your favorite statistical software.

Definition of time (in Stata)

- October 2016 (first month of intervention)

```
. display ym(2016,10)
681
```

Centering time t about the first month of intervention helps interpreting the intercept β_0.

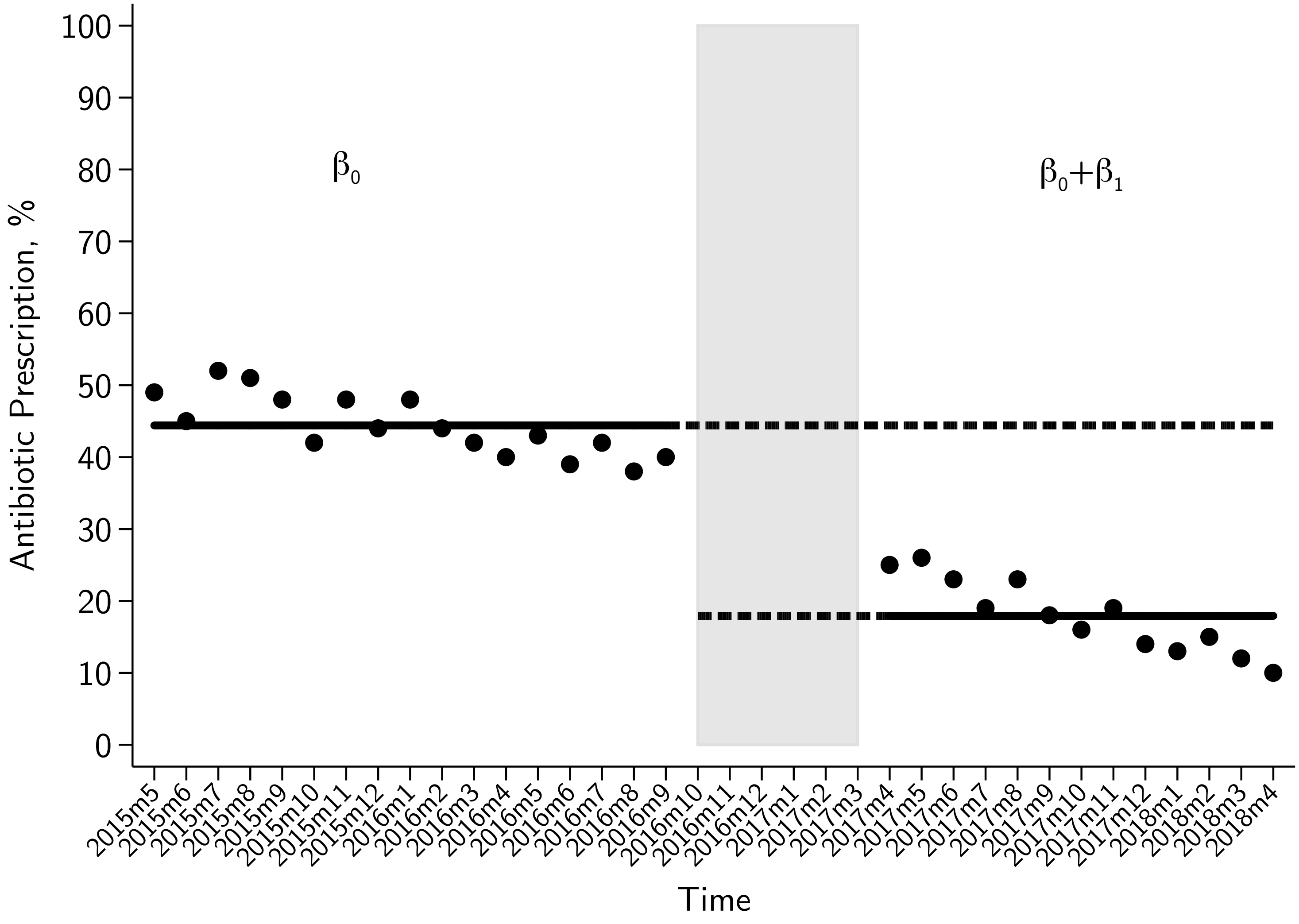
```
. gen t =  (time-681)
. gen x =  (t>0)*(time-681)^0
. gen xt = (t>0)*(time-681)^1
```

$$g(\hat{\mu}|t) = 44.4\ - 26.5x$$

Before the intervention, the percentage of antibiotic prescription is 44.4%.

After intervention, the percentage of antibiotic prescription decreases by 26.5% compared to the pre-intervention period.

The change in outcome is immediate and permanent until the end of the study period.



100
90
80
70
60
50
40
30
20
10
0
Antibiotic Prescription, %
β0
β0+β1
2015m5
2015m6
2015m7
2015m8
2015m9
2015m10
2015m11
2015m12
2016m1
2016m2
2016m3
2016m4
2016m5
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2017m11
2017m12
2018m1
2018m2
2018m3
2018m4
Time

Key assumption

Without the intervention, the pre-intervention trend would continue unchanged into the post-intervention period.

