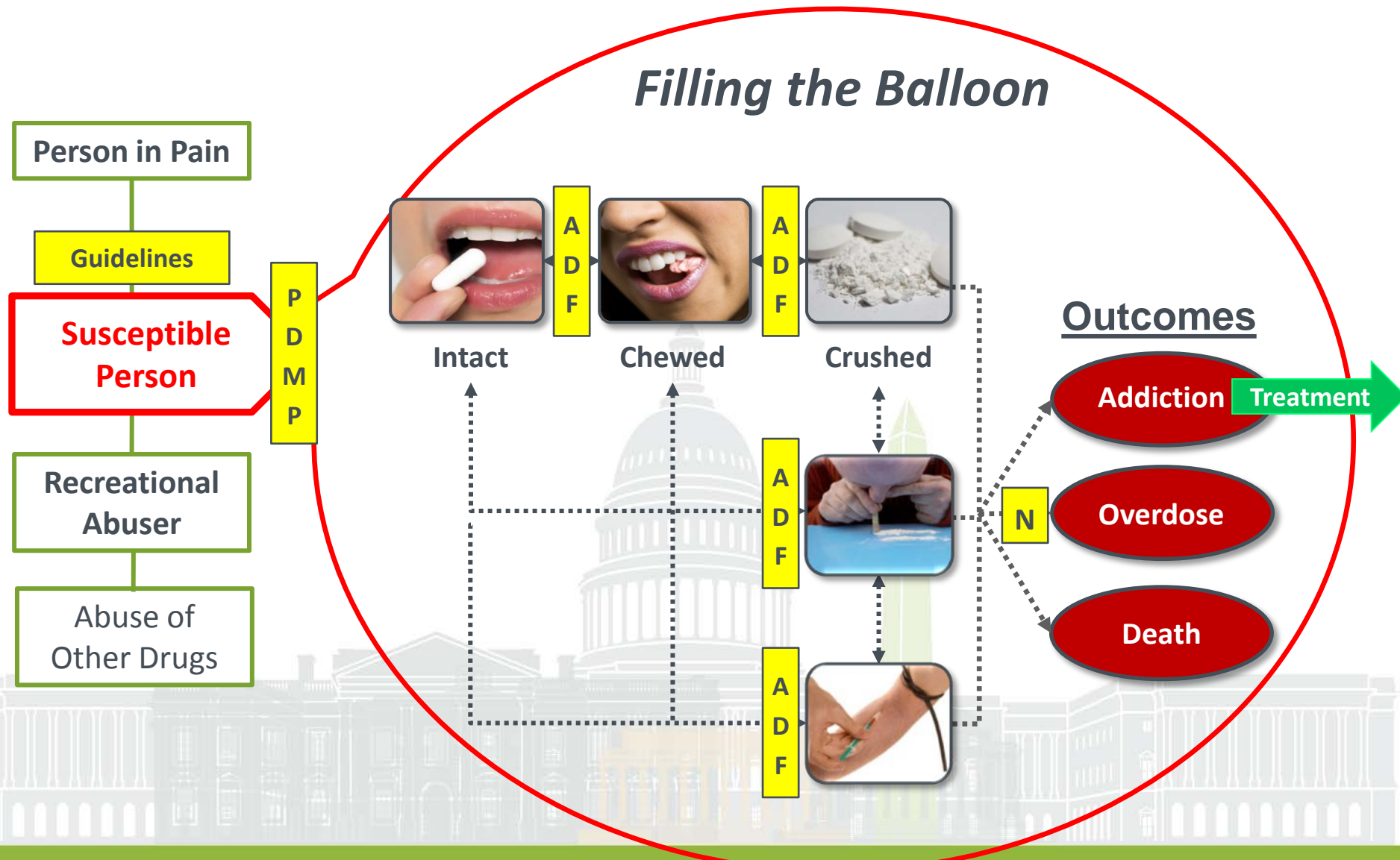




Abuse Deterrent (Tamper Resistant) Formulations State of the Evidence 2017

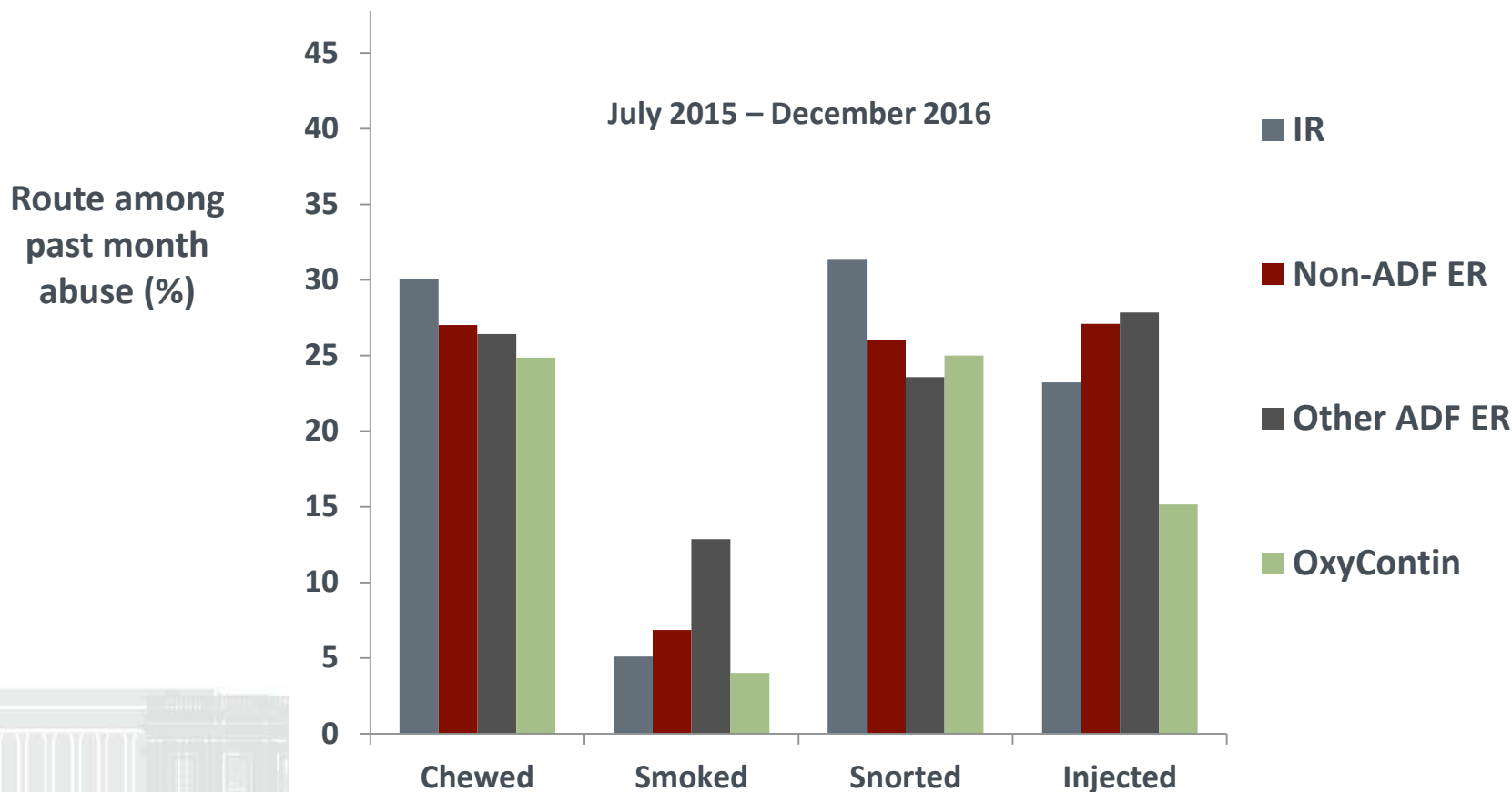
Richard C. Dart, MD, PhD
Executive Director, RADARS® System
Denver Health and Hospital Authority

