Learning the effects of dexamethasone and hydroxychloroquine on COVID-19 mortality outside of randomized trials: The stability-controlled quasi-experiment

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- Tell us when we cannot make an inference – not give equally confident estimate regardless of credibility.

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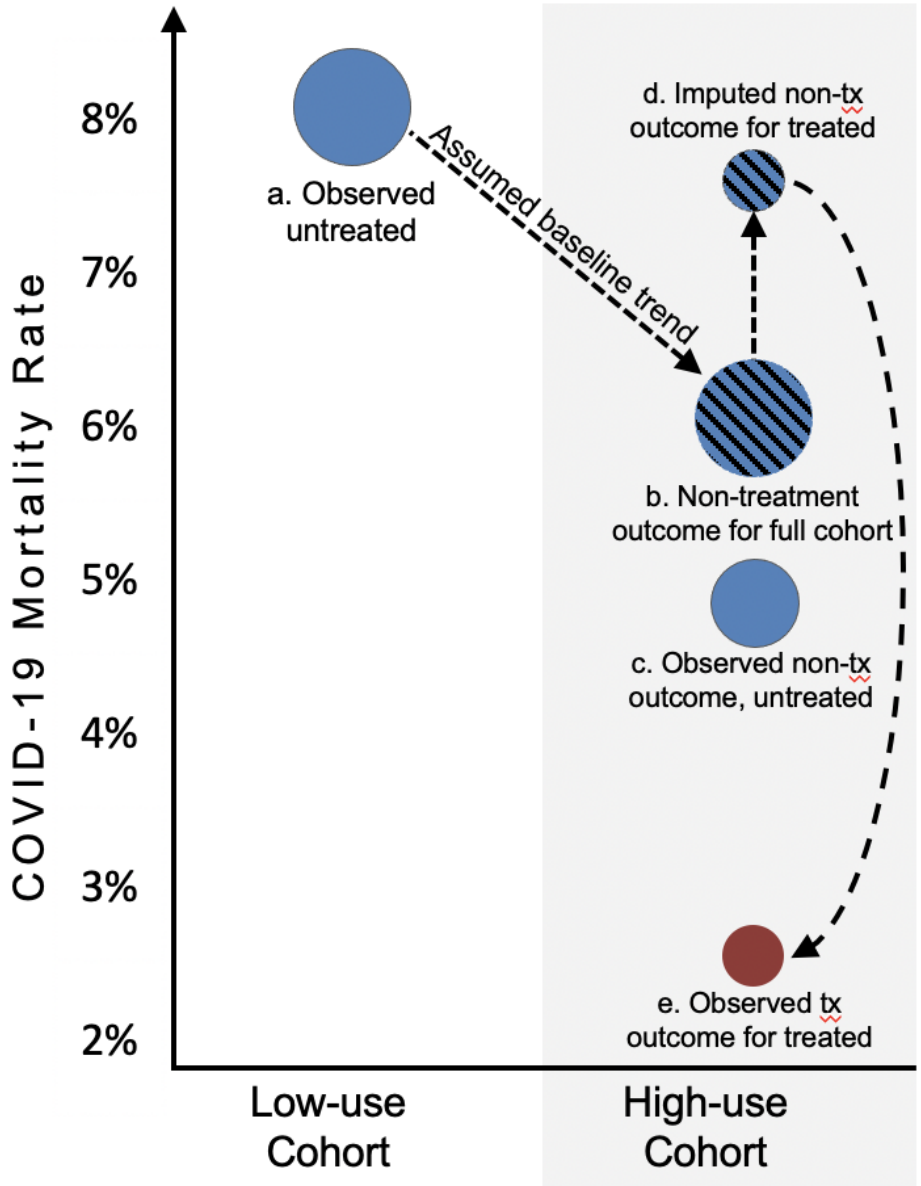
Yet, it can still be quite informative!

A graphical explanation: Dexamethasone and COVID-19 mortality



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"Change in the average outcome from one cohort to the next, not due to changes in the treatment."