There are no external factors systematically affecting the trends.

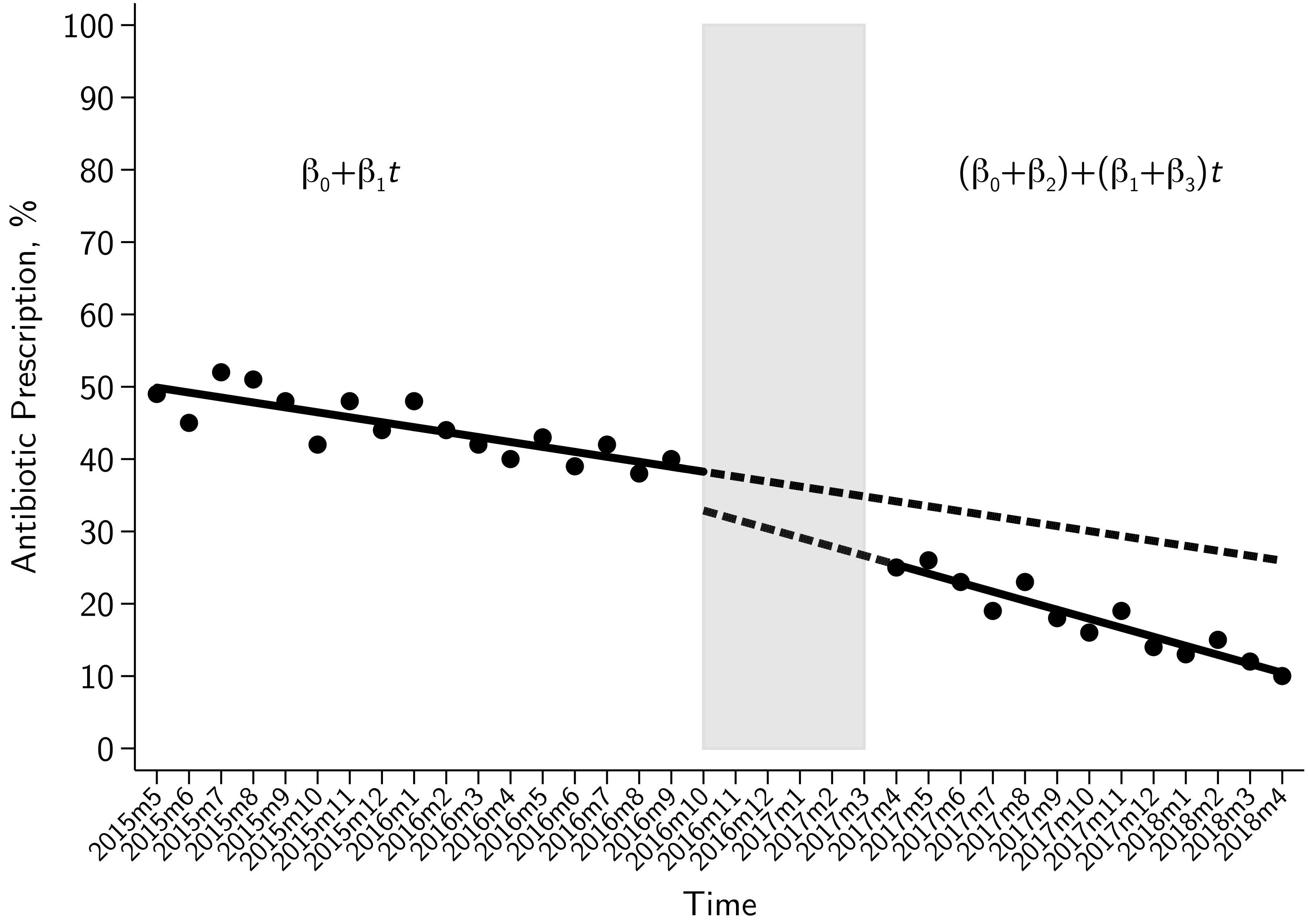
$$g(\hat{\mu}|t) = 38.3 - 0.7t - 5.4x - 0.6xt$$

The estimated percentage of antibiotic prescription in October 2016, right before intervention, is 38.3%.

Before intervention, the percentage of antibiotic prescription decreases by 0.7% every month.

Right after intervention, the percentage of antibiotic prescription decreases by 5.4%.

After intervention, the percentage of antibiotic prescription decreases by (0.7+0.6)=1.3% every month.



