BE CAREFUL WHAT YOU ASK FOR:

Stepped wedge trials with time-varying treatment effects

Jim Hughes
University of Washington and SCHARP

Joint work with Avi Kenny, Patrick Heagerty, Fan Xia, Emily Voldal

HPTN
HIV Prevention Trials Network

ANNUAL MEETING
2022

HPTN HIV Prevention Trials Network

Background on stepped wedge design and analysis

- Clusters randomized to <u>when</u> intervention is received
- Typically, measure outcome on each cluster, at each time step
- SW often used to measure effectiveness during roll-out

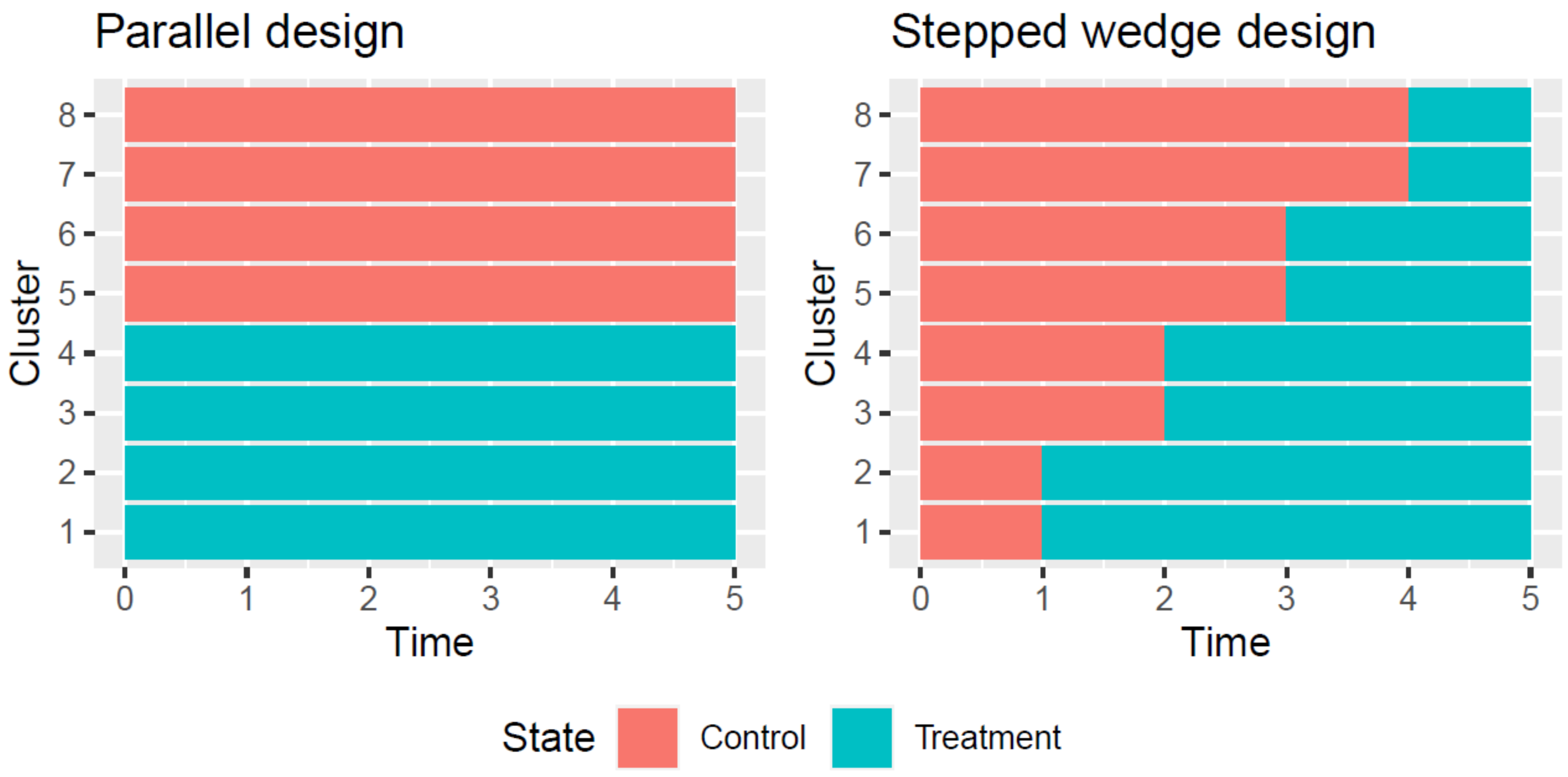


FIGURE 1 Schematic representations of a parallel CRT versus a stepped wedge CRT design with 8 clusters.