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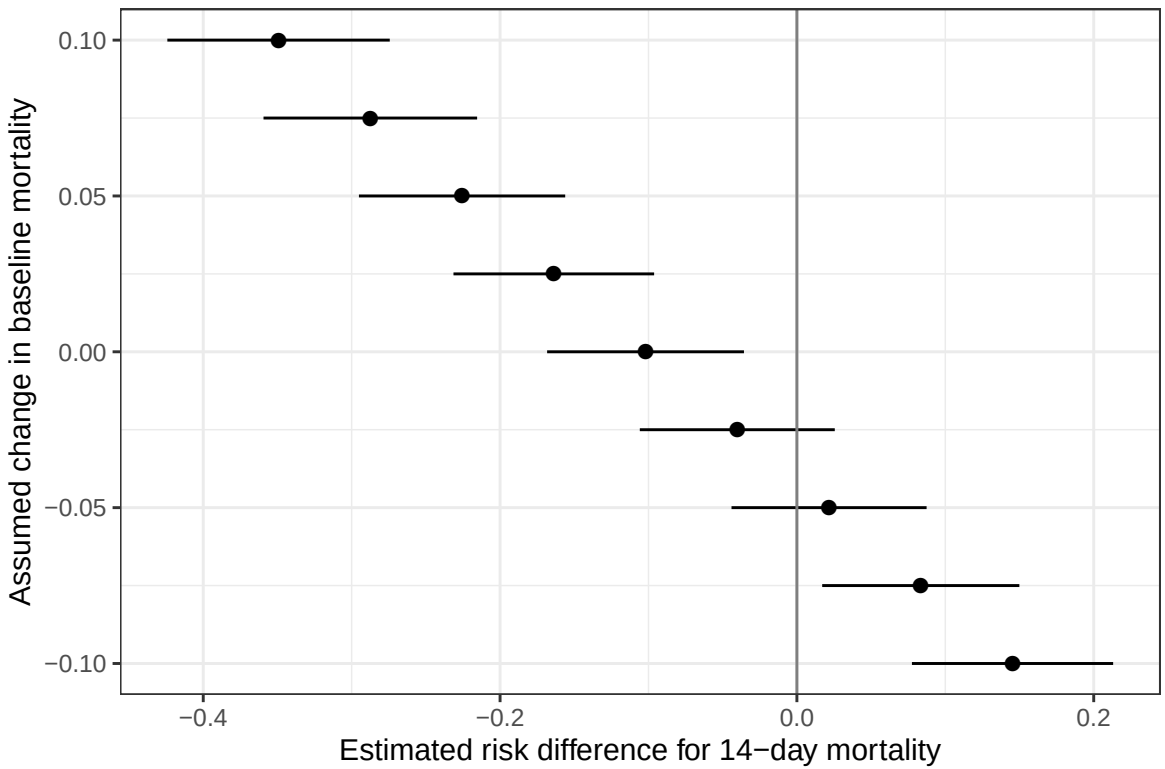

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- We can (and will) also use this when there are treatment-takers in the first period or not, as long as there is a big change in treatment probability
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For the methodologists:

- Yes, this is another way to say instrumental variables, but with violations of the exclusion restriction governed by the baseline trend
- Ask if you're curious about inference or other details

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The SCQE provides inferences based on these data and assumed baseline trends.

Baseline trends to consider

What baseline trends are *ex ante* (im)plausible?

- Unlikely that other changes drove mortality down by more than 50% (-5.8 percentage points).
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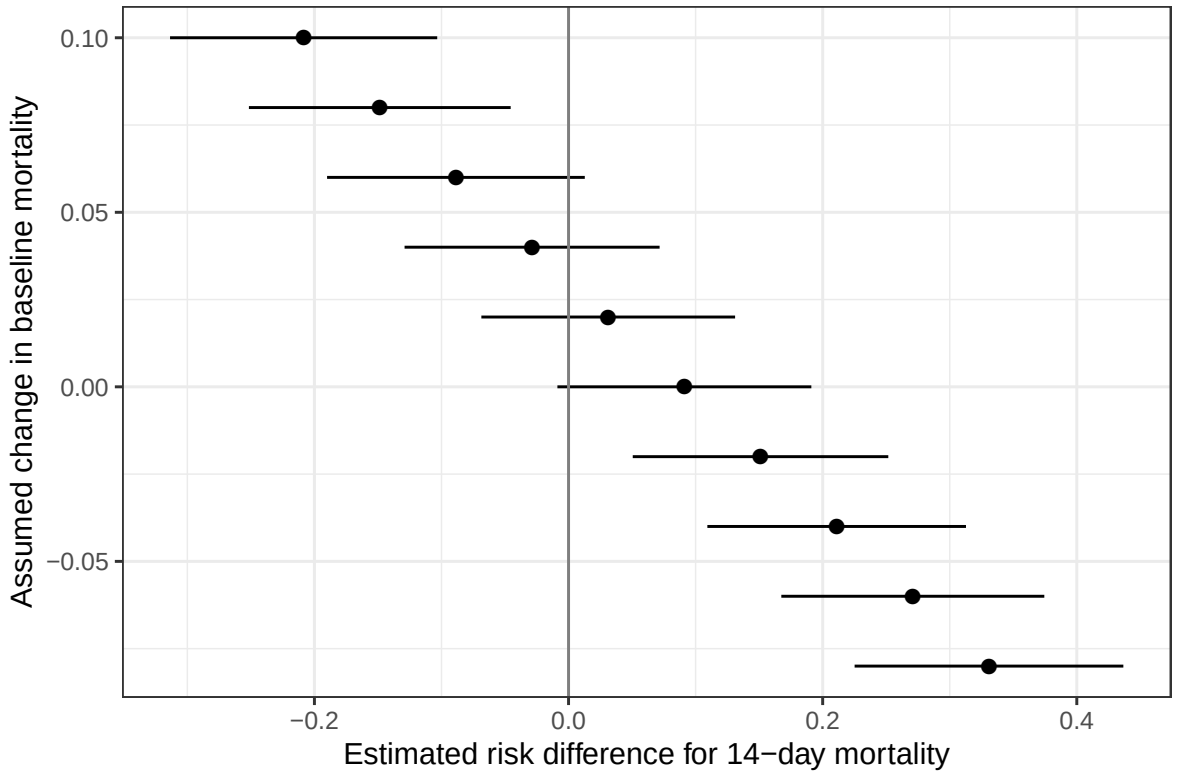
Empirical comparison:

- No major changes in patient population (age, gender, ethnicity, risk factors, initial severity), other treatments tried, or predicted risk.
- Except remdesivir use, up by 8 percentage points.