Antibiotic Prescription, %
100
90
80
70
60
50
40
30
20
10
0
β0+β1t
(β0+β2)+(β1+β3)t
2015m5
2015m6
2015m7
2015m8
2015m9
2015m10
2015m11
2015m12
2016m1
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2017m11
2017m12
2018m1
2018m2
2018m3
2018m4
Time

Expressing intervention effect

What is the predicted outcome at time *m* after intervention?

$$g(\mu|t = m, x = 1) = \beta_0 + \beta_1 m + \beta_2 + \beta_3 m$$

What is the predicted outcome at time *m* had not been intervene?

$$g(\mu|t = m, x = 0) = \beta_0 + \beta_1 m$$

What is the intervention effect at *m* months?

$$g(\mu|t = m, x = 1) - g(\mu|t = m, x = 0) = \beta_2 + \beta_3 m$$

In April 2018, 18 months after beginning of intervention, the percentage of antibiotic prescription is

$$g(\hat{\mu}|t = 18, x = 1) = 38.3\ - 0.7 * 18 - 5.4 * 1 - 0.6 * 18 = 10\%$$

In April 2018, in the absence of intervention, the percentage of antibiotic prescription would have been

$$g(\hat{\mu}|t = 18, x = 0) = 38.3\ - 0.7 * 18 = 26\%$$

The intervention decreased the percentage of antibiotic prescription by 16% at 18 months from intervention (assuming the trend before intervention would have been the same until the end of the study period).

Two groups and one intervention

Let's consider another variable *z* identifying controls (if possible) or different subgroups within the intervention populations.

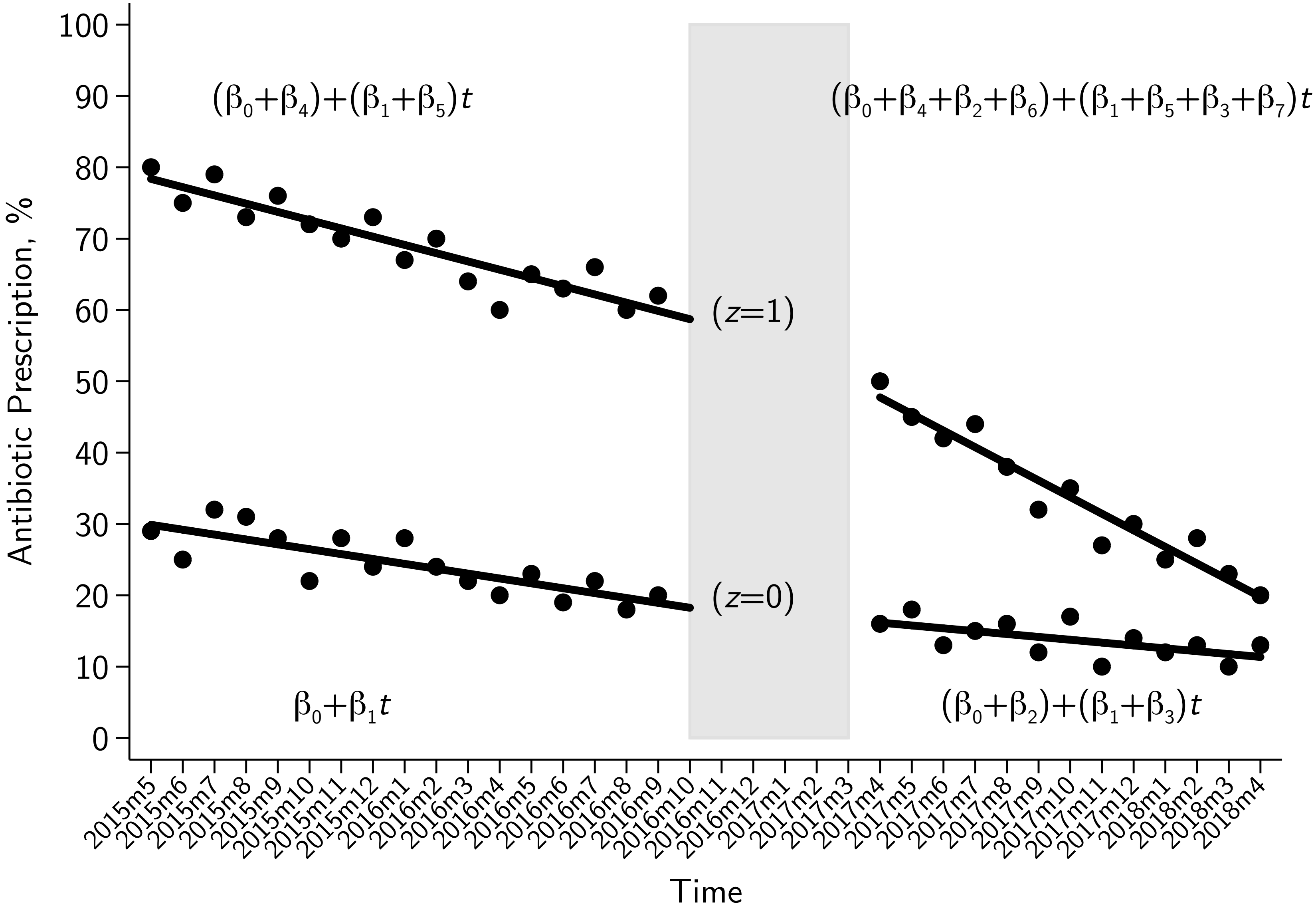
$$g(\mu|t,x,z) = \beta_0 + \beta_1 t + \beta_2 x + \beta_3 xt + \beta_4 z + \beta_5 zt + \beta_6 zx + \beta_7 zxt$$