Progression of Rx Drug Abuse



Who Cares About Chewing?

RADARS SKIP: Adults meeting DSM-IV criteria for substance abuse with a primary drug that is an opioid



Systematic Review of Abuse Deterrent (Tamper Resistant) Formulations

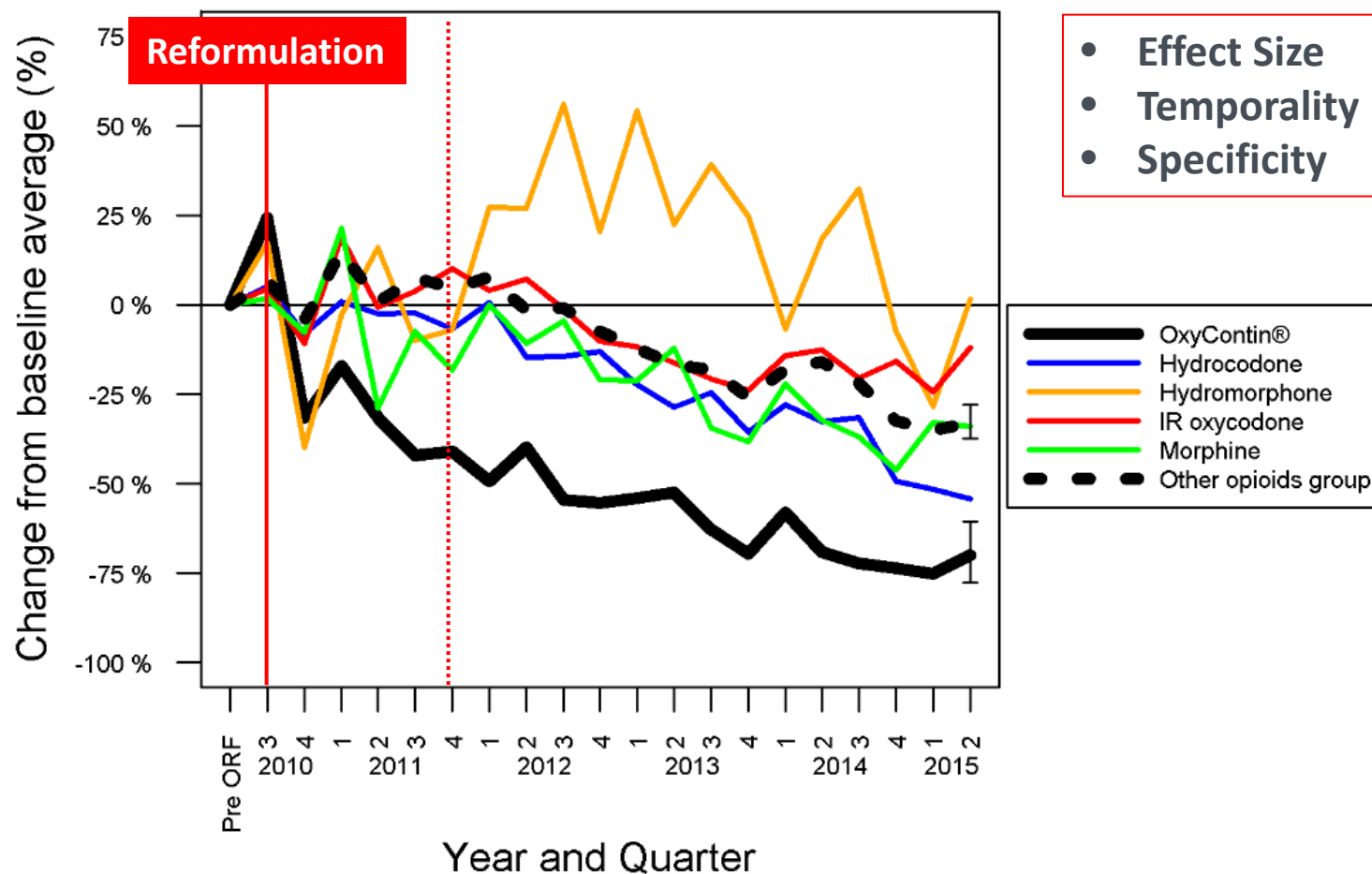
- Question: What is the evidence that opioid analgesics with abuse deterrent labeling improve outcomes (abuse, misuse, overdose, death)?
- 44 reports on opioids with abuse deterrent labeling
 - Hydrocodone (n=7)
 - Morphine (n=5)
 - Oxycodone (n=32)*
- Hill Criteria
- Also assessed confounding factors and bias

Dart, Iwanicki, Dasgupta, Cicero, Schnoll, 2017, in press.