Hydroxychloroquine: Results

Figure 1: SCQE Estimates of risk difference for hydroxychloroquine



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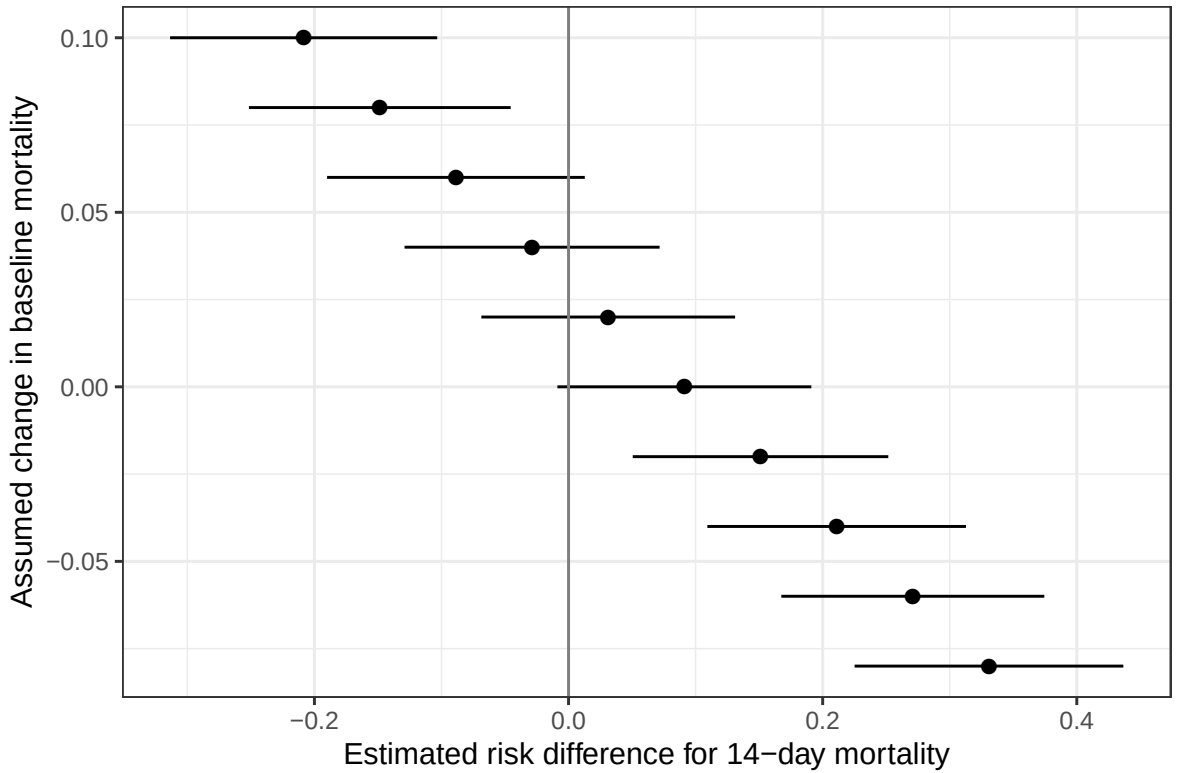

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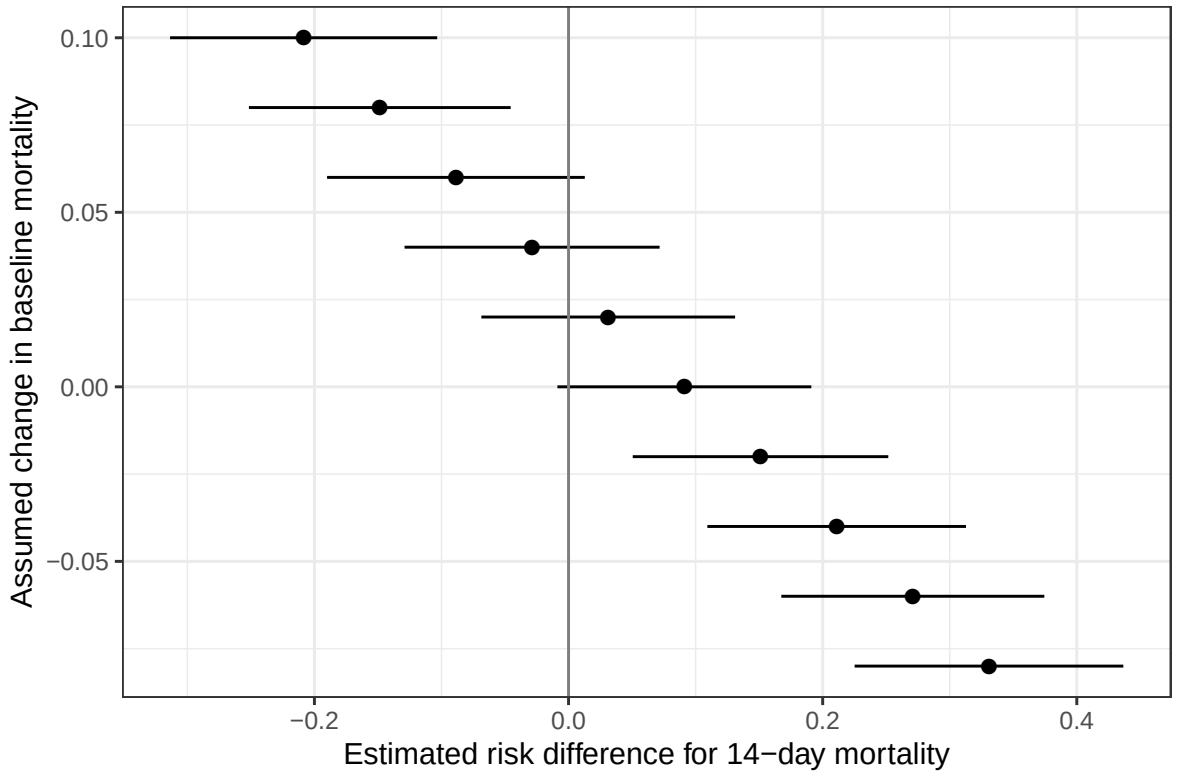

- HCQ beneficial (p=0.05) only if baseline mortality **decreased by 6.4 percentage points, a 55% reduction**
- Harmful (p=0.05) if baseline mortality instead worsened over-time by just 0.3 percentage points (2.6% of the prior mortality rate!)