Group 0 (*z*=0). Before and after intervention.

$$g(\mu|t,z=0) = \beta_0 + \beta_1 t + \beta_2 x + \beta_3 xt$$
$$g(\mu|t,x=0,z=0) = \beta_0 + \beta_1 t$$
$$g(\mu|t,x=1,z=0) = (\beta_0 + \beta_2) + (\beta_1 + \beta_3)t$$

Group 1 (*z*=1). Before and after intervention.

$$g(\mu|t,z=1) = (\beta_0 + \beta_4) + (\beta_1 + \beta_5)t + (\beta_2 + \beta_6)x + (\beta_3 + \beta_7)xt$$
$$g(\mu|t,x=0,z=1) = (\beta_0 + \beta_4) + (\beta_1 + \beta_5)t$$
$$g(\mu|t,x=1,z=1) = (\beta_0 + \beta_4 + \beta_2 + \beta_6) + (\beta_1 + \beta_5 + \beta_3 + \beta_7)t$$



Antibiotic Prescription, %
100
90
80
70
60
50
40
30
20
10
0
$(\beta_0+\beta_4)+(\beta_1+\beta_5)t$
$(\beta_0+\beta_4+\beta_2+\beta_6)+(\beta_1+\beta_5+\beta_3+\beta_7)t$
$(z=1)$
$(z=0)$
$\beta_0+\beta_1 t$
$(\beta_0+\beta_2)+(\beta_1+\beta_3)t$
2015m5 2015m6 2015m7 2015m8 2015m9 2015m10 2015m11 2015m12 2016m1 2016m2 2016m3 2016m4 2016m5 2016m6 2016m7 2016m8 2016m9 2016m10 2016m11 2016m12 2017m1 2017m2 2017m3 2017m4 2017m5 2017m6 2017m7 2017m8 2017m9 2017m10 2017m11 2017m12 2018m1 2018m2 2018m3 2018m4
Time

Possible measures of interests

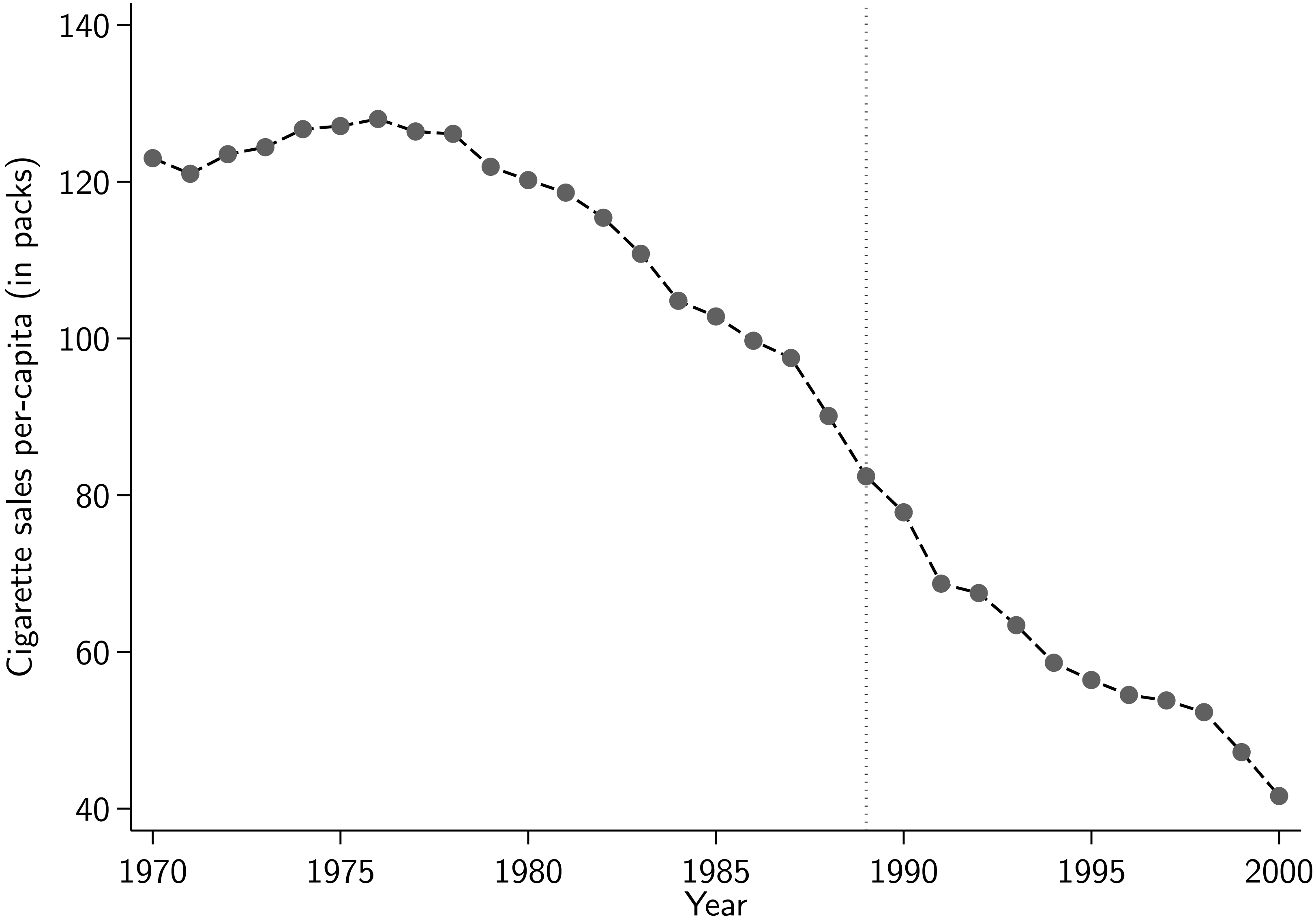
β_5 represents the group difference in trend before intervention

