Assessment of the Impact of the Ontario Fentanyl Patch-for-Patch Return Program

by the Ontario Drug Policy Research Network (ODPRN)

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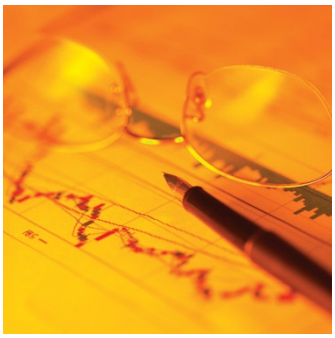

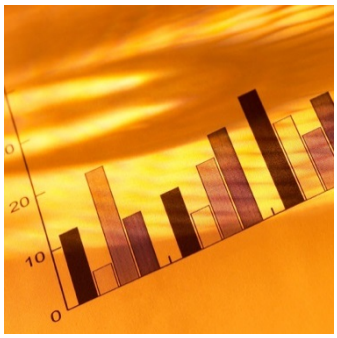

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Abstract

Rising use of prescription opioids has led to Canada having the second highest consumption per capita worldwide. These trends have been associated with a rise in opioid abuse and mortality. One major area of concern has been the abuse of fentanyl, a synthetic opioid 100 times more potent than morphine. Fentanyl is available as a patch formulation and diversion of these patches is a common form of illicit use. To curb the abuse of fentanyl patches, a Patch-for-Patch (P4P) initiative was launched in some counties in collaboration with the Ontario Provincial Police (OPP) between 2013 and 2016.

This study evaluates the impact of the P4P programs implemented between February 2013 and April 2016. Cross-sectional time-series analyses were conducted to evaluate the impact of program initiation on fentanyl dispensing, non-fentanyl opioid dispensing, opioid-related hospital visits and deaths, and fentanyl-related police incidents. Overall, the program reduced the dispensing of fentanyl patches, without detectable benefit or risk for measured outcomes. This study also found that the number of fentanyl-patch related police incidents has been increasing across the province, with no differences between participating or non-participating P4P counties. Our findings may be more reflective of shifts in police awareness than actual increases in fentanyl abuse.

The findings of this report support P4P programs as part of a larger opioid-abuse reduction strategy. The lack of a significant increase in harm should raise confidence in the use of the program in other jurisdictions. Importantly, similar programs should include increased access to addiction therapy and harm-reduction programs.

Author's Note

The views expressed are those of the authors and do not necessarily reflect those of Public Safety Canada. Correspondence concerning this report should be addressed to:

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Introduction

Canada has the second highest consumption of opioids per capita in the world (Board, 2012). Consequently, Canada has high rates of opioid abuse, misuse and related mortality (Dart et al., 2015; Dhalla et al., 2009; Franklin et al., 2005; T. Gomes, M. M. Mamdani, et al., 2014; Gomes, Mamdani, Dhalla, Paterson, & Juurlink, 2011). The emerging opioid crisis in Canada has been identified by public health and police agencies at all levels of government ("CDC grand rounds: prescription drug overdoses - a U.S. epidemic," 2012; Fischer, Kurdyak, Goldner, Tyndall, & Rehm, 2016; "Notice of Decision for OxyNeo," 2012; Ontario Ministry of Health and Long-Term Care, 2010, 2016). In Ontario Canada, the rate of opioid-related deaths increased 3-fold between 1990 and 2010, with recent studies estimating that 1 in 170 deaths were related to opioids. The impact of this growing problem is even more pronounced among younger adults with 1 in 8 deaths being associated with opioid use among those aged 24 to 35 (T. Gomes, M. M. Mamdani, et al., 2014). Harms related to opioid use include drug-related deaths, increases in non-fatal overdoses, drug-impaired driving, occurrences of neo-natal abstinence syndrome, and illicit use of fentanyl and other opioids (Dubois, Bedard, & Weaver, 2010; Gomes & Juurlink, 2016; T. Gomes, M. M. Mamdani, et al., 2014; Gomes, Mamdani, Paterson, Dhalla, & Juurlink, 2014; T. Gomes, D. Martins, et al., 2014; Gomes et al., 2015; Sehgal, Colson, & Smith, 2013; Trescot, 2016). These harms correlate with a large increase in the overall use of opioids in the population. In Ontario, the rate of high-dose opioid use among public beneficiaries has risen between 2009 and 2014 (Spooner et al., 2016). Approximately 14% of all Ontarians and 25% of Ontario public drug beneficiaries are dispensed a prescription opioid annually (Ministry of Health and Long-Term Care, 2016; Spooner et al., 2016).

Fentanyl

A recent rise in overdoses related to fentanyl has raised concern across North America. Fentanyl is a synthetic opioid 100 times more potent than morphine and is available by prescription in Ontario in a transdermal patch formulation in various strengths (25mcg, 50mcg, 75 mcg, 100 mcg per hour) (Canadian Pharmaceutical Association, 2008; Trescot, 2016). Diversion of prescription patches is a common form of illicit fentanyl use, and the potential for fentanyl abuse is high given its rapid onset and potency. Recent research has highlighted that a major source of illicit fentanyl use in Canada has been via illegal diversion of prescriptions (Young, Pirie, Buxton, & Hosein, 2015). Fentanyl is highly soluble, allowing it to be diverted easily through a variety of methods for consumption, including using the gel from the patch to dissolve under the tongue, as well as eating, smoking, or injecting the fentanyl. The street names for illicit fentanyl include Apache, China Girl, China White, Dance Fever, Friend, Goodfella, Jackpot, Murder 8, TNT and Tango & Cash (Young et al., 2015). Illegally diverted patches have high value since used patches retain up to 80% of their original dosage in the patch matrix. In Ontario, diverted patches are reported to be sold for $200 to $300 in Southern regions and as high as $500 in northern regions (Ontario Association of Chiefs of Police – Substance Abuse Committee, 2014).

Recently, illegally produced fentanyl powder has also been circulating, with the powder used to manufacture pills or being combined with cocaine or heroin (Karen Howlett, 2016; Young et al., 2015). Illicitly produced fentanyl presents even greater risks than diverted pharmaceutical fentanyl due to the lack of quality control and accuracy of dosing measures. Compounds can mislead a buyer who could easily underestimate the drug’s potency, thereby increasing the risk of an overdose and death. Despite growing concern around the dangers associated with illegally

produced fentanyl, a large portion of fentanyl is still diverted from pharmaceutical patches (Young et al., 2015).

The growing fentanyl availability and use has led to the recognition that it is one of the most prevalent opioids contributing to the current opioid problem (Tara Gomes et al., 2014). Recent analysis by the Canadian Centre on Substance Abuse (CCSA) found that 655 deaths in Canada were attributable to fentanyl between 2009 and 2014 and that this number is considered to be largely underestimated due to poor capturing of opioid-related deaths nationally (Canadian Centre on Substance Abuse, 2015). In Ontario, where data is captured by the Office of the Chief Coroner, the number of deaths caused by fentanyl toxicity has risen from 10 deaths in 2002 to 176 in 2014 (Chief Coroner of Ontario, 2015).