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No major observed differences between cohorts on characteristics, other treatments, or modeled risk, excepting remdesivir use (16 pp change)

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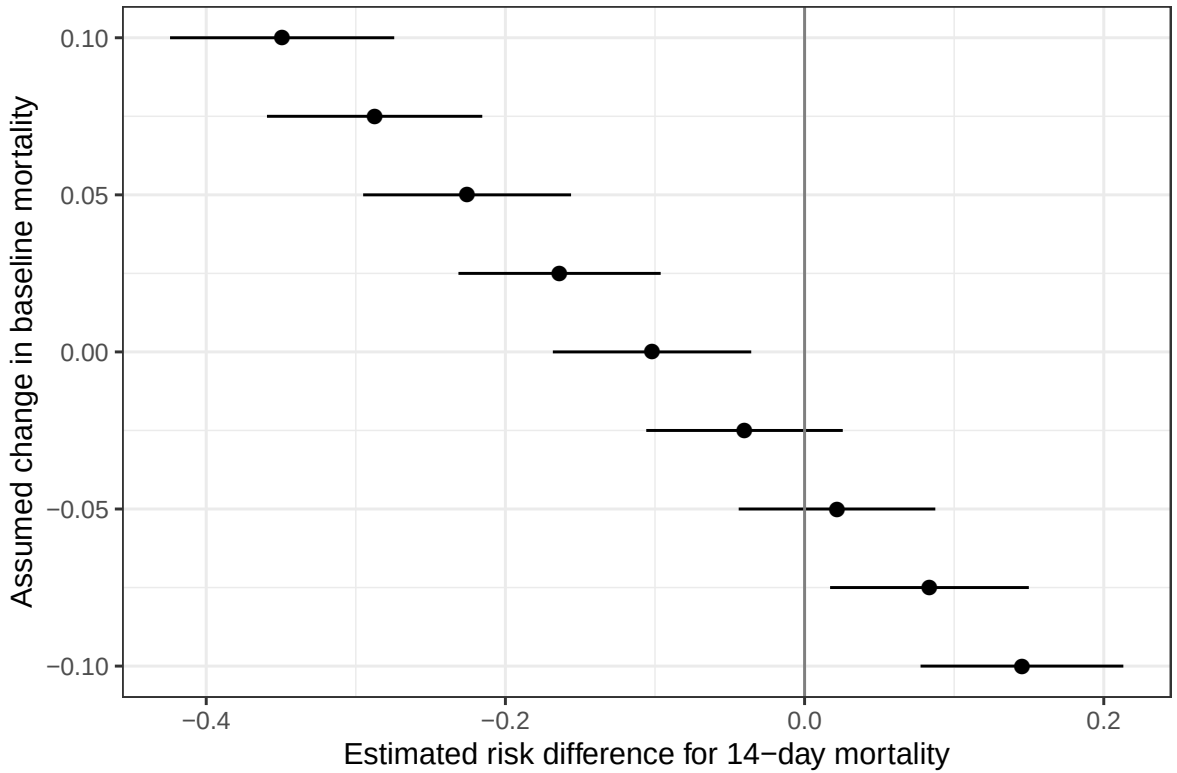
Figure 2: SCQE Estimates of risk difference for dexamethasone



- Beneficial (p=0.05) if baseline mortality increasing, flat, or fell by 1.5 percentage points (26% of earlier mortality rate).
- Harmful (p=0.05) if baseline mortality fell by 6.8 percentage points (a 93% reduction in baseline mortality, leaving mortality of just 0.4%.)

Conclusions: Hydroxychloroquine and dexamethasone

- **Hydroxychloroquine**: Hard to support a beneficial claim; easy for it to be harmful.
- **Dexamethasone**: Plausibly but not definitively beneficial; harmful average effect was nearly impossible.

Conclusions

Use-cases for SCQE in medicine:

- While we wait for RCTs people will look to observational studies – let's make them safe.
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Software:

- `R` package (under development): `https://github.com/chadhazlett/scqe`
- Plug in some cohort-wise averages and get some answers: `https://amiwulf.shinyapps.io/SCQE_demo/`

Extra slides

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Define the change in non-treatment average outcomes,

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Yielding the ATT,

$$\begin{aligned}ATT &= \mathbb{E}[Y(1)|D=1,T=1] - \mathbb{E}[Y(0)|D=1,T=1] \\ &= \mathbb{E}[Y|D=1,T=1] - \left(\frac{\mathbb{E}[Y|T=0] - \mathbb{E}[Y|D=0,T=1](1-\pi_1)+\delta}{\pi_1}\right).\end{aligned} \tag{3}$$

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Reminds us: only need a shift in probability of treatment, not totally new treatment (for LATE instead of ATT).