$\beta_5 + \beta_7$ represents the group difference in trend after intervention

Effect of a policy on smoking

In 1988, California passed the voter-initiative Proposition 99, which was a widespread effort to reduce smoking rates by raising the cigarette excise tax by 25 cents per pack and to fund anti-smoking campaigns and other related activities throughout the state.

Per capita cigarette sales (in packs) is the most widely used indicator of smoking prevalence found in the tobacco research literature and serves here as the aggregate outcome variable under study, measured at the state level from 1970 until 2000 (with 1989 representing the first year of the intervention). (Linden, 2015)


Cigarette sales per-capita (in packs)
140
120
100
80
60
40
1970
1975
1980
1985
1990
1995
2000
Year

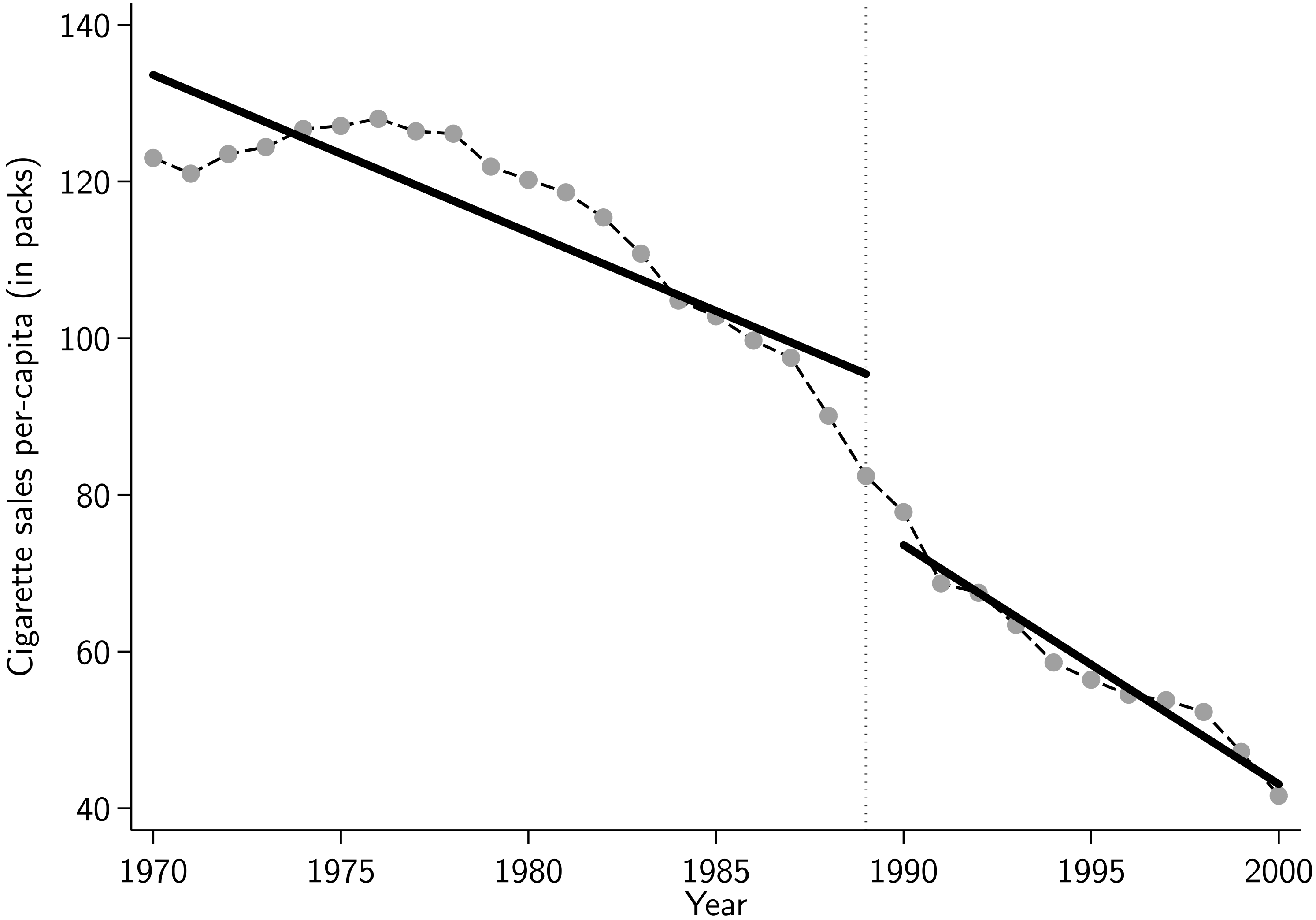
```
. gen t = year - 1989
. gen x = (t>0)
. gen xt = x*t

. clist state year t x xt

             state   year         t         x        xt
 16.    California   1985        -4         0         0
 17.    California   1986        -3         0         0
 18.    California   1987        -2         0         0
 19.    California   1988        -1         0         0
 20.    California   1989         0         0         0
 21.    California   1990         1         1         1
 22.    California   1991         2         1         2
 23.    California   1992         3         1         3
 24.    California   1993         4         1         4
```