Patch-for-Patch Program

In response to concerns regarding overdoses from diverted fentanyl patches, one recommended strategy has been the implementation of fentanyl Patch-for-Patch (P4P) return programs (Ontario Public Drug Programs Division- Ministry of Health and Long-Term Care, 2016). These programs dictate that patients prescribed fentanyl must return their used patches to the pharmacy before receiving a refill of their prescription. If there is evidence that patches have been tampered with, or if the patient does not return the full amount of patches, the prescription will be altered according to the number of patches returned. Along with changing the number of patches dispensed, the pharmacist will also notify the police and the prescriber if they suspect fraudulent behavior and the police will investigate.

These P4P return programs were first popularized in Nipissing County in December 2013 as a collaboration between law enforcement, public health officials, and pharmacies (Ontario Association of Chiefs of Police – Substance Abuse Committee, 2014). The program was later expanded to multiple other counties over subsequent years. Province-wide expansion of the P4P program was introduced as a private members bill (Bill-33) which received Royal Assent in December 2015 with an official province wide launch on October 1, 2016 (Ontario Public Drug Programs Division- Ministry of Health and Long-Term Care, 2016).

Although the P4P program was designed with the expectation that avoiding the diversion of fentanyl patches would lead to reduced availability in the illicit market, and therefore improved patient outcomes, the impact in Ontario is unknown. Furthermore, there have been concerns that restrictions on fentanyl patch diversion might lead to the displacement of fentanyl, with other prescribed or non-prescribed (i.e. heroin) opioids replacing fentanyl on the illicit market (Costa, 2008). In this scenario, it is possible that a P4P program could lead to worsening patient outcomes as patient transition to other opioids of differing potency.

Project Objectives

The objective of this study was to evaluate the impact of the P4P return programs implemented across Ontario between February 2013 and April 2016 on opioid dispensing and toxicity events.

This evaluation included an analysis of the following among counties where the P4P program was introduced:

- Volume of fentanyl patches and other long-acting non-fentanyl opioids dispensed from retail pharmacies in Ontario
- Rate of opioid toxicity-related hospital visits (i.e. emergency department and hospital admissions) and deaths

- Frequency of police (OPP only) incidents involving fentanyl patches (e.g., criminal incidents, investigations, arrests)

Methods

Data Sources

The following data sources were used:

1. Ontario Drug Benefit (ODB) Claims Database (2008-2016): To explore pharmacy dispensing the ODB database was leveraged, which contains all provincially-funded prescriptions dispensed in Ontario. Provincially-funded drug coverage in Ontario is available for all residents with financial needs (due to high drug costs and/or low income) and for all residents 65 years of age and older. This data does not include prescriptions paid for by private insurance or out-of-pocket cash payments.
2. Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) (2008-2016): The CIHI-DAD database captures details on diagnoses and procedures during an inpatient hospitalization in Ontario. This database was used to identify all inpatient hospitalizations related to opioid overdoses.
3. Canadian Institute for Health Information National Ambulatory Care Reporting System (CIHI-NACRS) (2008-2015): The CIHI-NACRS database captures details on diagnoses and procedures received during all emergency department (ED) visits in Ontario. This database was used to identify all ED visits related to opioid overdoses.
4. Drug and Drug/Alcohol Related Deaths (DDARD) Database (2008-2015): The DDARD database contains details on all deaths related to opioid overdoses in Ontario. This data has been abstracted from the Office of the Chief Coroner of Ontario (OCCO) by our study team and linked to the Institute for Clinical Evaluative Sciences data holdings. The DDARD is considered to be the most valid method for identifying opioid-related deaths in Ontario and has been regularly used to publish high impact research in this area. This database includes details on opioid-related deaths, including location of residence of the deceased and post-mortem toxicology.
5. Ontario Provincial Police (OPP) Data (2008-2016): Police measured statistics provide information on fentanyl-patch related incidents from all OPP precincts. The data includes information on arrests, charges, location of the incident, and drug seizures. Precincts were mapped to overlapping counties and reported on a county level to remain consistent with other outcomes (**See Appendix D**). Incidents for this report excluded those related to illicit fentanyl powder.

Overarching Study Design

The study design is based on cross-sectional time-series analysis between April 1, 2008 and March 31, 2015. The day in which the P4P program was launched was defined as the intervention date for each county (see **Table 1** for dates). All prescription outcomes were reported as rates per 10,000 population eligible for public drug benefits. This is calculated as the number of individuals dispensed any drug in the ODB database in the year of interest. All rates of opioid-

related hospital visits overdoses and deaths were reported per 10,000 population using Statistics Canada population estimates. Prescription and adverse event outcome rates measured in a series of 30 day windows over the observation period were reported. Throughout the report, these windows are referred to as "months" for all outcomes for simplicity of reporting. The observation period following the launch of the P4P program varied by region since the launch was staggered across counties. To account for this, results were reported in two ways:

Individual county analysis (fentanyl-prescribing outcome only): Each county contributed different lengths of observation time based on their intervention date (see **Table 1**). Therefore, rates are reported for each county separately in the 60 months prior to program initiation to provide sufficient baseline data. Rates are also reported for every month following the *intervention date*. The exact duration of follow-up was subject to data availability for each outcome and therefore differs by county and outcome.

Combined county analysis: Analysis was conducted by combining counties to assess the overall impact of the policy for each outcome. Only counties with sufficiently long follow-up were included in each analysis. For example, in a 12 month analysis only those counties with 12 months or greater follow-up time were included. Due to the differing intervention dates for each county, data were zeroed on intervention date using a standardized centered method and the mean of county rates in the 60 months prior to intervention and 12 months following intervention were reported. For each outcome, either 6 and 12 month analyses, or 12 and 24 month analyses were reported depending on data availability (see **Table 1** for details for each outcome).

Table 1: Launch dates of P4P program across counties, listed chronologically

#	*County*	*Launch Date*	*Months of prescription Data*	*Months of Death Data*	*Months of Hospital Data*
25	Ottawa Division	February 2, 2013	44	35	38
44	Nipissing District	December 6, 2013	34	25	28
26	Oxford County	April 1, 2014	30	21	24
4	Elgin County	June 30, 2014	27	18	21
35	Kawartha Lakes	October 14, 2014	23	14	17
34	Stormont, Dundas and Glengarry	November 1, 2014	23	14	17
37	Wellington County	November 7, 2014	23	13	17
40	Algoma District	February 1, 2015	20	11	14
20	District Municipality of Muskoka	March 1, 2015	19	10	13
41	Cochrane District	April 2, 2015	18	9	12
19	Middlesex County	April 10, 2015	17	8	11
47	Greater Sudbury Division	June 1, 2015	16	7	10
48	Sudbury District	June 1, 2015	16	7	10
10	Regional Municipality of Halton	August 13, 2015	13	4	7
5	Essex County	October 7, 2015	11	2	5
14	Lambton County	October 14, 2015	11	2	5
24	Durham Municipality	November 5, 2015	11	1	4
43	Manitoulin District	December 8, 2015	9	0	3
16	Leeds and Grenville United Counties	February 2, 2016	8	--	--
2	Bruce and South Bruce County	April 16, 2016	5	--	--
7	Grey County	April 16, 2016	5	--	--
			Counties with 12 Months of Data: 14	Counties with 6 Months of Data: 13	Counties with 6 Months of Data: 14
			Counties with 24 Months of Data: 4	Counties with 12 Months of Data: 7	Counties with 12 Months of Data: 10

Analytical Plan

Statistical Analysis

Interventional time series autoregressive integrated moving average (ARIMA) models were used to conduct time-series analyses to determine the impact of the introduction of the P4P program on each outcome (described below). For each outcome measure, the ARIMA model was fitted to the data and a ramp intervention function used at the intervention date to assess the impact of the P4P program on the rate of each outcome event. A ramp function was used to detect a gradual change in the rates following the introduction of the policy due to the voluntary nature of these programs and slow roll-out. To ensure model fit, the residual autocorrelation correlograms for model parameter selection and appropriateness were examined, and remaining residual autocorrelation using the Ljung-Box chi-square test was assessed.