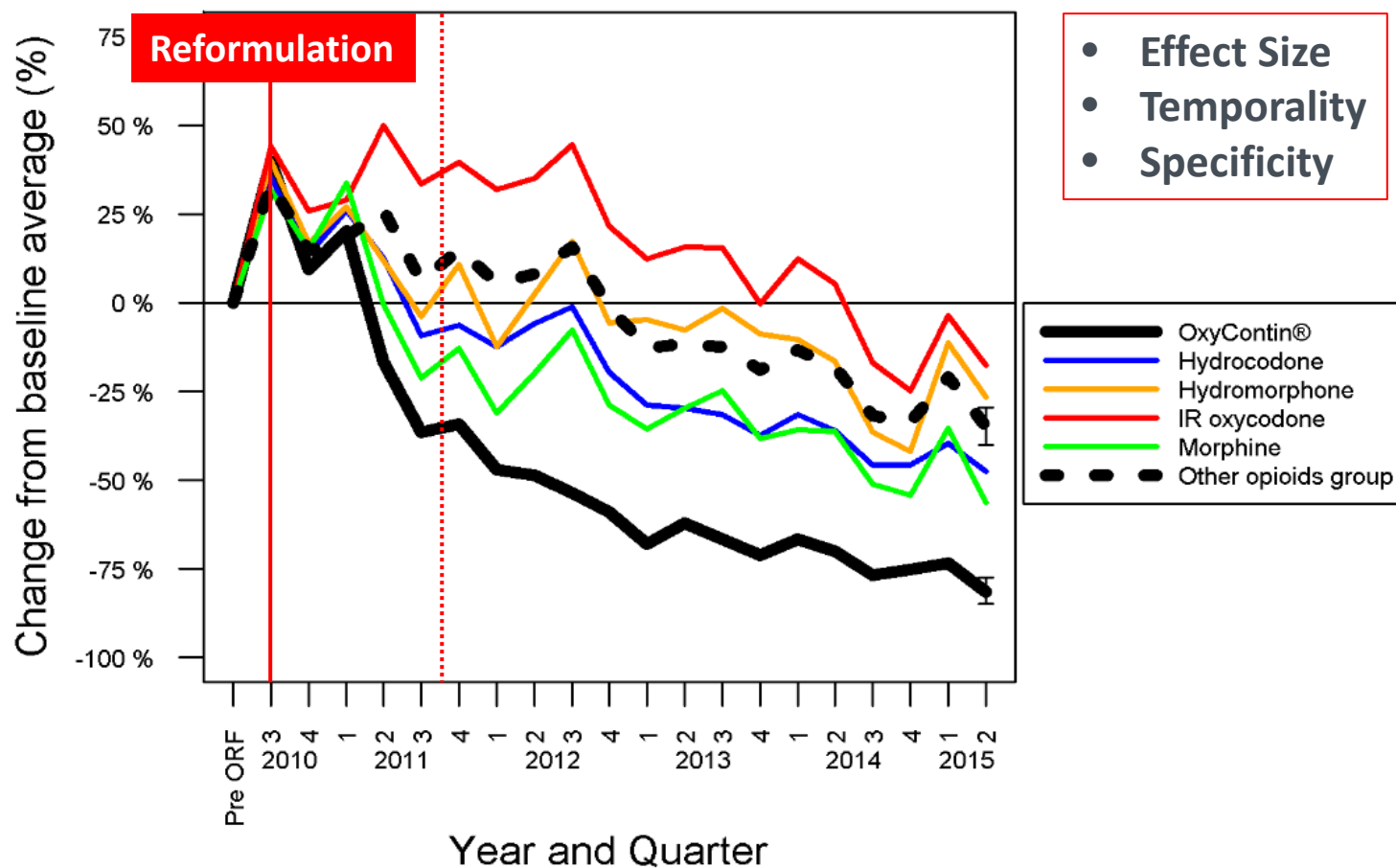
Bradford Hill Criteria

Factor	Description
Strength (<u>effect size</u>):	The larger the association, the more likely that it is causal.
Consistency (<u>reproducibility</u>):	“Has it been repeatedly observed by different persons, in different places, circumstances and times?”
Specificity	Causal relationship is supported by a very specific population at a specific site and disease with no other likely explanation
Temporality	The effect has to occur after the cause and after expected delay
Biological gradient	Greater exposure should generally lead to greater incidence.
Plausibility	A plausible mechanism between cause and effect
Coherence	Coherence between epidemiological and laboratory findings
Experiment	"... some preventive action is taken. Does it in fact prevent?"
Analogy	The effect of similar factors may be considered.
Additional Criteria	
Confounding	Alternative explanations for the observed associations
Bias	Systematic artifacts of data collection or study design

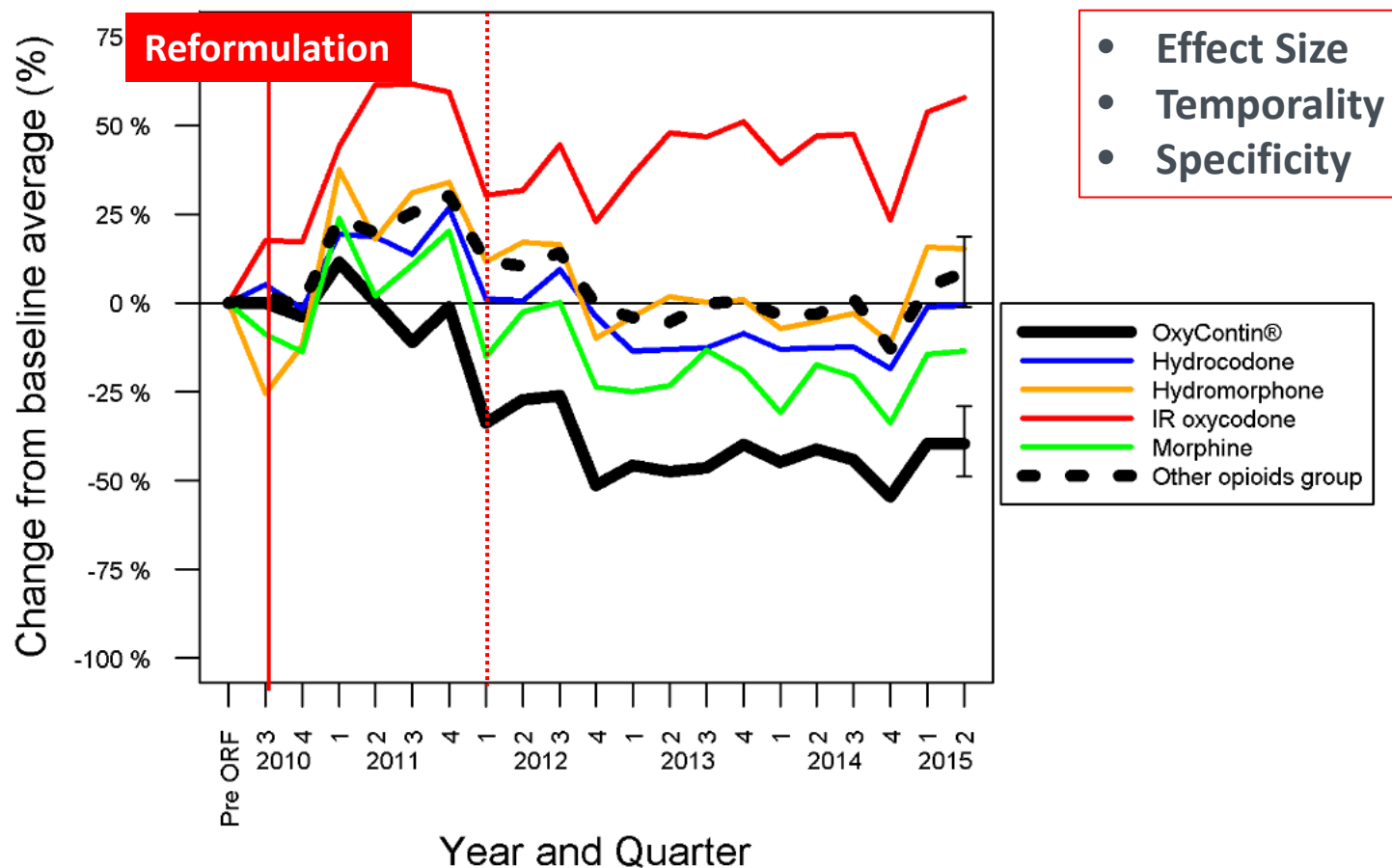
Cases Involving Intentional Abuse, Poison Center Program