One-group and one-intervention

```
. newey cigsale t x xt , lag(1)

Regression with Newey-West standard errors      Number of obs     =         31
maximum lag: 1                                   F(  3,        27) =     308.98
                                                 Prob > F          =     0.0000

------------------------------------------------------------------------------
             |             Newey-West
     cigsale |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
           t |         -2          0    -4.84   0.000           -3          -1
           x |        -19          5    -3.79   0.001          -29          -9
          xt |         -1          0    -2.43   0.022           -2          -0
       _cons |         95          4    22.69   0.000           87         104
------------------------------------------------------------------------------

. lincom _b[t] + _b[xt]

------------------------------------------------------------------------------
     cigsale |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |       -3.1        0.2   -13.23   0.000         -3.5        -2.6
------------------------------------------------------------------------------
```

Abstract

In 1989, level of the per capita cigarette sales was estimated at 95 packs. Sales appeared to decrease significantly every year prior to 1989 by 2 packs (95% CI = −3, −1). In the first year of the intervention (1989), there appeared to be a significant decrease in per capita cigarette sales of 19 packs (95% CI = −29, −9), followed by a significant decrease in the annual trend of sales (relative to the preintervention trend) of 1 pack per capita per year ($P = 0.002$). After the introduction of Proposition 99, per capita cigarette sales decreased annually at a rate of 3 packs (95% CI = -3.5, -2.6).


Cigarette sales per-capita (in packs)
140
120
100
80
60
40
1970
1975
1980
1985
1990
1995
2000
Year

Two-groups and one-intervention

We now compare California's time-series with that of other 3 similar states.

We limit the analysis to only those states that are comparable with California on baseline level and trend of the outcome variable. Three comparison states meet this criteria: Colorado, Idaho, and Montana.

Ideally, a control group that is identical to the study group but does not experience the intervention is followed over the same time period as the intervention group.

Regression with Newey-West standard errors — Number of obs = 124
maximum lag: 1 — F(7, 116) = 251.48
Prob > F = 0.0000