Sensitivity Analysis

Sensitivity analyses were conducted for counties in which a statistically significant reduction in fentanyl dispensing following the introduction of the P4P program was observed. This analysis was designed to explore whether there were relatively greater effects on outcomes in the regions in which the P4P had the largest influence on fentanyl dispensing patterns. Therefore, analyses were replicated for all outcomes measured in this report among this subgroup of counties identified in **Table 2** below.

Outcome Definitions

Fentanyl dispensing

The rate of fentanyl patch dispensing was computed in each county by month in the 60 months prior to the launch of the program, up to September 30, 2016. The analysis was truncated at September 30, 2016 to avoid the confounding effects of the province-wide mandated P4P program, which was introduced October 1, 2016. Prescription rates were reported per 10,000 ODB eligible population for all counties over the study period. Time-series analysis was conducted at the county-level to determine whether the P4P program impacted the rate of fentanyl dispensing in each participating county. As described above, counties in which fentanyl dispensing was significantly impacted by the program were included in the *sensitivity analysis cohort*. In the combined county analysis, data was zeroed based on the date of intervention and the mean fentanyl dispensing rate was calculated among counties with 12 and 24 months of follow-up after the intervention date. A time-series analysis assessed the effect of the P4P program on the mean rate of fentanyl dispensing.

Finally, exploratory analyses were conducted to evaluate whether similar changes in fentanyl dispensing rates were observed in counties not participating in the P4P program. The intervention date for the control counties was set to December 2013 to align with announcement of the program's launch in Nipissing County because this announcement garnered the most media attention across the province. In this analysis, the mean fentanyl dispensing rates were reported among participating and non-participating counties from January 2008 to September 2016. Data for non-participating counties were reported separately for each county, and aggregated among all counties. Non-participating counties with reductions in fentanyl dispensing were then mapped to explore possible geographic patterns across the province.

Non-fentanyl long-acting opioid dispensing

The rate of non-fentanyl long-acting opioid volume dispensed (See Appendix A for details of opioids included) were reported as the number of units (i.e. tablets) dispensed in each county per 10,000 ODB eligible population in the 60 months prior to the launch of the program, up to September 30, 2016. In the combined county analysis, data was zeroed on the date of intervention and the mean non-fentanyl long-acting opioid dispensing rate was calculated among counties with 12 and 24 months of follow-up after the intervention date. A time-series analysis assessed the effect of the P4P program on the mean rate of non-fentanyl long-acting opioid dispensing.

Hospital visits for opioid toxicity

The rate of hospital visits due to opioid toxicity was measured in each county monthly in the 60 months prior to the launch of the program, up to March 31, 2016. Rates were reported per 10,000 population. Hospital visits for overdoses were defined as any ED visit or inpatient hospitalization with International Classification of Diseases 10th Revision (ICD-10) codes T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6 recorded in any diagnosis field (details in Appendix B). Suspected diagnoses and those from planned hospital visits were excluded. In the combined county analysis, data were zeroed on the date of intervention and the mean opioid-related hospital visit rate was calculated among counties with 6 and 12 months of follow-up after the intervention date. A time-series analysis assessed the effect of the P4P program on the mean rate of opioid-related hospital visits.

Fatal opioid overdose

The monthly rates of opioid-related death were computed for each county in the 60 months prior to the launch of the program, up to December 31, 2015 and were reported per 10,000 population. Opioid-related deaths were identified as all deaths investigated by the provincial coroner where it was determined that an opioid contributed to the cause of death (with or without alcohol). Rates were reported for all opioid-related deaths, and the subgroup of deaths involving fentanyl. In the combined county analysis, data were zeroed on the date of intervention and the mean opioid-related death rate was calculated among counties with 6 and 12 months of follow-up after the intervention date. A time-series analysis assessed the effect of the P4P program on the mean rate of opioid-related deaths.

Fentanyl-patch related police incidents and arrests

The number of fentanyl-patch related police incidents documented by the OPP was reported from January 1, 2008 to December 31, 2016. Characteristics of the incidents were aggregated including number of incidents that led to an arrest, number of individuals involved, median age and sex of individuals involved, location of incident, and most serious charge related to the incidents. Characteristics were reported overall and stratified by participating and non-participating P4P counties. Chi-squared tests and the Wilcoxon Rank Sum test were used to compare proportions and medians between P4P and non-P4P counties.

Additionally, the number of police incidents was reported by quarter among participating and non-participating counties. Trend lines were fitted using quartic polynomial functions to better visualize trends. A sensitivity analysis was conducted limited to counties without a police city service (see **Appendix D**). Among participating counties, the monthly number of incidents was zeroed on the date of intervention and the number fentanyl-patch related police incidents were calculated among all counties (2 month follow-up) and among those counties with at least 6 months of follow-up after the intervention date.