Investigations Opened, Drug Diversion Program



Drugs Used in Past 30 Days, Opioid Treatment Program



Drugs Used in Past 30 Days, Survey of Key Informants' Patients Program

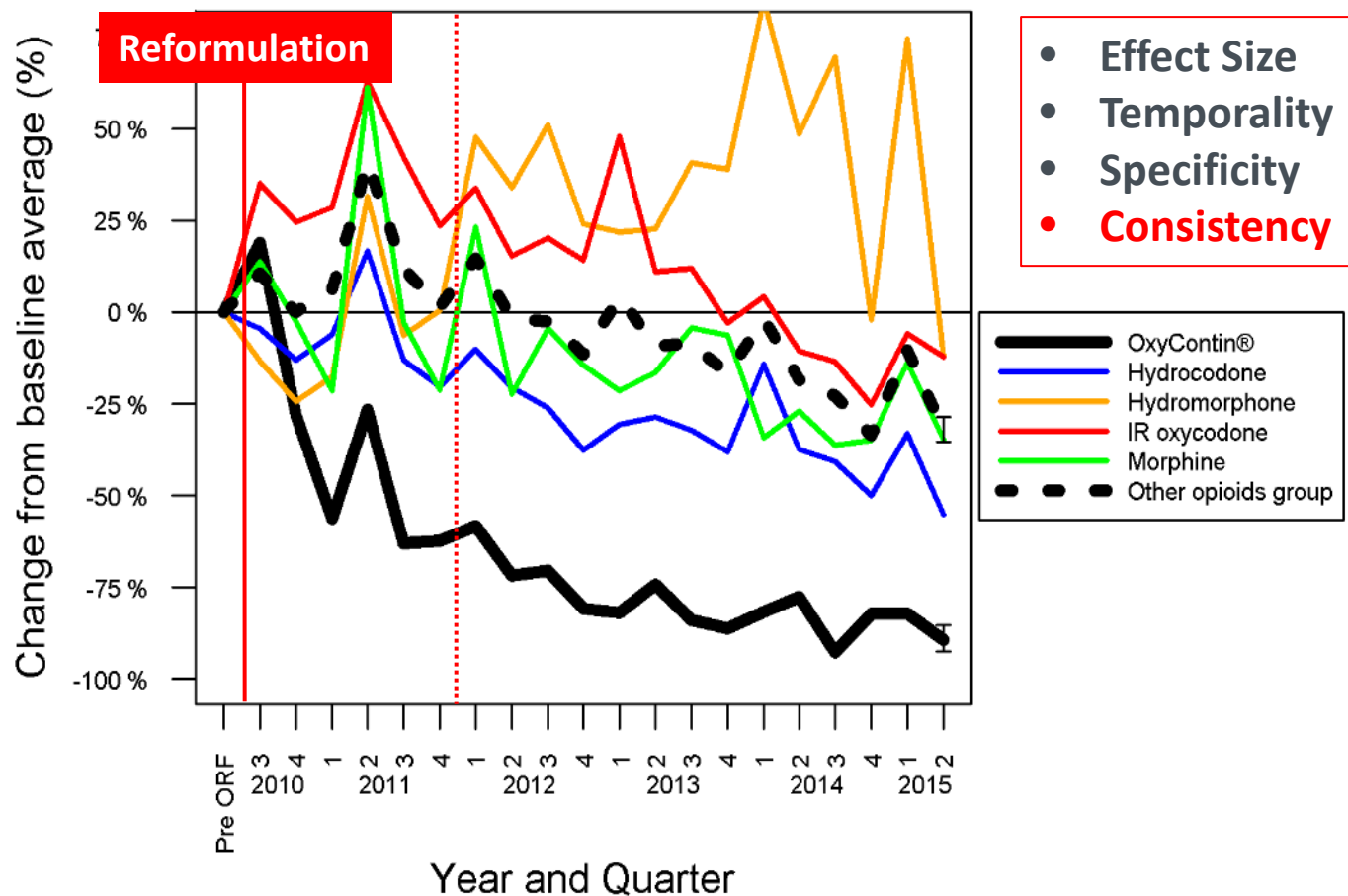
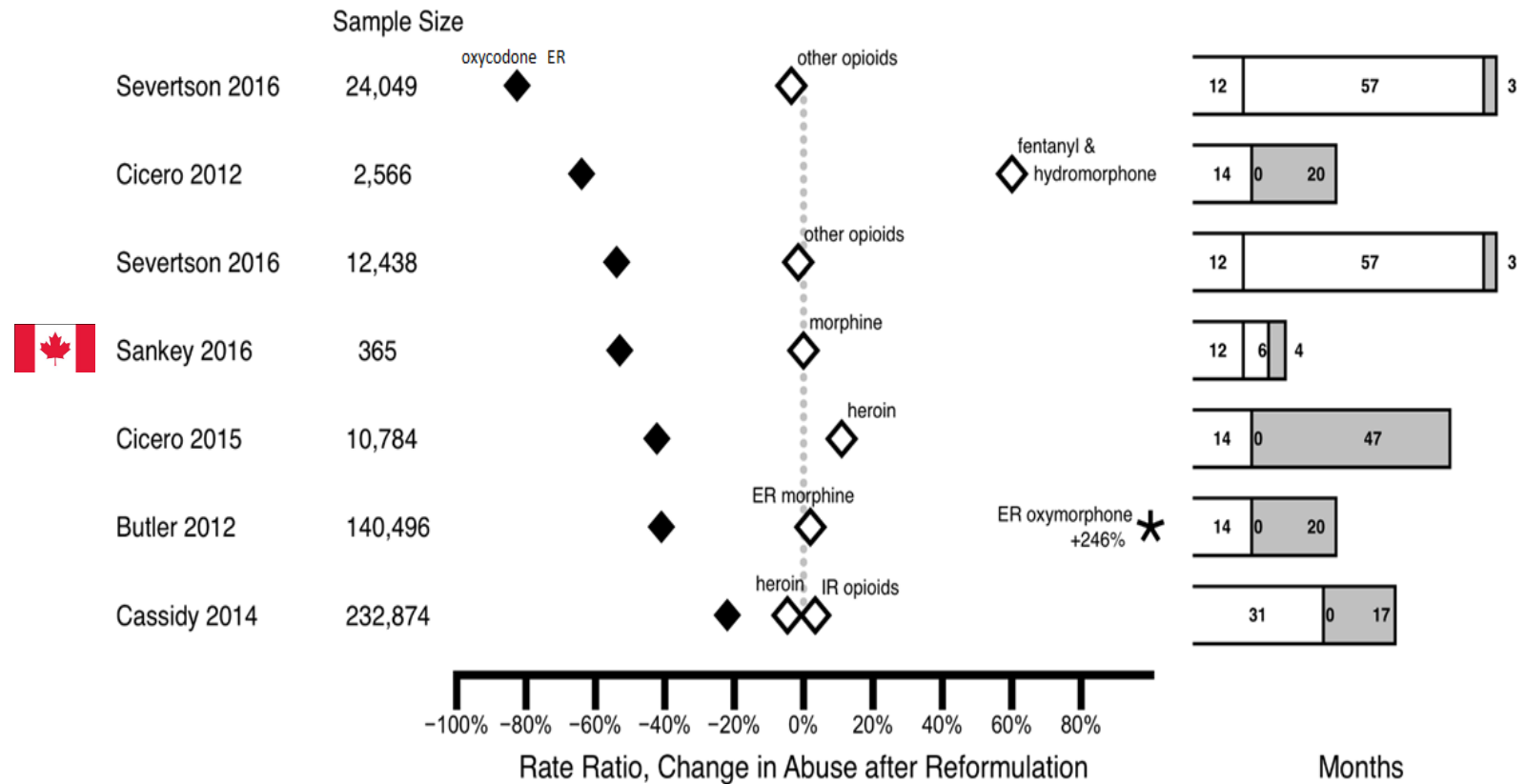