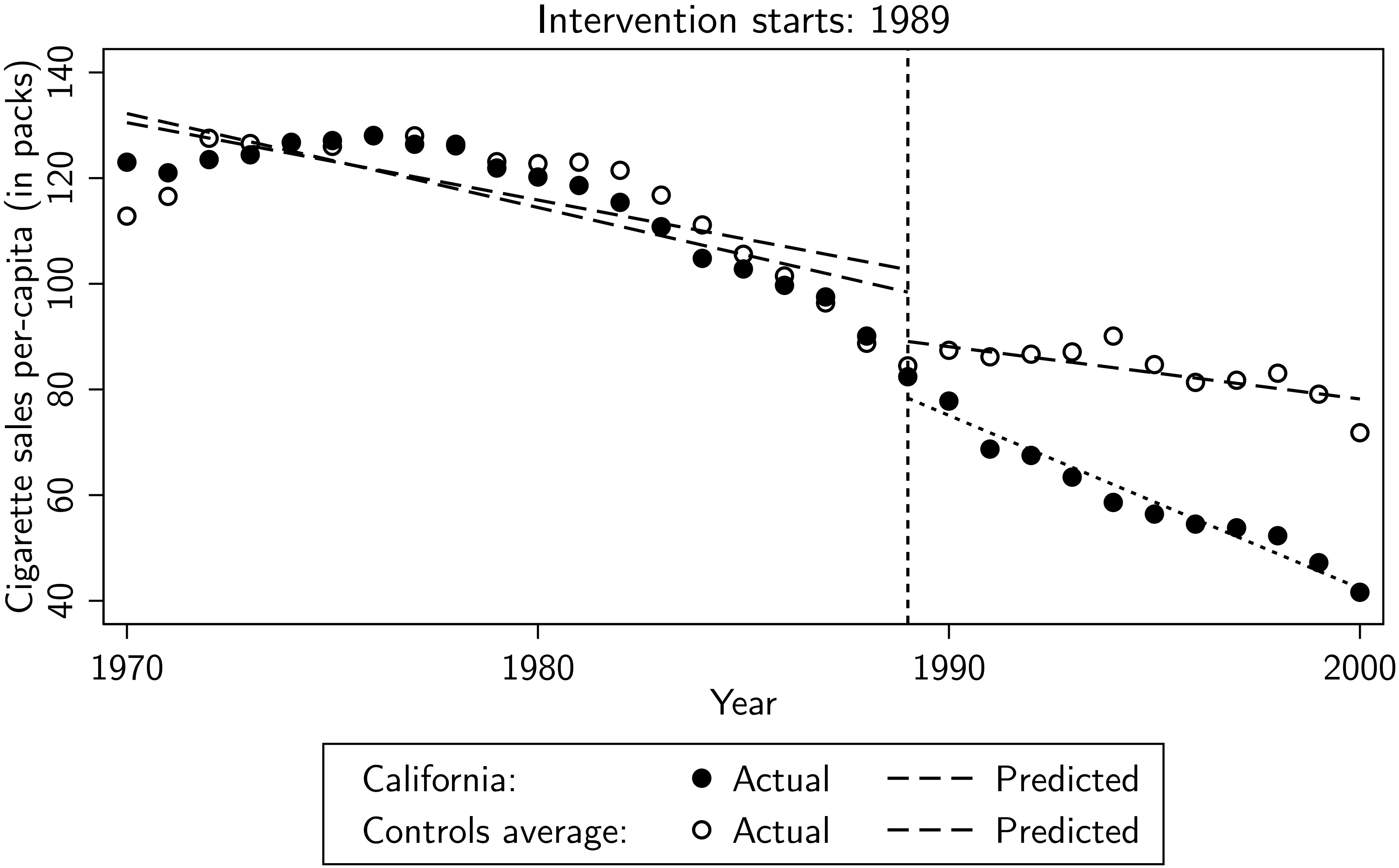
cigsale	Coef.	Newey-West Std. Err.	t	P>|t|	[95% Conf.	Interval]
_t	-1.5	0.4	-3.82	0.000	-2.2	-0.7
_z	2.0	6.2	0.33	0.743	-10.3	14.4
_z_t	-0.3	0.5	-0.59	0.556	-1.4	0.7
_x1989	-13.6	4.2	-3.25	0.002	-21.9	-5.3
_x_t1989	0.5	0.5	0.95	0.344	-0.5	1.5
_z_x1989	-6.5	6.2	-1.05	0.298	-18.7	5.8
_z_x_t1989	-2.0	0.7	-3.01	0.003	-3.3	-0.7
_cons	132.0	4.4	30.30	0.000	123.3	140.6

Comparison of Linear Postintervention Trends: 1989

Treated : _b[_t] + _b[_z_t] + _b[_x_t1989] + _b[_z_x_t1989]
Controls : _b[_t] + _b[_x_t1989]
Difference : _b[_z_t] + _b[_z_x_t1989]