Background on stepped wedge design and analysis

Immediate treatment (IT) model:
(Hussey & Hughes 2007)

$$Y_{ijk} = \alpha + \beta_j + \delta X_{ij} + \nu_i + e_{ijk}$$

Outcome

Time trend

Cluster random effect

Overall mean

Treatment effect

Treatment indicator

Error

The problem of a time-varying treatment effect

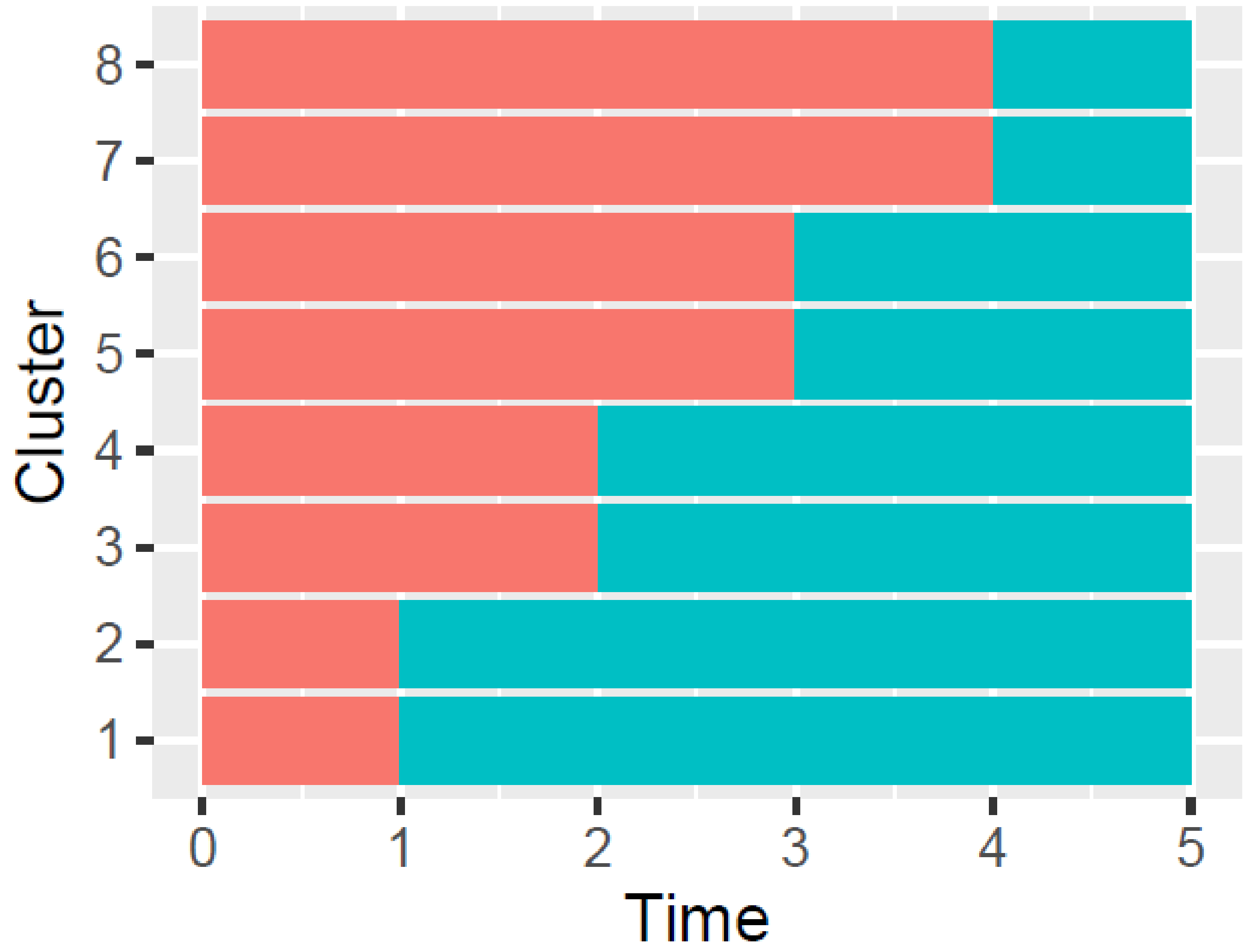
IT model: $$Y_{ijk} = \cdots + \delta X_{ij} + \cdots \qquad (1)$$