Figure 2. Reported Change in Treatment Measures of Abuse After Reformulation of Oxycodone ER



The Difference is Research



Studying abuse deterrent opioid formulations in Australia

Medicine

National Drug and Alcohol Research Centre

National Opioid Medication Abuse Deterrence (NOMAD) study

Following the introduction of Reformulated OxyContin®...

1. Population-level utilisation of oxycodone and other opioids?
2. Extra-medical use of OxyContin®?
3. Extra-medical use of other forms of oxycodone?
4. Extra-medical use of other pharmaceutical opioids and heroin?
5. Attractiveness for tampering?
6. Methods of tampering/oxycodone extraction evolve/become widespread?
7. Unintended consequences?



NOMAD prospective cohort

Methods

- N=606 people who tamper with pharmaceutical opioids

Eligibility: Reported (a) past month injecting, snorting, chewing or smoking of pharmaceutical opioid(s) and (b) engaged in this practice at least monthly in the past six months.

- 3 study jurisdictions: NSW, TAS and SA
- 3 waves of data collection
 - Wave 1: Nov 2013 – Mar 2014
 - Wave 2: May 2014 – Aug 2014
 - Wave 3: May 2015 – Sep 2015
- Excellent cohort retention
 - 92% of eligible participants at Wave 2
 - 90% of eligible participants at Wave 3

Baseline cohort characteristics

- Majority (96%) injected a drug (past 6 months)
- Demographically similar to other studies of PWID
 - Predominantly male (69%); High levels of unemployment (82%); homelessness (17%); prison history (62%).
- Significant comorbidity
 - 61% current mod-severe depression; 54% chronic pain or disability past 6 months.
- Half (54%) in OST (past 6 months).

Participants referred into
the study (n=1321)

Participants assessed for
eligibility (n=1176)

Could not contact n=123
No longer interested n=22

Eligible participants n=692

Ineligible n=484

In prison past month n=11, Did not use or tamper
with pharmaceutical opioids n=283, Only used OST
medication n= 146, Did not use opioid medication for
long enough n=42, Not living in jurisdictions n=2

Completed
baseline
n=606

Baseline interviews:
November 2013-March
2014 (prior to
reformulation)

Loss after eligibility n=86

Withdrew consent n=1, Could not contact n= 4, Did
not complete n=81

Completed follow-up 1 ,
n=547 (90%), (92% of
eligible, participants)

Follow-up 1- May-August
2014

Not interviewed at follow-up 1 n=59

In prison n=9, Withdrew consent n=4,
Inpatient facility n =2, Could not contact n=44

Completed follow-up 2,
n=499, (82%) (90% of
eligible participants)

Follow-up 2- May-Sept 2015

Not interviewed at follow-up 2 n=107

In prison n=31, Excluded n=3, Deceased n=8,
Withdrew consent n=8, Inpatient facility n=3, Could
not contact n=54

Oxycodone injection (past month)