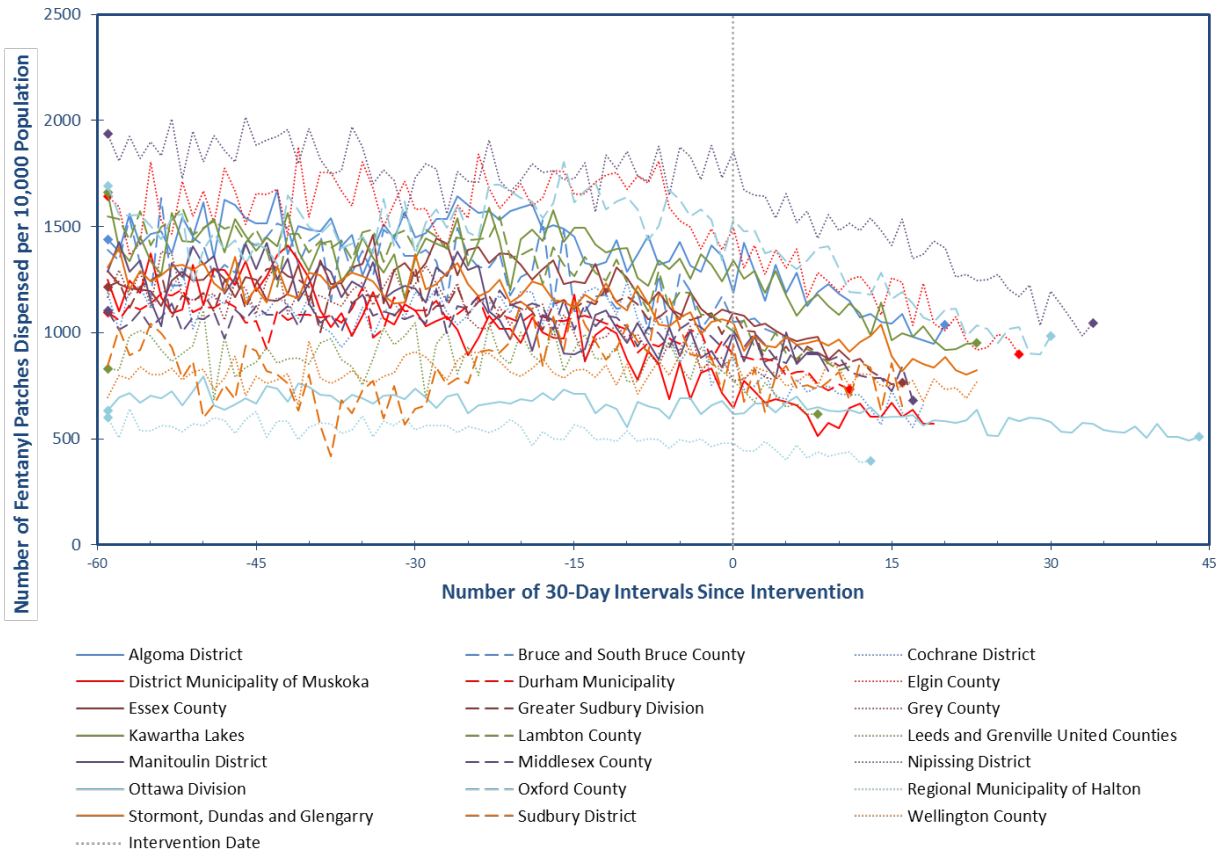
Results

Opioid Prescription Utilization

Fentanyl Dispensing

Figure 1 reports the population adjusted rates of fentanyl patches dispensed to ODB eligible individuals by county in Ontario. There is large variation in the rates across counties with Nipissing county having the highest rates of fentanyl dispensing over the study period (average monthly dispensing of 1,647 patches per 10,000 eligible) and Halton county consistently having the lowest rate of fentanyl dispensing (average monthly dispensing of 520 patches per 10,000 eligible). Geographic differences in the use of opioids are common with factors such as socioeconomic status, rurality, and access to primary care playing important roles in driving these trends.

Figure 1: Rate of prescription fentanyl units dispensed by county before and after the initiation of the P4P program



Note: Lines with terminal points (dots) highlight counties with statistically significant (<0.05) reductions in fentanyl patch dispensing, see Table 2.

Eleven (n=11) of the 21 counties analyzed had a statistically significant reduction in the rate of fentanyl patch dispensing after the introduction of the P4P program (see **Table 2)**. Counties with higher rates of fentanyl dispensing prior to program implementation and with earlier intervention dates were more likely to demonstrate a significant reduction in dispensing after the P4P program was introduced. One potential driver of these patterns could be the level of participation among pharmacies and prescribers which would impact the county's ability to comprehensively implement the program. For example, counties with low levels of pharmacy participation may demonstrate little effect of the P4P program on fentanyl prescribing because individuals looking to by-pass the program can easily go to a non-participating pharmacy in the area. In contrast, Algoma county reported that in its major urban centre of Sault Ste. Marie they were able to recruit all but one pharmacy to participate in the program and demonstrated a statistically significant reduction in fentanyl dispensing (p=0.03) (Kelly., 2015). Furthermore, counties with higher rates of pharmacy participation that demonstrated significant reductions in fentanyl dispensing may have been those with greater media attention to illegal trafficking of patches, possibly higher-rates of diversion, or higher overall rates of fentanyl use. Thus, there would be substantial motivation for prescribers, pharmacies, and law enforcement to participate in the program.

Table 2: Impact of the Patch-for-Patch program on fentanyl dispensing for each county

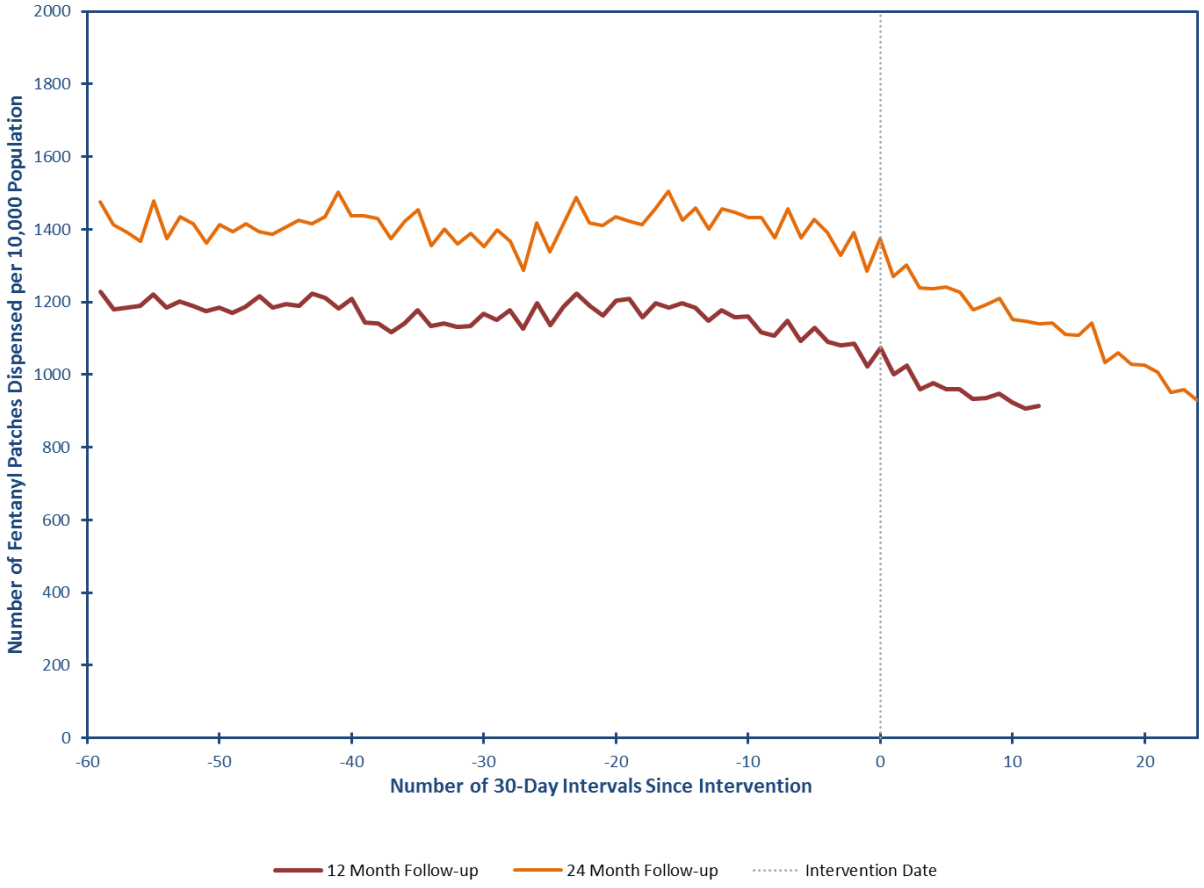
County	% Change*	Impact of P4P Implementation (p-value)
Nipissing District	-43.7%	<0.01*
Elgin County	-39.8%	0.01*
Oxford County	-35.7%	<0.01*
Middlesex County	-32.6%	<0.01*
Sudbury District	-31.0%	0.65
Kawartha Lakes	-29.0%	0.01*
Cochrane District	-25.5%	0.16
Stormont, Dundas and Glengarry	-21.2%	0.08
Leeds and Grenville United Counties	-20.4%	<0.01*
Essex County	-20.3%	0.10
Regional Municipality of Halton	-17.3%	0.01*
Ottawa Division	-17.0%	<0.01*
Lambton County	-16.8%	0.06
Durham Municipality	-15.5%	0.02*
Greater Sudbury Division	-14.6%	<0.01*
Wellington County	-13.9%	0.09
Algoma District	-12.7%	0.03*
District Municipality of Muskoka	-11.2%	0.45