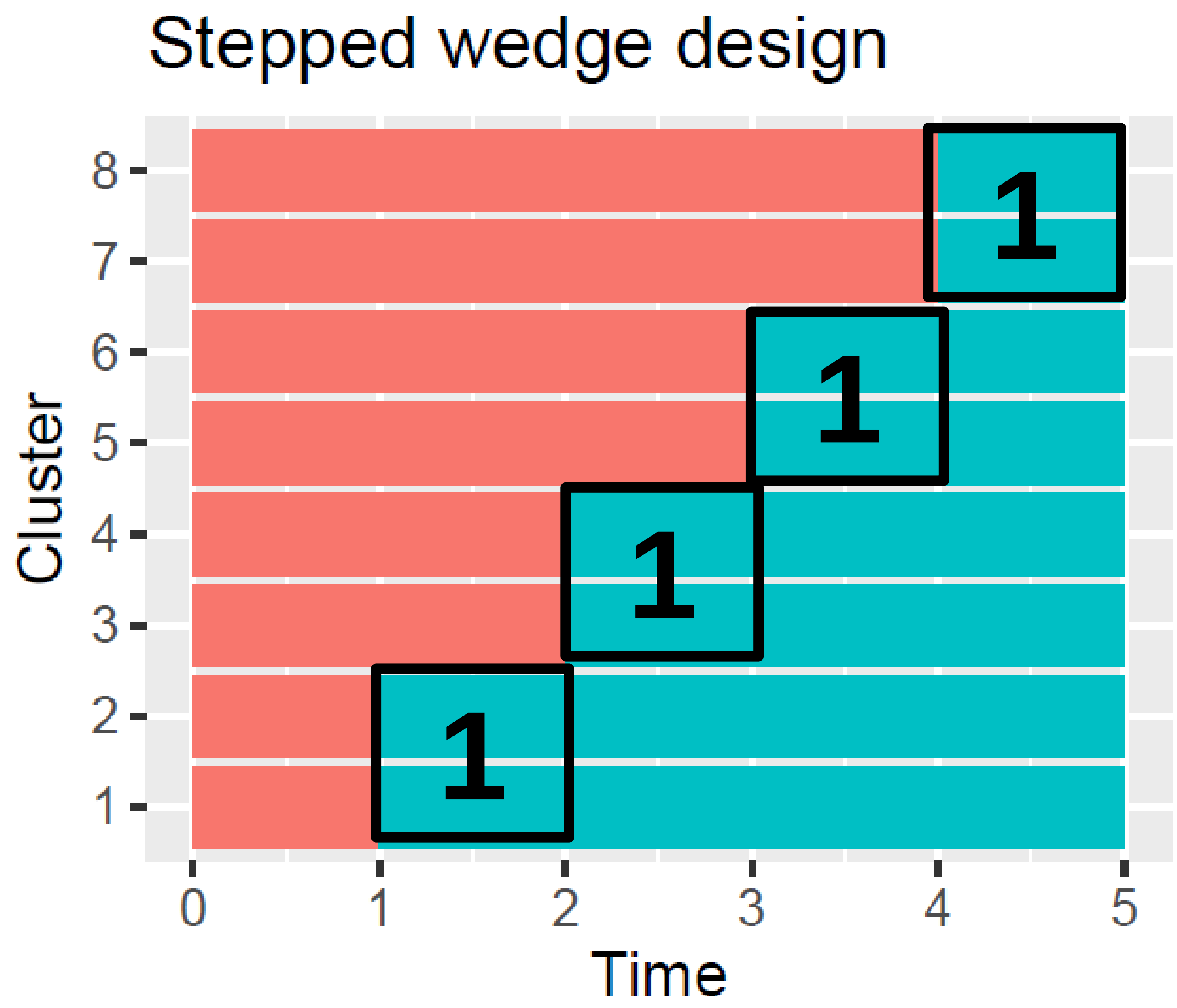
ETI model: $$Y_{ijk} = \cdots + \delta(s_{ij}) X_{ij} + \cdots \qquad (2)$$

(Kenny et al, 2022)