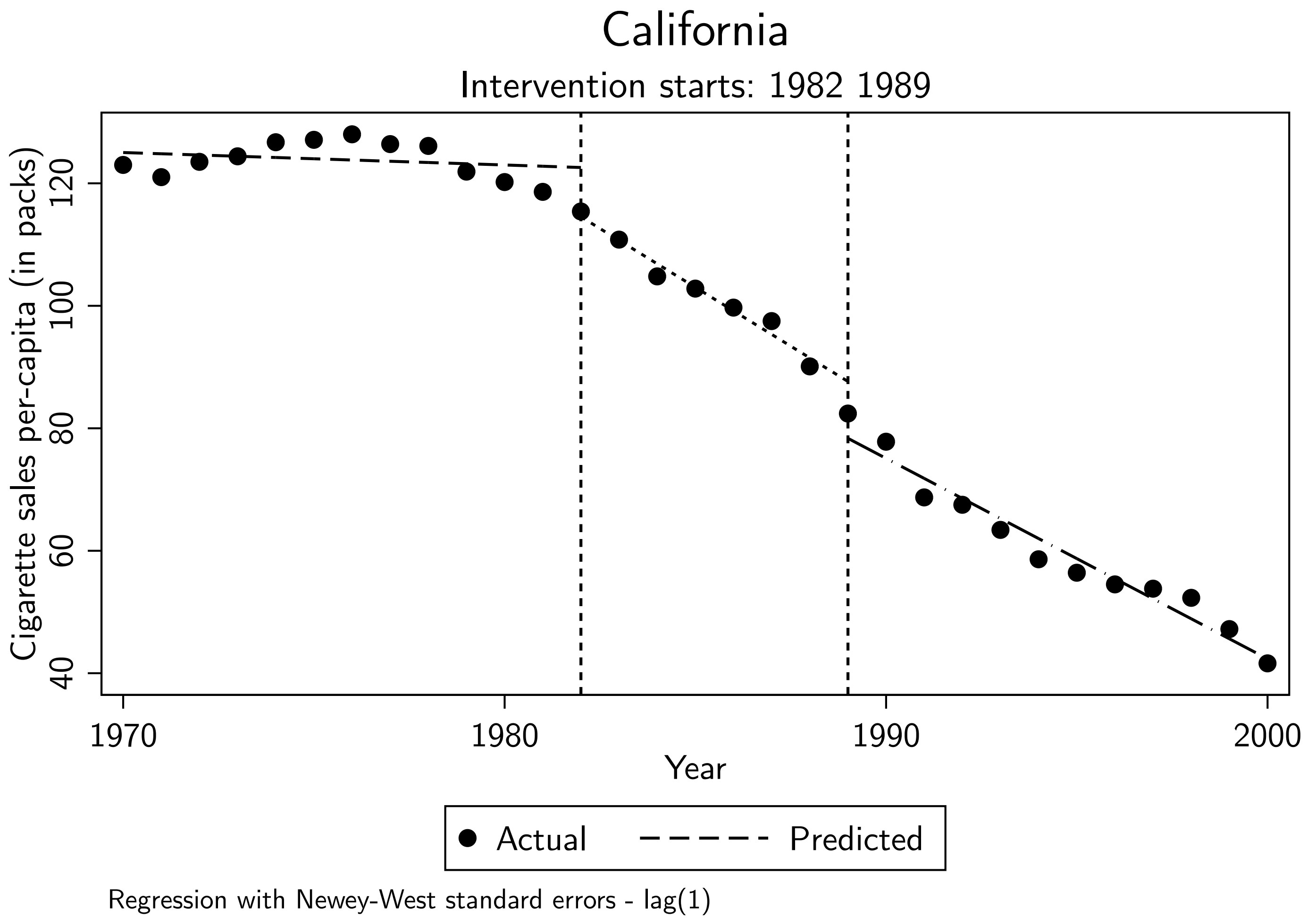
Linear Trend	Coeff	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Treated	-3.2741	0.2594	-12.6234	0.0000	-3.7878	-2.7604
Controls	-0.9899	0.2883	-3.4336	0.0008	-1.5608	-0.4189
Difference	-2.2843	0.3878	-5.8905	0.0000	-3.0523	-1.5162

California and average of controls



Regression with Newey-West standard errors - lag(1)

One group and multiple-interventions



Strengths

- Time series designs are considered the strongest, quasi-experimental designs to estimate the intervention effects in non-randomized settings.
- Times series analysis allow the analyst to control for prior trends in the outcome and to study the dynamics of change in response to an intervention
- Time series graphs presents the dynamic of a series showing whether an effect is immediate or delayed, abrupt or gradual, and whether or not an effect persists or is temporary.

Limitations

- Other factors related to the outcome and that changed at the time of intervention. For example:

  ✓ effect of simultaneously occurring interventions or co-interventions,
  ✓ seasonal changes that happen during the time of intervention,
  ✓ changes in composition of the study population,
  ✓ changes in measurement of the outcome at the time of intervention

- The common linearity assumption for the time series before and after intervention may not hold. Changes may follow non-linear patterns. Checking departure from linearity can be a problem when there are only a few pre-intervention time points and is impossible with only two.

- Detecting seasonality requires series that span enough periods to detect these cyclic patterns.

- Lack of consistency of recording the outcome routinely collected.

Selected References

Recent paper on a top medical journal

- Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ* 2015;350:h2750

A book on quasi experimental designs (a chapter is on interrupted time-series)

- William R. Shadish, Thomas D. Cook, Donald Thomas Campbell. *Experimental and Quasi-experimental Designs for Generalized Causal Inference.* 2002.

Statistical software component for the case N = 1 (Smoking example)

- Linden A. Conducting interrupted time-series analysis for single- and multiple-group comparisons. The *Stata Journal.* Volume 15 Number 2: pp. 480-500.