Manitoulin District	-9.1%	0.60
Bruce and South Bruce County	-7.7%	0.16
Grey County	-7.5%	0.52

**A p-value < 0.05 denotes statistical significance. These counties are included in the sensitivity analysis described earlier. Percent change calculated from intervention date to last observation.*

Figure 2 reports the average rate of fentanyl dispensing among all counties that had at least 12 and 24 months of follow-up after the P4P program initiation. In the 12-month analysis, rates of fentanyl dispensing were relatively stable prior to P4P implementation, ranging between 1,023 patches dispensed per 10,000 and 1,229 patches dispensed per 10,000. Following the implementation of the P4P, a reduction in fentanyl dispensing rates was found, falling 16% from time zero to 12 months later, however this did not reach statistical significance (p=0.06). In the 24 month analysis, a statistically significant reduction in the rate of fentanyl dispensing was found following the P4P program implementation, with rates falling 32% between intervention date and the 24 month follow-up (p<0.001). Interestingly, in both analyses there appears to have been a reduction in fentanyl dispensing rates prior to the launch of the P4P program, signaling that changes in dispensing may have started in some regions prior to the launch of the program.

Figure 2: Average rate of prescription fentanyl patches dispensed by participating counties before and after the initiation of the P4P program at 12 and 24 months

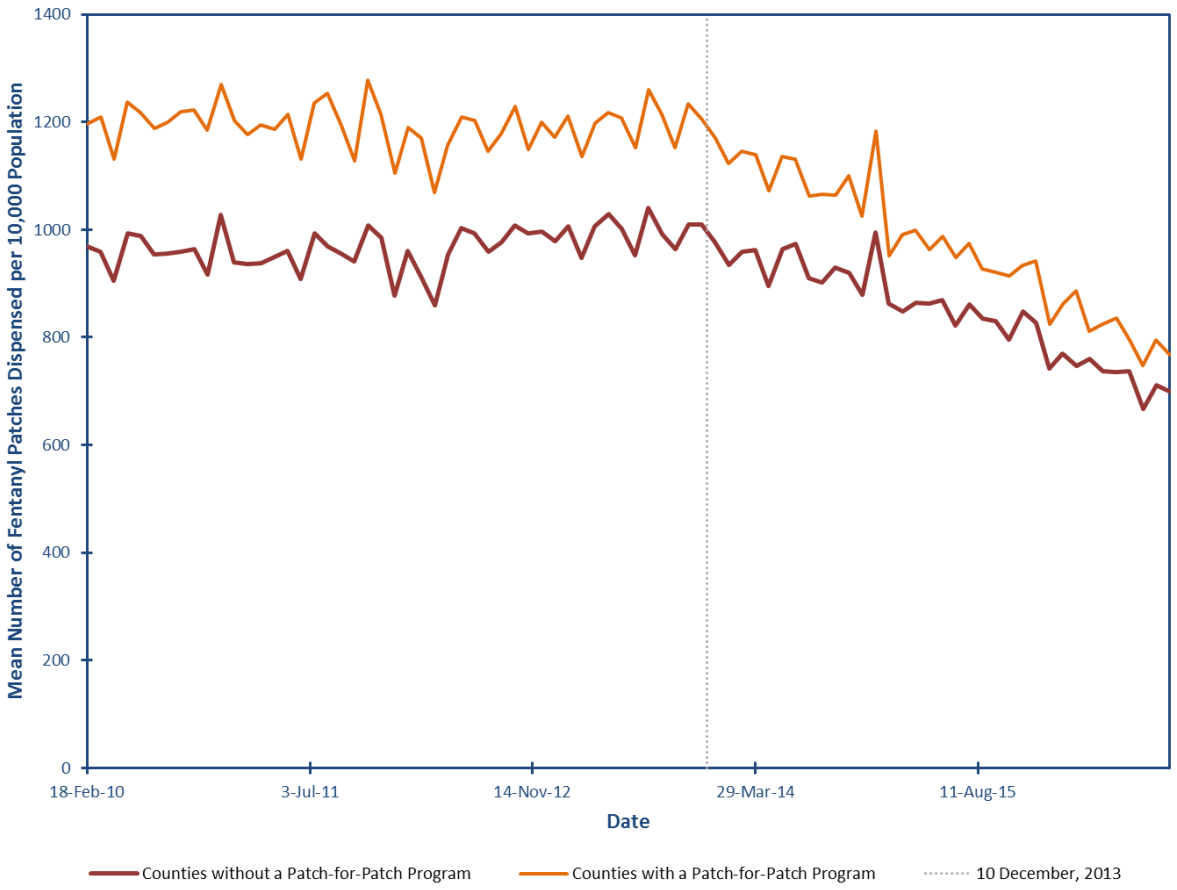


Note: 12 and 24 month follow-up above only include counties with sufficiently long follow-up.

Exploratory Analysis: Overall rates of fentanyl patches dispensed among non-participating counties

In an exploratory analysis, changes in the rate of fentanyl dispensing across Ontario stratified on the basis of participation in P4P programs were evaluated. In this analysis, in general, the fentanyl dispensing rate was higher among participating counties compared to non-participating counties (see **Figure 3**). However, there was a similar pattern towards reduced fentanyl dispensing after the first major P4P program was launched in Nipissing County on December 10, 2013 in both participating (32% reduction) and non-participating (25% reduction) counties.