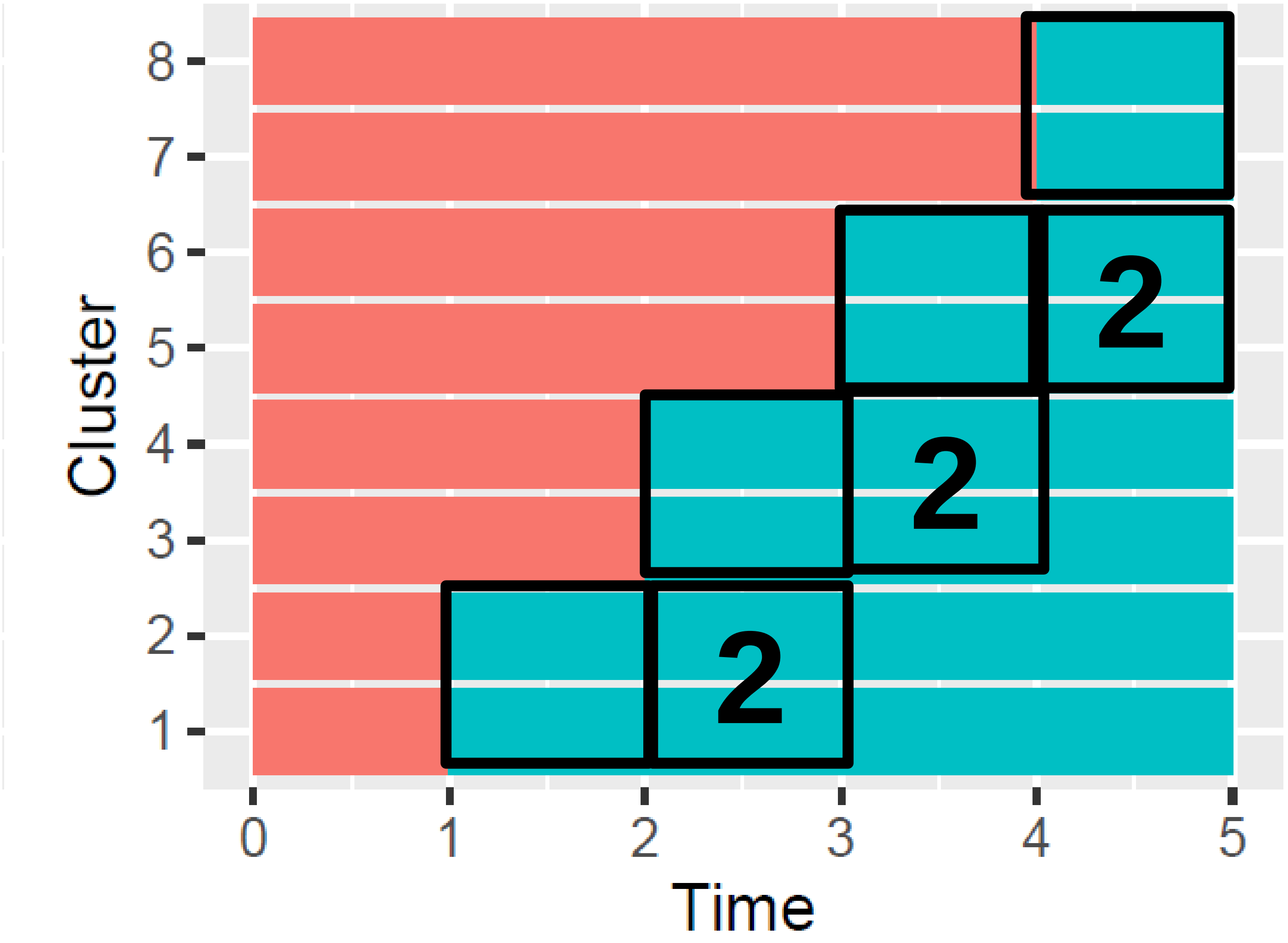
- In model (2), the treatment effect δ is a function of *exposure time* s_{ij} (time since intervention start).