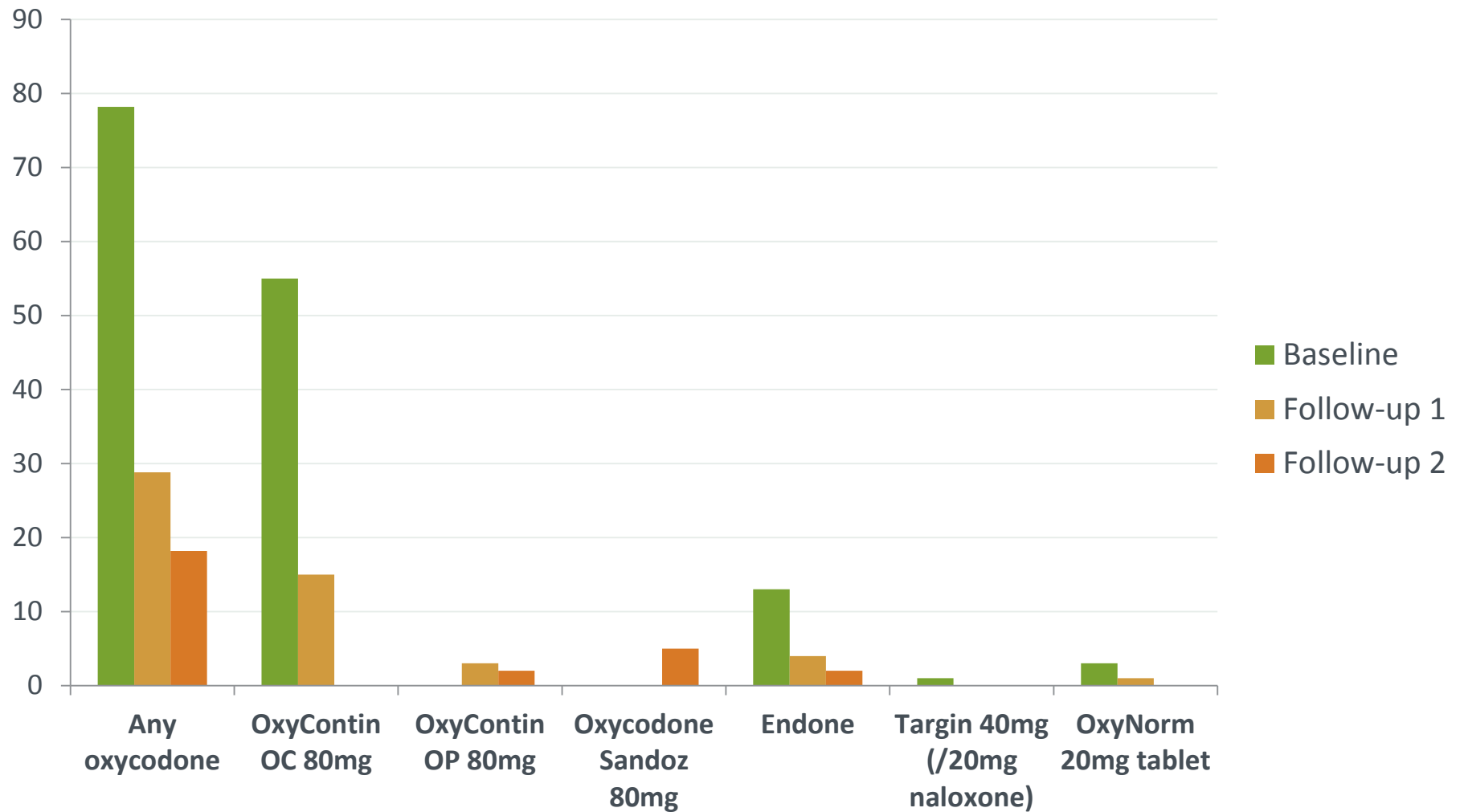
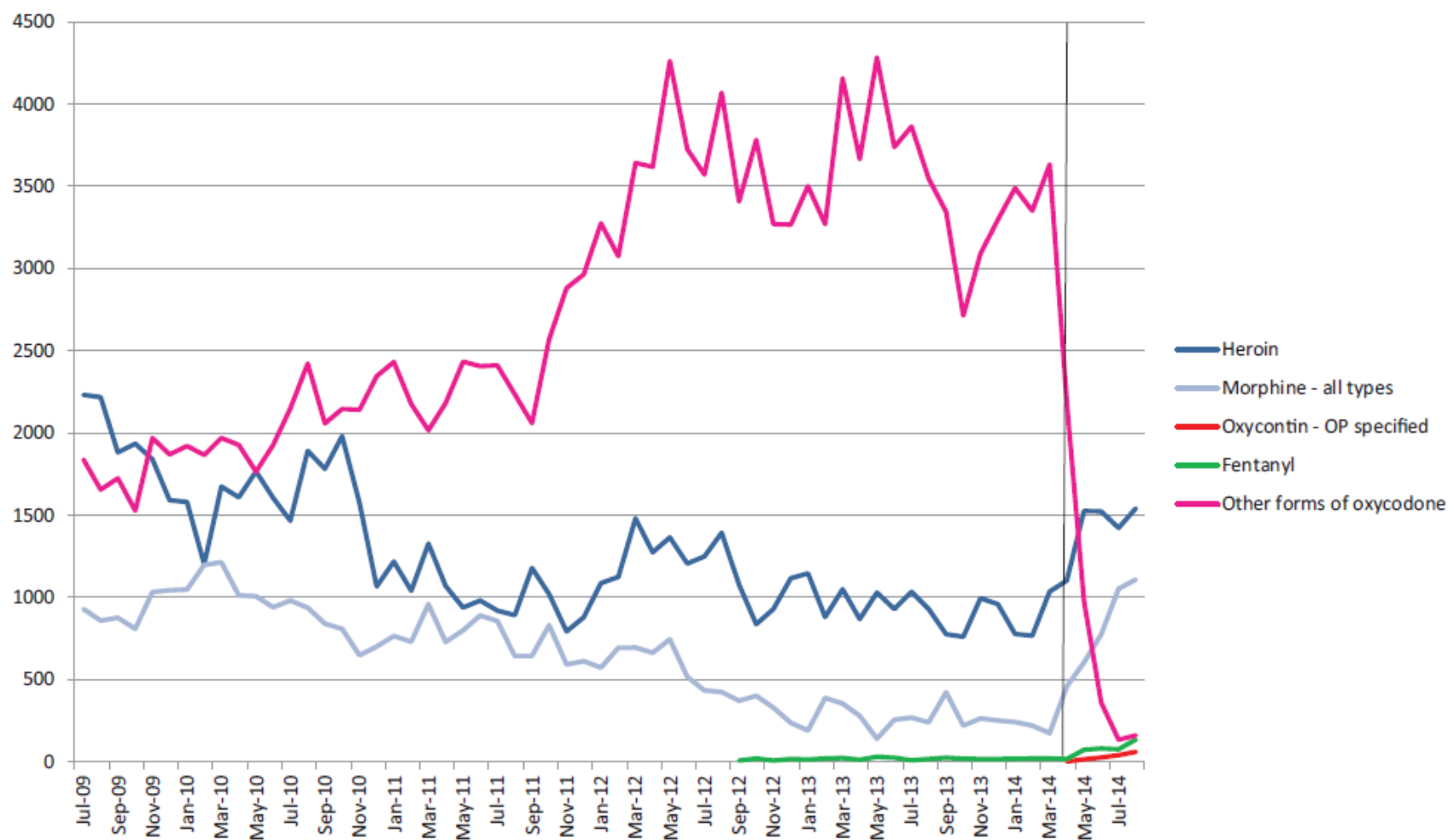