Figure 3: Average rate of prescription fentanyl patches dispensed in counties that participated in the P4P program compared to counties that did not participate



In the county-level analysis of fentanyl dispensing among non-participating counties, the majority of counties were found to have stable rates of dispensing over the study period (Figure 4). However, it appears that there are a small number of non-participating counties (Chatham-Kent, Huron, Northumberland, Peterborough, and Parry Sound) where rates of fentanyl dispensing started to decline in December 2013 (see **Figure 4 and 5**). Interestingly, four of these counties are neighboured by counties that participated in the P4P program and had statistically significant reductions in fentanyl dispensing. This suggests that the P4P program's impacts may have diffused outside county borders into nearby regions (see **Figure 6**). Furthermore, the decline observed in Peterborough County is likely due to the introduction of its own P4P program in February 2014 which was run independently from the Public Health-OPP program evaluated in

this report (Peterborough County-City Health Unit, 2013). It also appears that the launch of the P4P program in Peterborough County may have impacted fentanyl dispensing rates in neighboring Northumberland County. Overall, these findings suggest that the introduction of P4P programs led to a decline in dispensing patterns among bordering counties which impacted the overall fentanyl utilization in Ontario beginning in December 2013.

Figure 4: Rate of prescription fentanyl patches dispensed by counties that did not participate in the P4P program before and after first major launch in December 2013

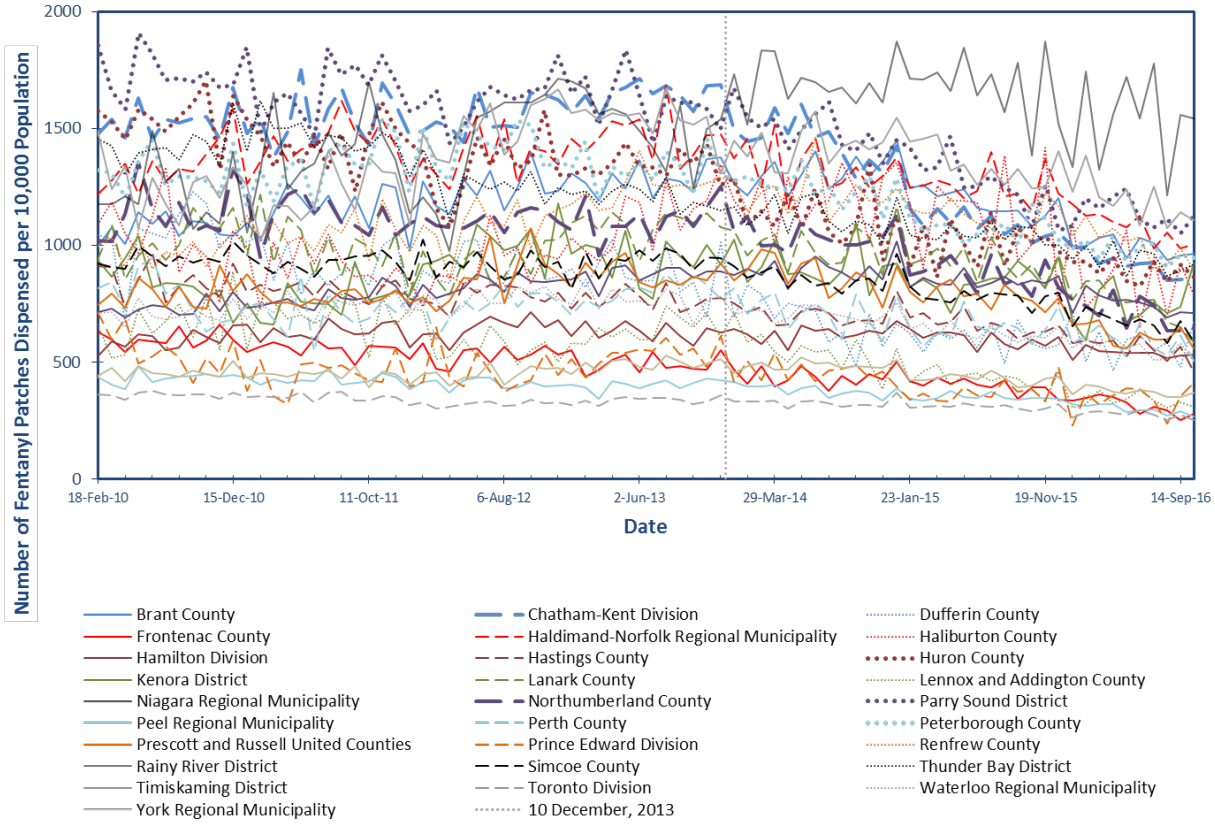


Figure 5: Rate of prescription fentanyl patches dispensed by counties that did not participate in the P4P program before and after the first major launch in December 2013, limited to counties with reductions in fentanyl dispensing