Stepped wedge design

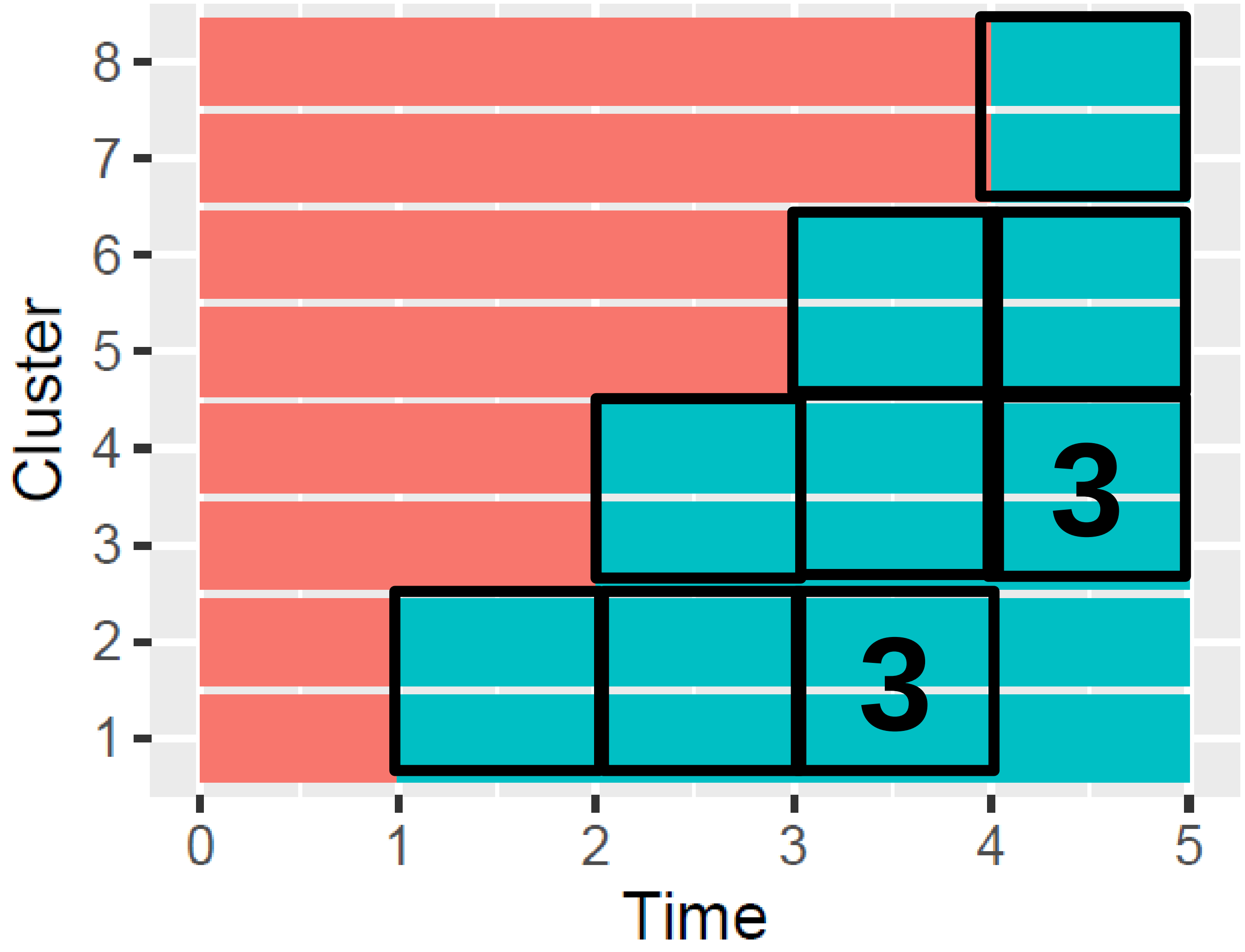



Stepped wedge design
8
7
6
5
4
3
2
1
Cluster
1
1
1
1
0
1
2
3
4
5
Time

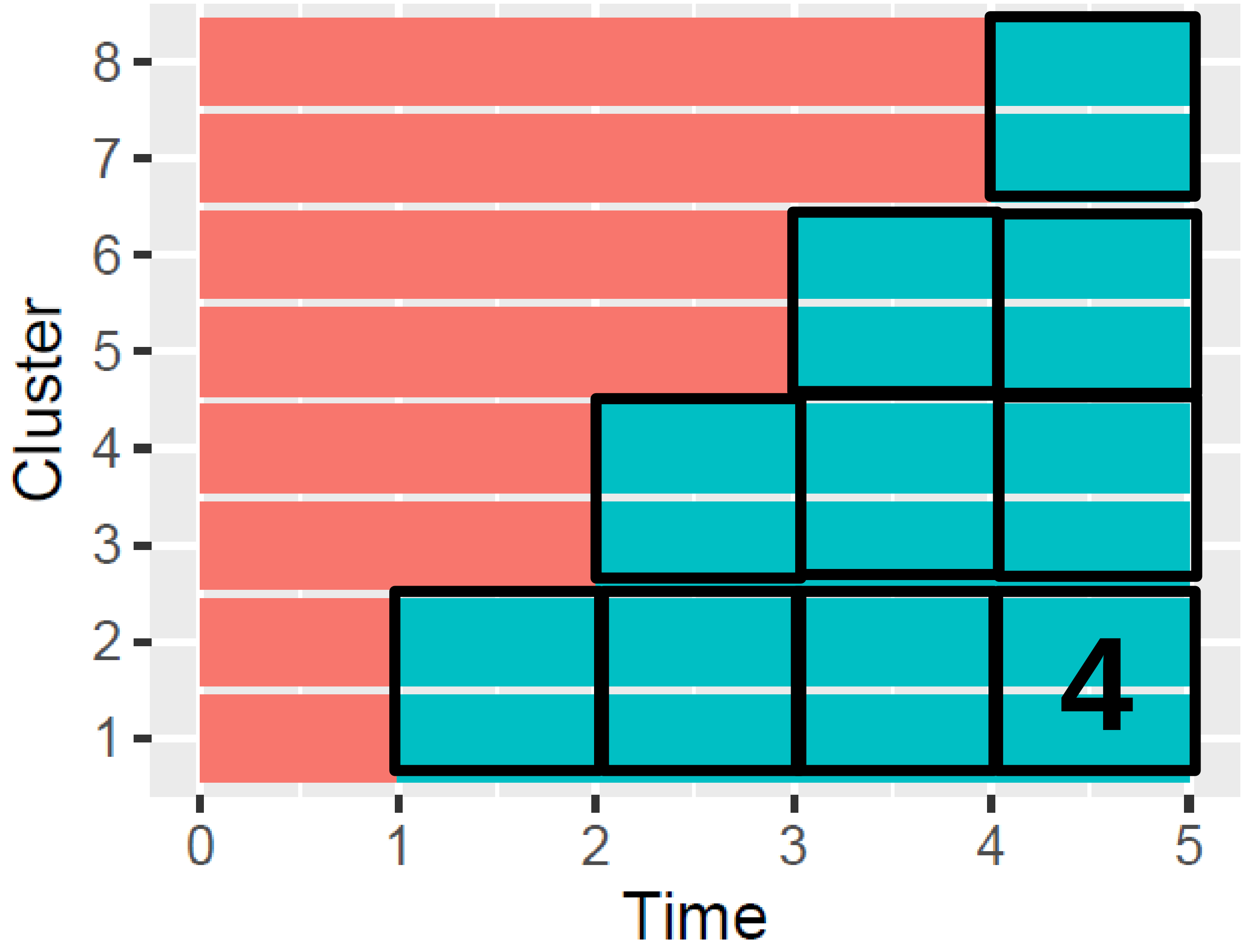
Stepped wedge design



Stepped wedge design



Stepped wedge design