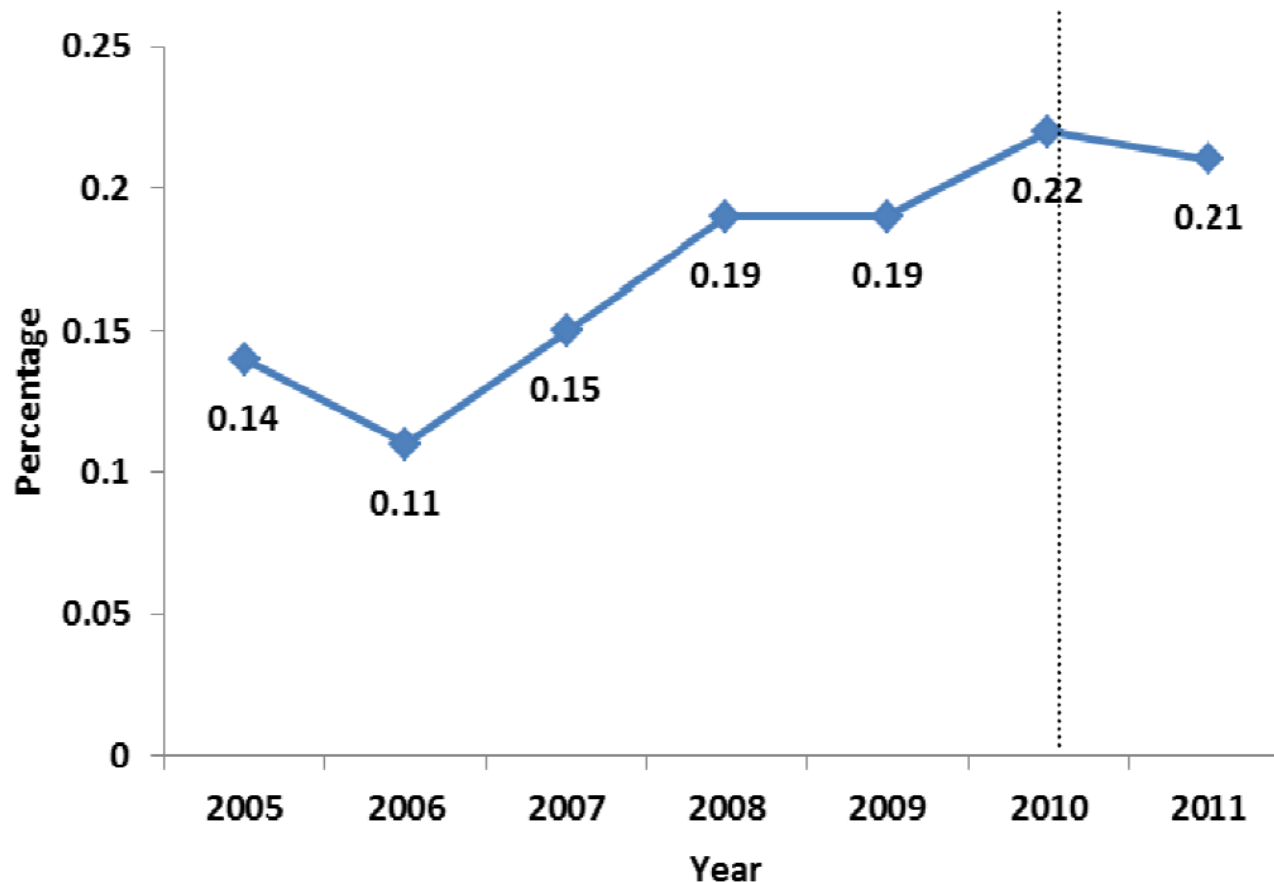
Fig. 4. Client visits per month where oxycodone, morphine, fentanyl and heroin were injected, Sydney Medically Supervised Injecting Centre (MSIC), July 2009–August 2014



NOMAD study summary

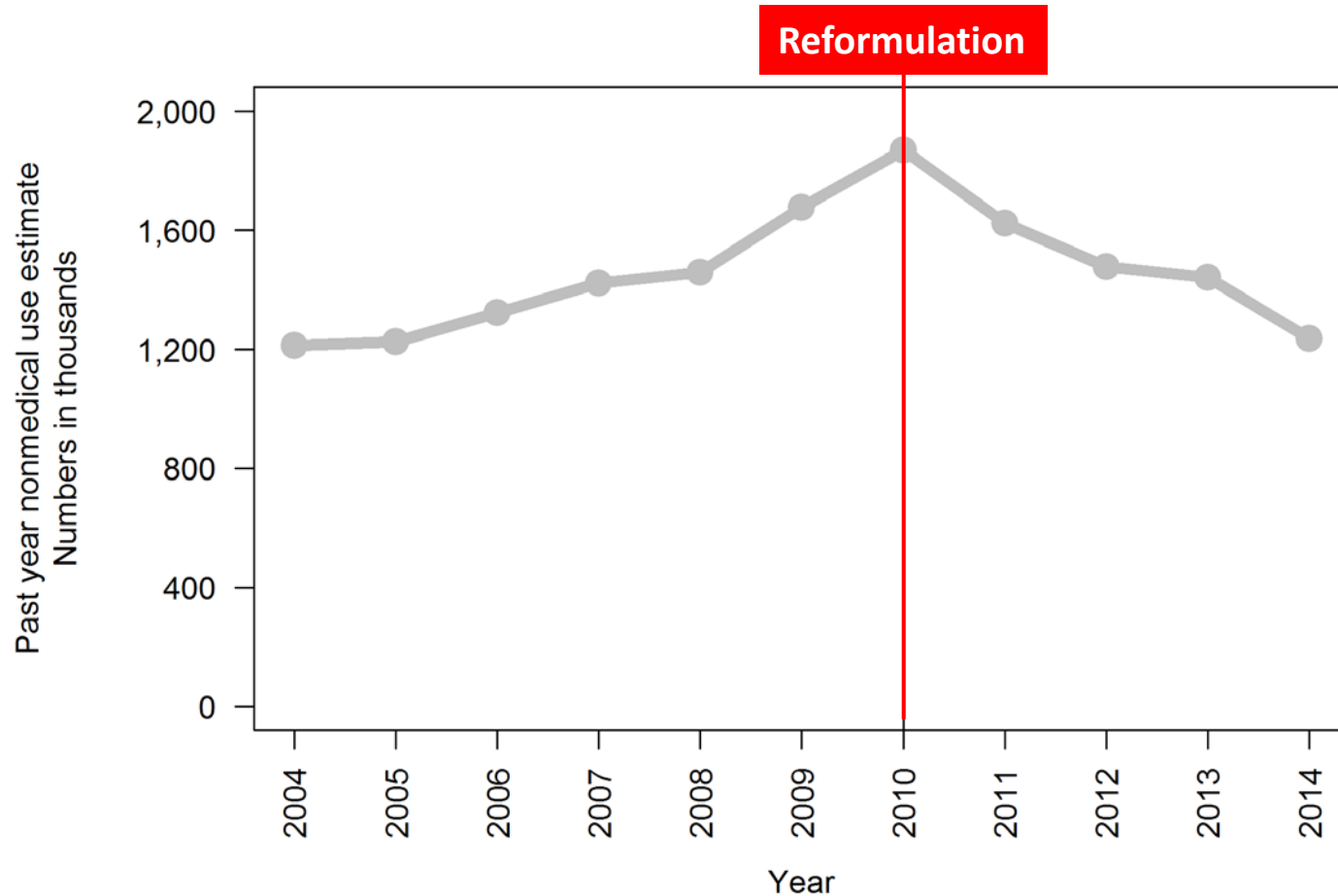
- Prior to reformulation, 80mg OxyContin® were most frequently diverted/injected
- Observed declines in OxyContin®/oxycodone use and injection following introduction of reformulation among the NOMAD cohort and NSP/MSIC data
- ❖ Heroin and methamphetamine remain primary drugs of injection among NOMAD cohort and NSP/MSIC clients.
- ❖ Some tampering with Reformulated OxyContin has persisted at follow-up 2 (27% attempted in past month), but overall, Reformulated OxyContin® was viewed as less attractive for tampering/injection