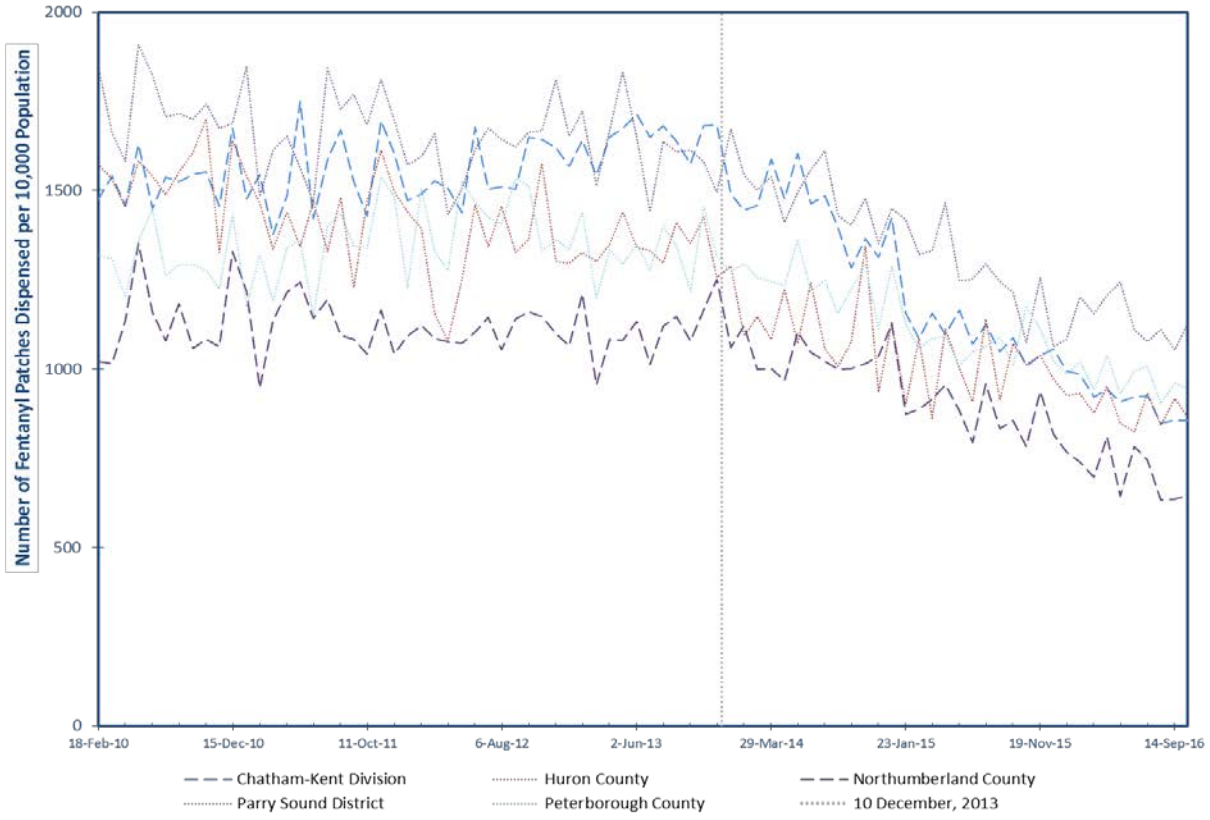
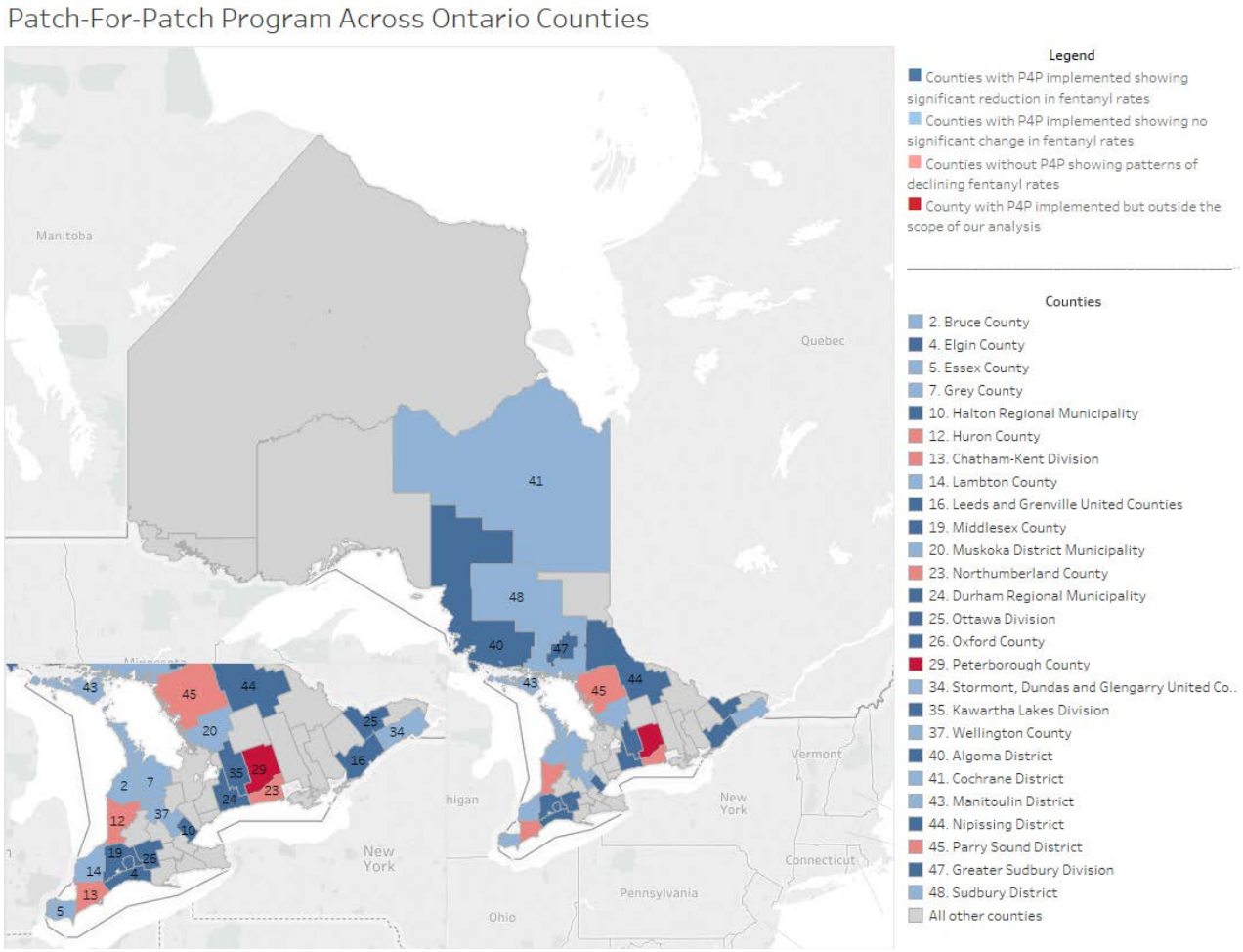


Figure 6: Ontario county map presenting change in fentanyl patch dispensing by P4P program participation