The problem of a time-varying treatment effect

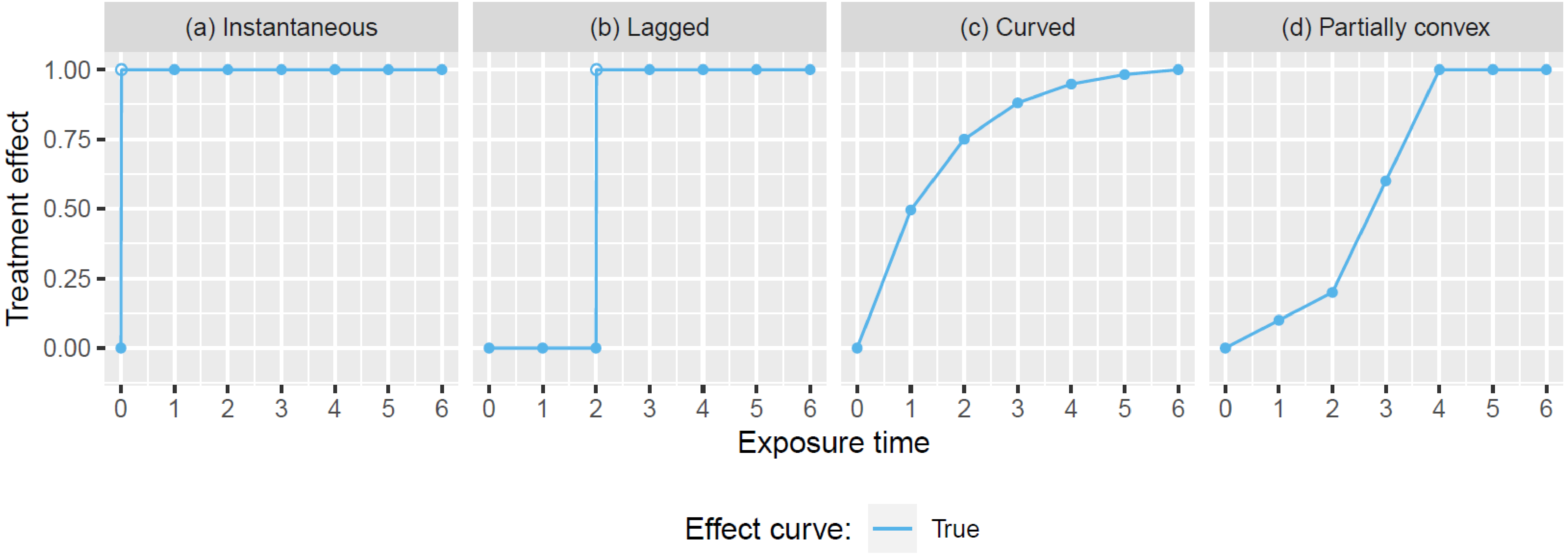
IT model: $$Y_{ijk} = \cdots + \delta X_{ij} + \cdots \qquad (1)$$

ETI model: $$Y_{ijk} = \cdots + \delta(s_{ij}) X_{ij} + \cdots \qquad (2)$$

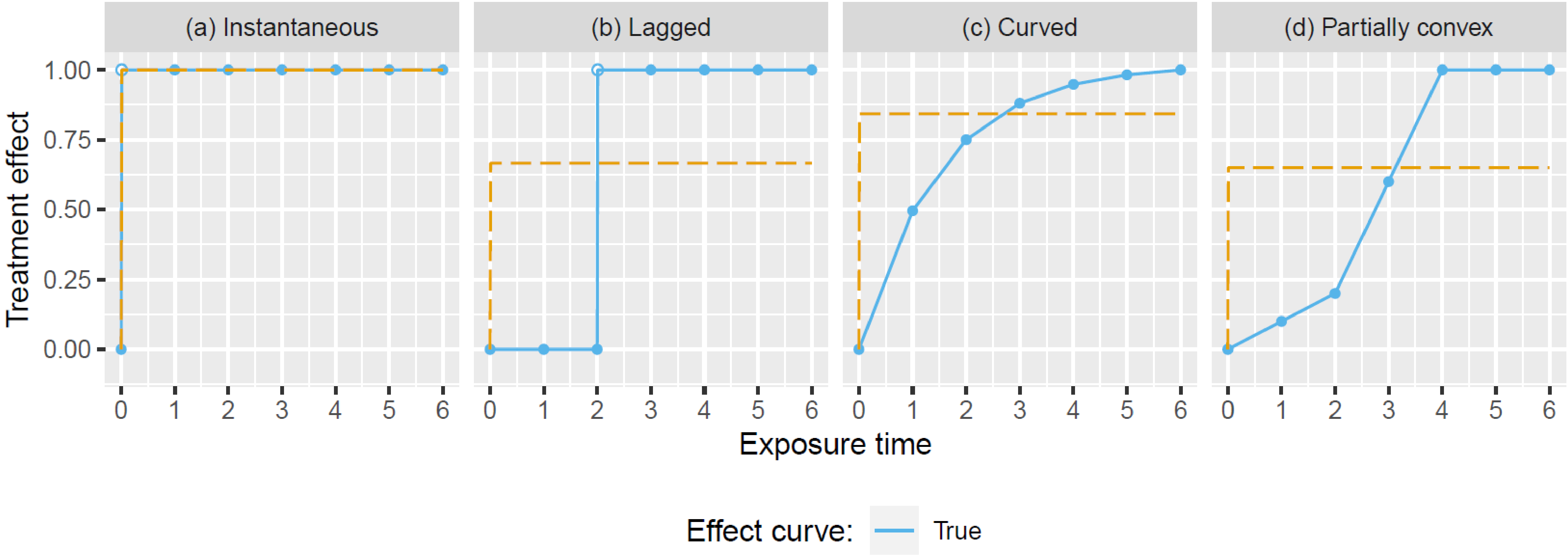
(Kenny et al, 2022)