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- So dividing by the proportion treated (π_1) recovers "how large the treatment effect must be for each of the treated on average," i.e. the ATT.
- This is the logic of the Wald estimator for IV, which SCQE equals:

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Inference

Consider the regression using $\tilde{Y}_i$,

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$$\widehat{SE}(\hat{\beta}_{SCQE}) = \frac{\hat{\sigma}_\mu}{\sqrt{N}\,\hat{\rho}_{D,T}\,\hat{\sigma}_D}, \tag{5}$$

where $\hat{\rho}_{D,T}$ is the sample correlation of the treatment and time indicators.

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- get 95% CI from the 2.5^{th} and 97.5^{th} percentile of estimates.

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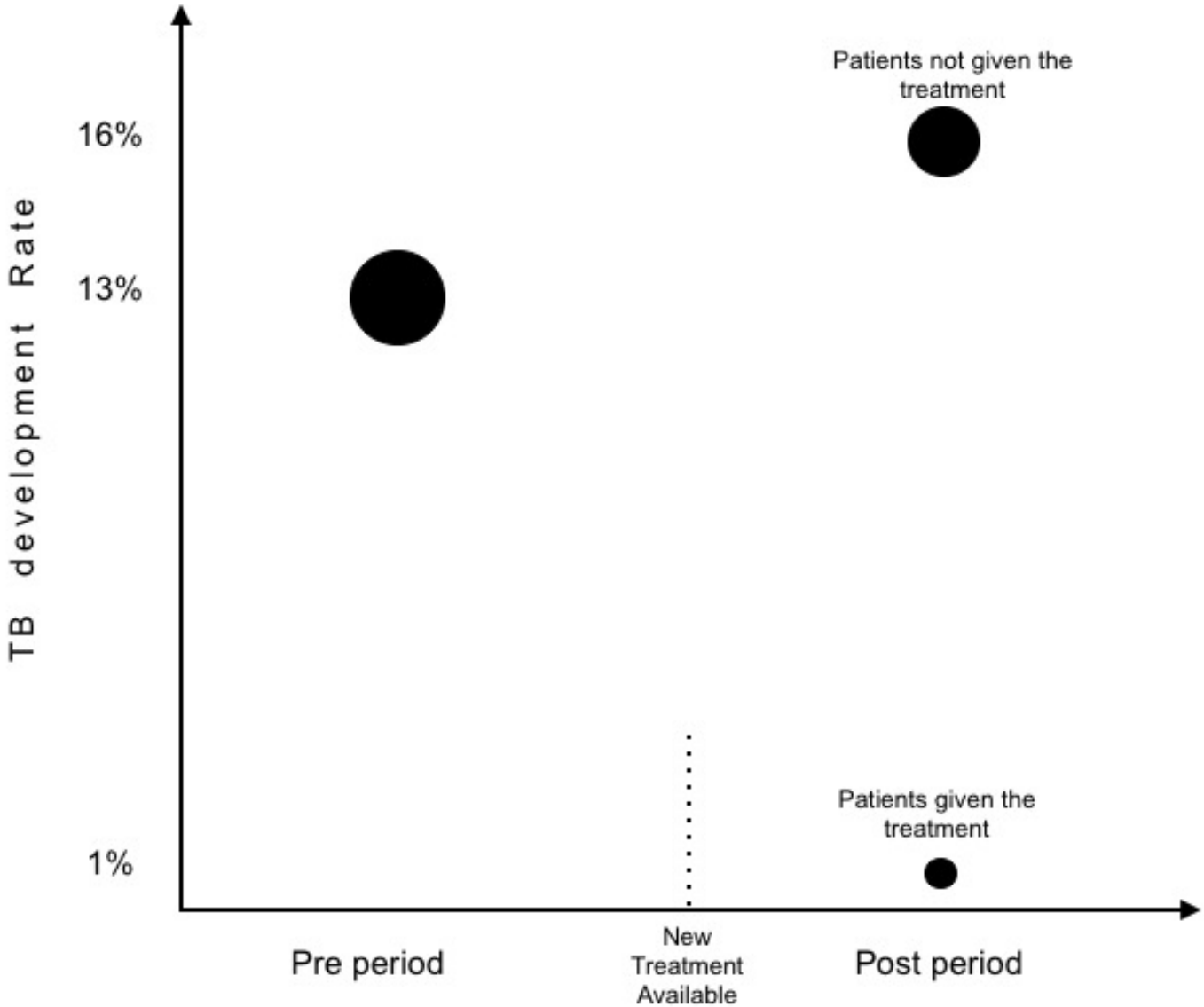
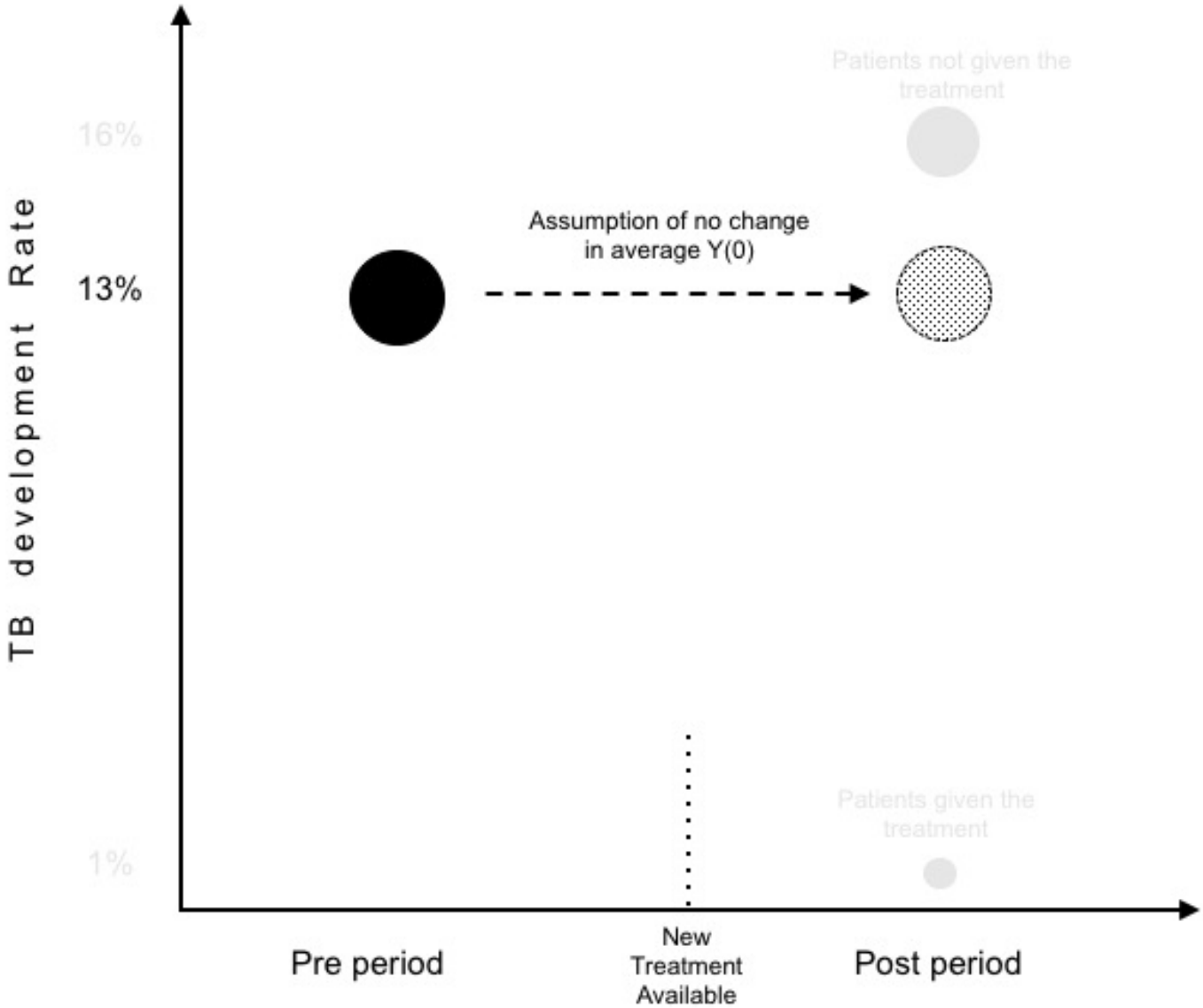
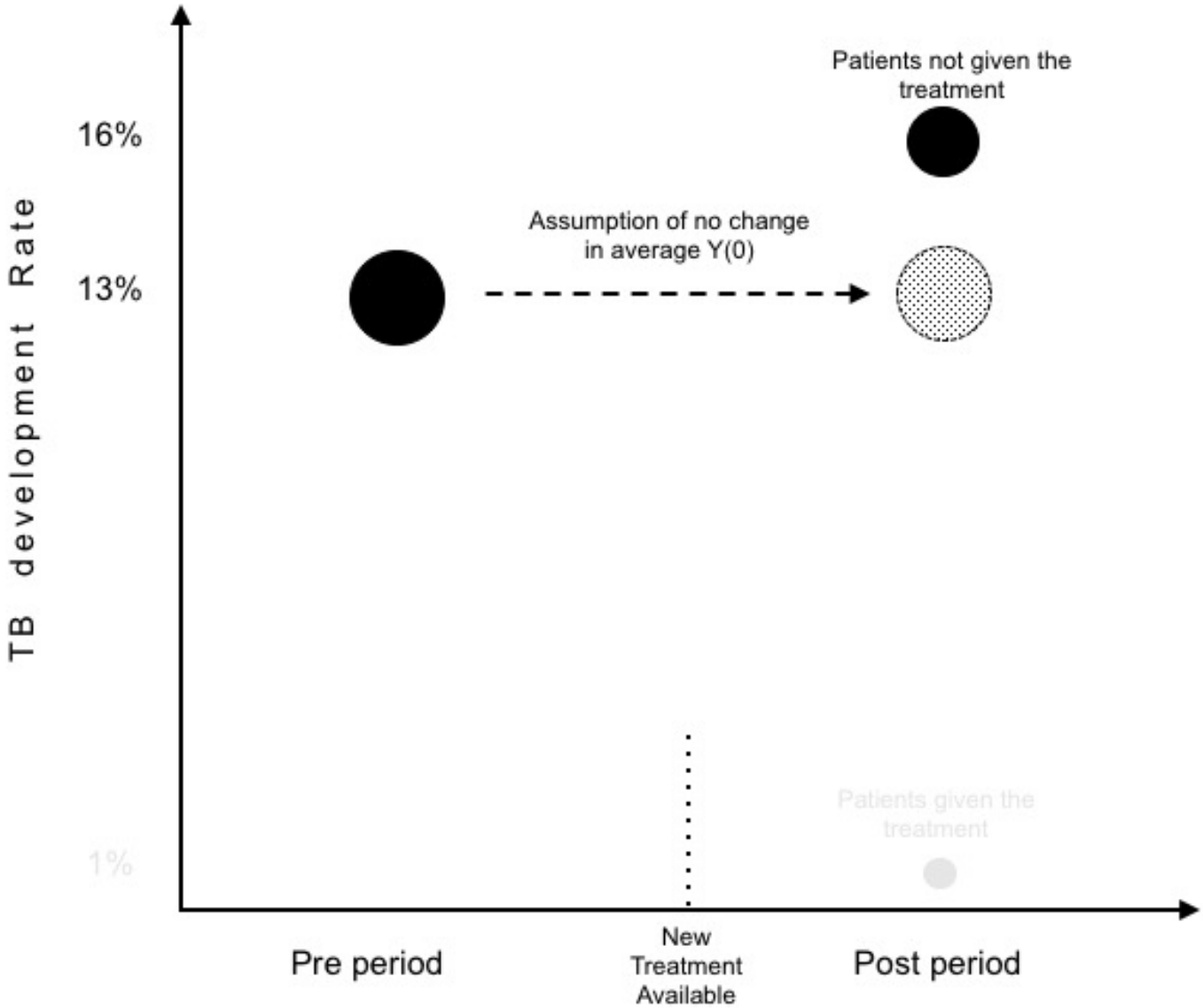
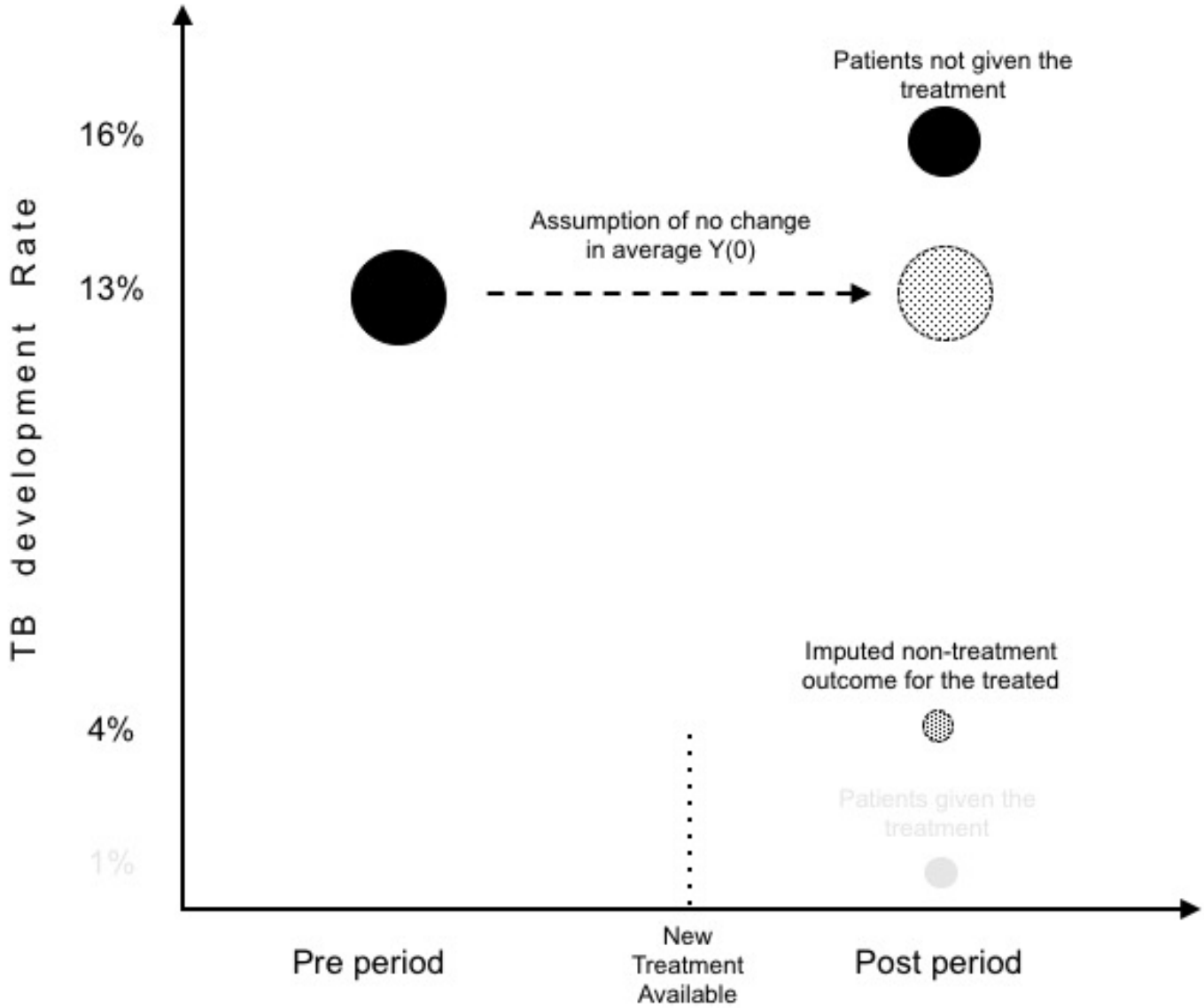
- Bonus: you aren't asked to compare a treated and control group on either level or trends of $Y(0)$.