Negative Data – NSDUH past 30 day Nonmedical Use

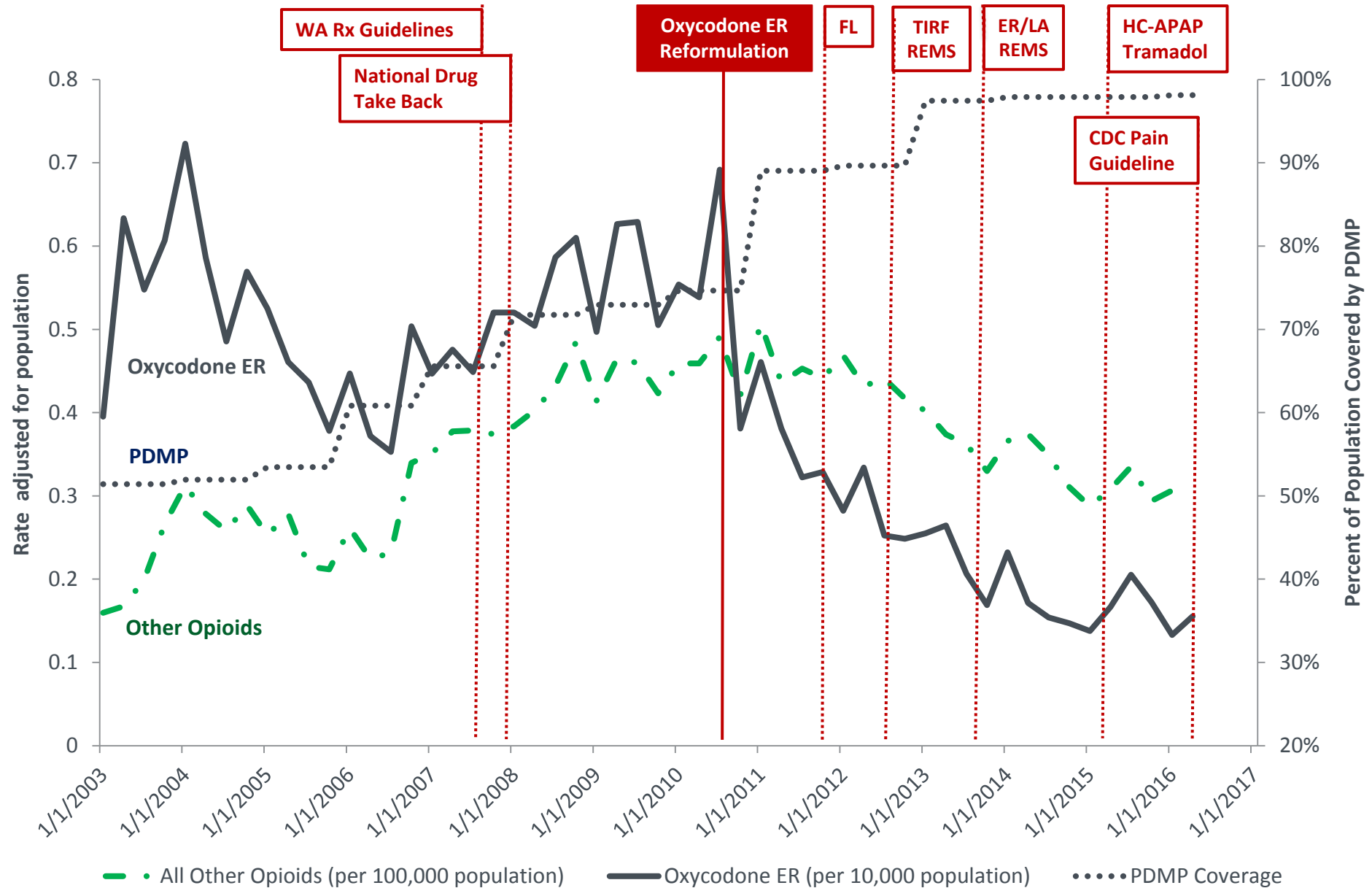


Novak S. FDA-2013-D-0045, 2013

Nonmedical Use of OxyContin[®], National Survey of Drug Use and Health, 2006 – 2014



Timeline of Interventions vs. Oxycodone ER, Other Opioids



Summary

- Introduction of oxycodone ER was followed by improved outcomes related to oxycodone ER
- Other opioids have increased over the same time period (heroin)
- The results are similar in 3 different countries with different baseline conditions, different measurement instruments and timeframes.
- The early initial decrease in oxycodone ER contrasted with increases for most other opioids during the first year or more, but was then followed by decreases for almost all opioids.
- Multiple sources of bias and confounding are present, however, we conclude that none of these accounts for the observed decrease.