- In model (2), the treatment effect δ is a function of *exposure time* s_{ij} (time since intervention start).
- What happens if data are generated according to (2) but analyzed with (1)?

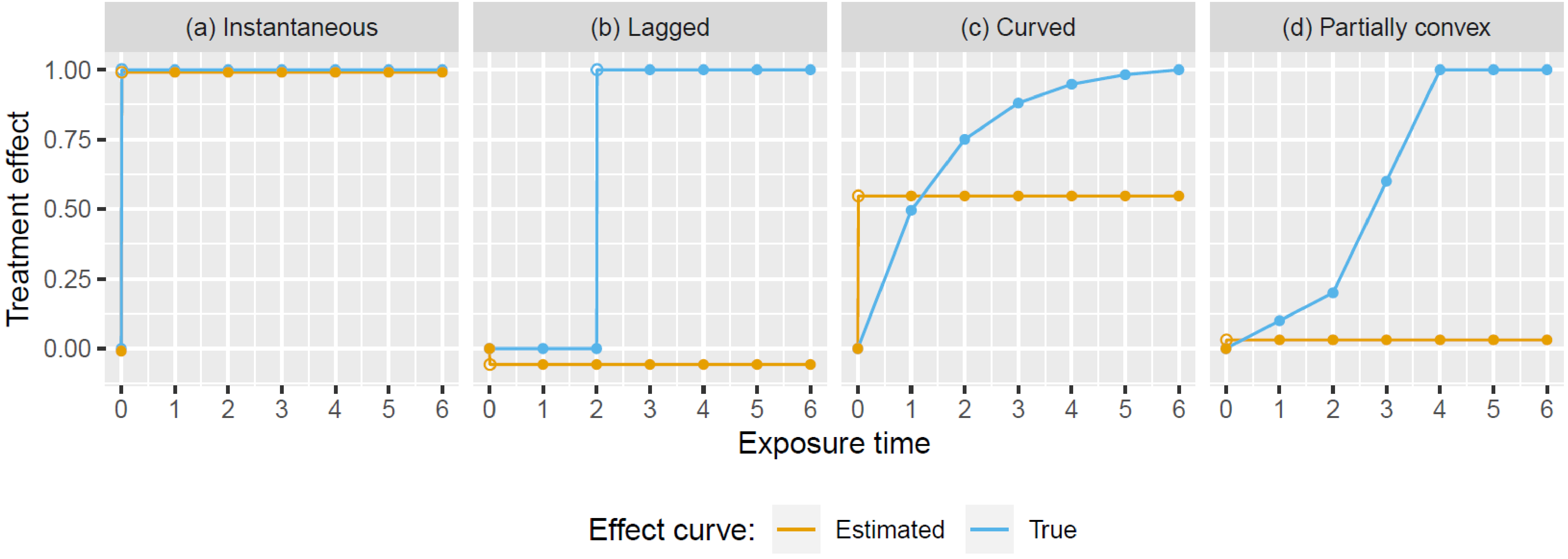
The problem of a time-varying treatment effect



The problem of a time-varying treatment effect



The problem of a time-varying treatment effect



Analysis of stepped wedge with time-varying treatment effect

So what do we do???

Analysis of stepped wedge with time-varying treatment effect

1. Think hard about what you mean by "Treatment effect"
    - Treatment effect at a particular time?
    - Average treatment effect over an interval?
    - Average treatment effect after a lag?
2. Avoid modelling assumptions

Analysis of stepped wedge with time-varying treatment effect

ETI model

$$Y_{ijk} = \cdots + \delta(s_{ij})X_{ij} + \cdots$$

ATE estimator: $\widehat{\Psi}_{[s_1,s_2]} = \frac{1}{s_2 - s_1 + 1}\sum_{r=s_1}^{s_2} \hat{\delta}(r)$

PTE estimator: $\widehat{\Psi}_s = \hat{\delta}(s)$

HPTN
HIV Prevention
Trials Network

Key findings:

- Estimate from IT model is biased for ATE/PTE in all cases, except when IT model is true
- ATE/PTE estimator is unbiased in all cases
- ATE/PTE is less “efficient” (bigger standard error) than IT model estimator when IT model is true

Conclusions:

- In stepped wedge studies, be careful fitting models that assume immediate, constant treatment effect
- Think carefully about how you want to define the "treatment effect"
- In most cases, we recommend constructing a robust estimate of the treatment effect based on the $\hat{\delta}(s)$

Acknowledgments

- Overall support for the HIV Prevention Trials Network (HPTN) is provided by the National Institute of Allergy and Infectious Diseases (NIAID), Office of the Director (OD), National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), the National Institute of Mental Health (NIMH), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) under Award Numbers UM1AI068619-15 (HPTN Leadership and Operations Center), UM1AI068617-15 (HPTN Statistical and Data Management Center), and UM1AI068613-15 (HPTN Laboratory Center).

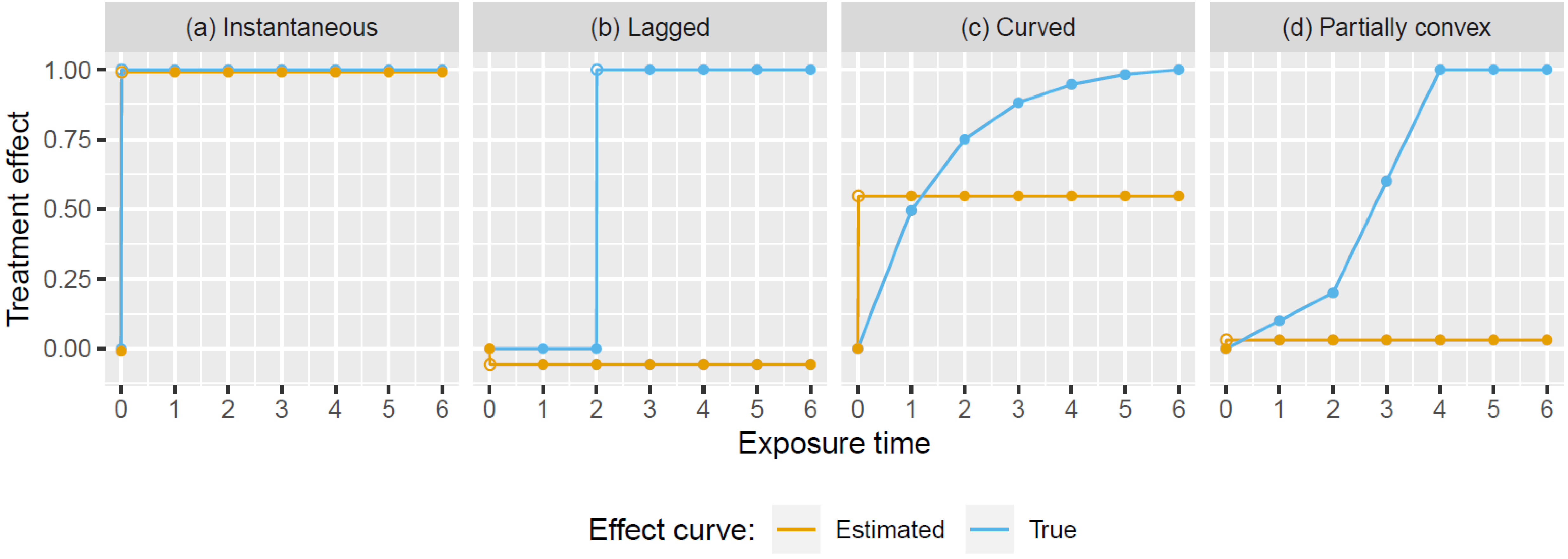
- The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The problem of a time-varying treatment effect

Why does this happen?

- The usual IT estimator can be written as $\hat{\delta} = \sum_s w(s)\hat{\delta}\,(s)$
- $w(s)$ are weights that sum to 1.0
- BUT w(s) can be >1 or <0 !
  - This can occur when you combine multiple correlated estimators (of the same parameter) that have variable precision
- In the examples given, w(1) > 1 and w(6) < 0

The problem of a time-varying treatment effect



Treatment effect is not constant - Power

- Specify the SW design via design matrix X (including time-varying treatment effect)
- Use GLMM framework to specify variance Σ
- Specify the estimator $\hat{\Psi} \equiv \frac{1}{s_2 - s_1 + 1} \sum_{r=s_1}^{s_2} \hat{\delta}_r$

$$Var(\hat{\Psi}) = H^T \left(\boldsymbol{X}^{\boldsymbol{T}} \boldsymbol{\Sigma}^{-\boldsymbol{1}} \boldsymbol{X} \right)^{-1} H$$

For testing H_o: $\Psi = 0$,

$$Power(\Psi) = \Phi \left(\sqrt{\frac{\Psi^2}{Var(\hat{\Psi})}} - Z_{1-\frac{\alpha}{2}} \right)$$