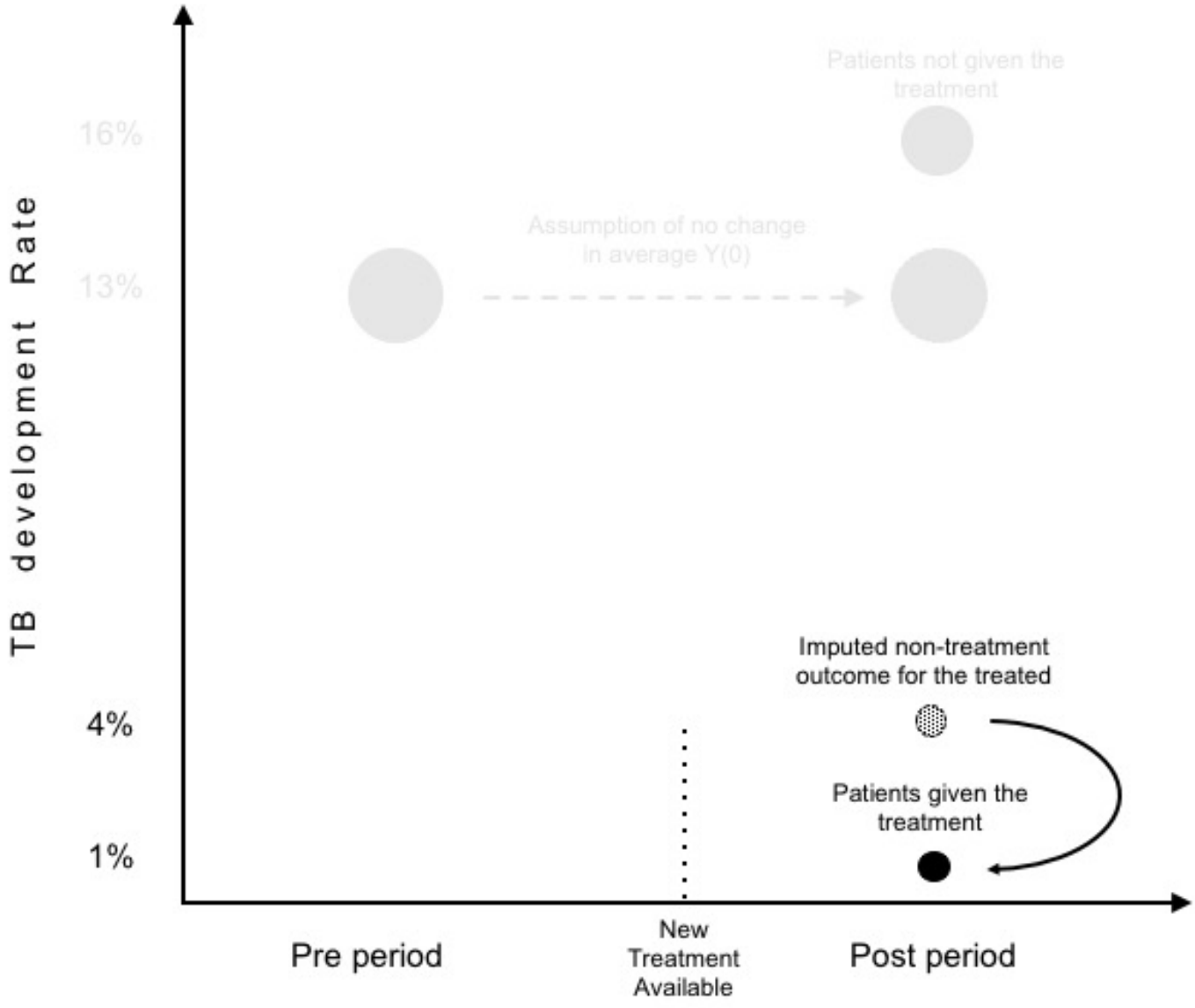
A graphical explanation:




TB development Rate
16%
13%
1%
Patients not given the treatment
Assumption of no change in average Y(0)
Patients given the treatment
Pre period
New Treatment Available
Post period


TB development Rate
16%
13%
1%
Patients not given the treatment
Assumption of no change in average Y(0)
Patients given the treatment
Pre period
New Treatment Available
Post period


Patients not given the treatment
16%
Assumption of no change in average Y(0)
13%
TB development Rate
Imputed non-treatment outcome for the treated
4%
Patients given the treatment
1%
Pre period
New Treatment Available
Post period


TB development Rate
16%
13%
4%
1%
Patients not given the treatment
Assumption of no change in average Y(0)
Imputed non-treatment outcome for the treated
Patients given the treatment
Pre period
New Treatment Available
Post period

Hydroxychloroquine: cohort comparison

Table 1: Comparison of hydroxychloroquine cohorts

	Cohort means:	
A. Characteristics	High-use	Low- use
age	57.86	55.75
over 65 y.o.	0.36	0.33
female	0.42	0.46
ethnicity: Hispanic	0.38	0.49
weight (Lb)	194.08	186.83
BMI	31.37	31.54
clinic referral	0.05	0.04
From Skilled Nursing Facility	0.04	0.09
ICU in first 24h	0.18	0.15
CRP (mg/L)	115	108
WBC (per mcL)	7.72	8.63
ferritin (μg/L)	747	601
procal (ng/mL)	0.89	1.11