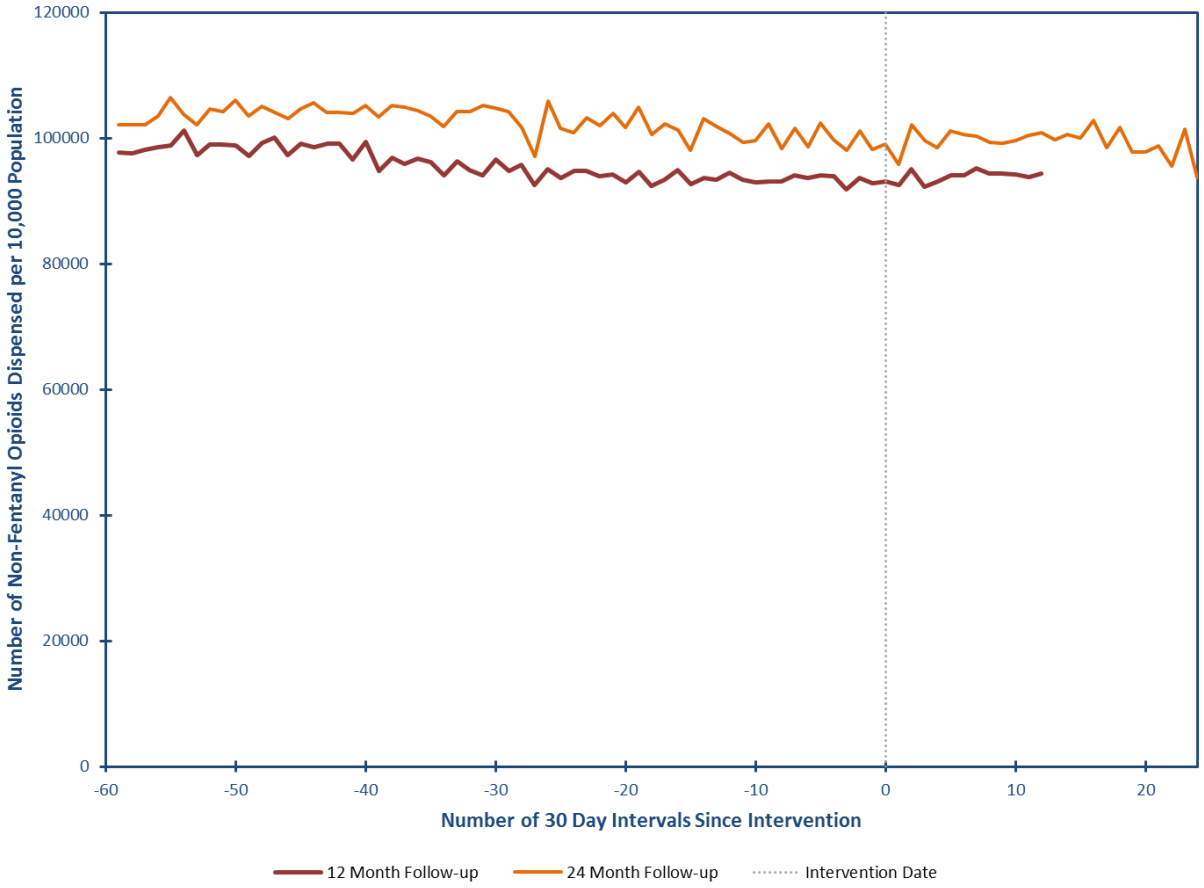


*Note: See **Appendix C** for full county map of Ontario.*

Non-Fentanyl Opioid Utilization

Figure 7 reports the population adjusted mean rates of non-fentanyl opioid dispensing to ODB eligible individuals in the 12 and 24 months following program implementation. Overall, non-fentanyl opioid dispensing was relatively stable over the entire study period, and was not impacted by the introduction of the P4P program (p= 0.27 and p=0.49, for 12 and 24 month follow-up, respectively). These results remained consistent in the sensitivity analysis limited to counties with a significant reduction in fentanyl dispensing (p=0.29 for 12 month follow-up). These findings are important as there was concern that the P4P program may lead to changes in the dispensing patterns of non-fentanyl opioids that do not have similar restrictions. Patients using fentanyl patches appropriately for clinical purposes would have minimal difficulty complying with this program and would not require a change in therapy. Therefore, the observed drop in dispensing rate of fentanyl patches, with no correlated increase in dispensing of non-fentanyl opioids, suggests that the P4P program was successful in reducing excess dispensing of fentanyl patches used for diversion, without driving any measurable rise in dispensing of alternative opioids that may also be diverted for illicit use.

Figure 7: Average rate of prescription non-fentanyl opioid units dispensed by participating county before and after the initiation of the P4P program at 12 and 24 months



Note: 12 and 24 month follow-up above only include counties with sufficiently long follow-up.

Opioid-Related Hospital Visits and Death

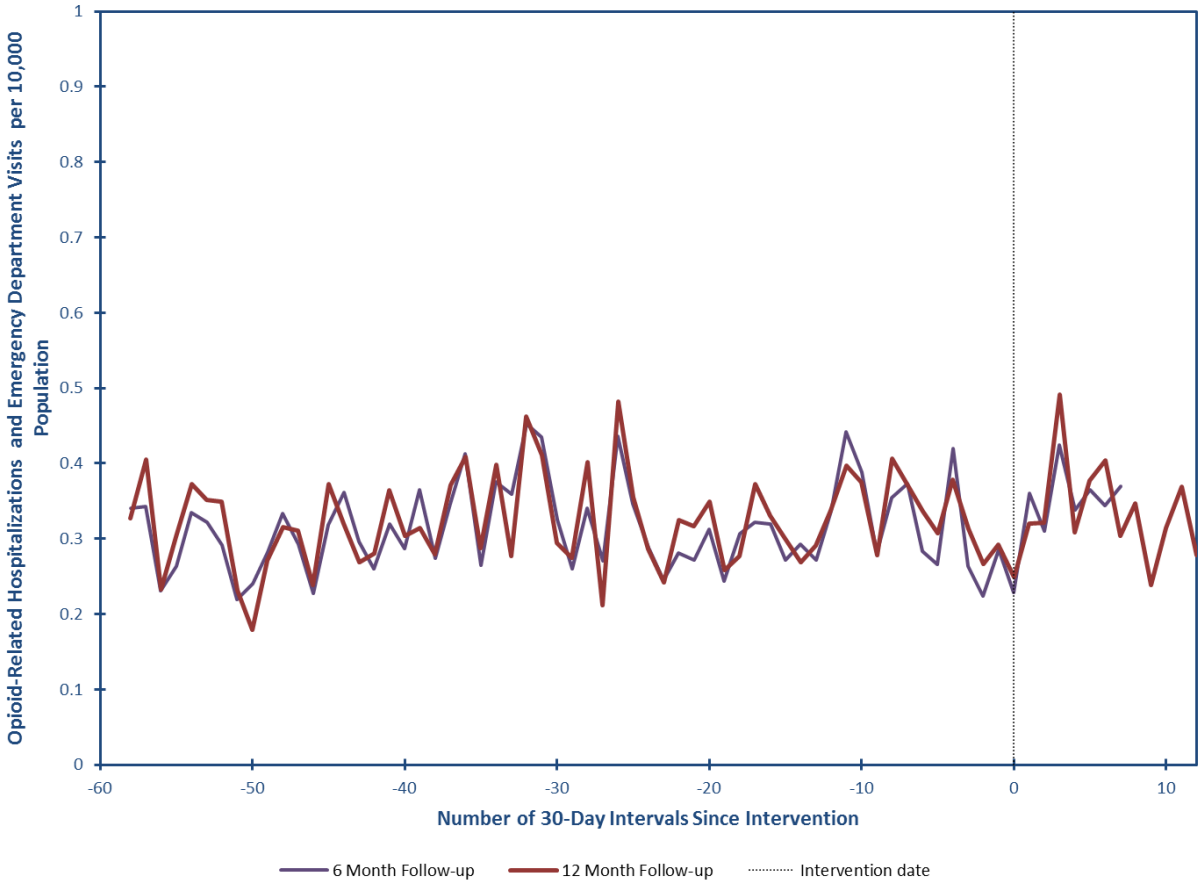
Figure 8 reports the population adjusted mean rates of hospital visits per month among counties participating in the P4P program and with at least 6 or 12 months of follow-up. Given the small number of events, there was considerable variation in rates reported over the study period, ranging between 0.23 and 0.47 hospitalizations per 10,000 population among counties with 6 months of follow-up. The 12 month range is more volatile since it only contains data from 10 counties with sufficient follow-up. No statistically significant impact of the P4P program on rates of opioid-related hospital visits after both 6 (p=0.30) and 12 months (p=0.59) of follow-up was found. These results were consistent in the sensitivity analysis among counties with a significant reduction in fentanyl dispensing (p=0.15 for 12 month follow-up). This suggests that, although the volume of fentanyl dispensing decreased after the P4P program was introduced, this had no measurable impact on overall rates of hospital visits for opioid-toxicity. Therefore, given that there was no observed significant reduction in fentanyl dispensing in the 12 month analysis, it is possible that changes to patient outcomes may be observed over a longer follow-up time.

Figure 9 reports the population adjusted mean rates of opioid-related deaths per month among counties participating in the P4P program and with at least 6 or 12 months of follow-up. Similar to hospital visits, there were a small number of events which caused considerable variation in

reported rates. The rates of death ranged between 0.02 and 0.08 deaths per 10,000 population among counties with 6 months of follow-up. The 12 month range is more volatile as it contains data from only 7 counties that had sufficient follow-up. No statistically significant impact of the P4P program on rates of opioid-related deaths were found after both 6 months (p=0.50) and 12 months (p=0.96) of follow-up. In our subgroup analysis of fentanyl-involved deaths, the rates ranged between 0.003 and 0.036 deaths per 10,000 population among counties with 6 months of follow-up. No statistically significant impact of the P4P program on rates of fentanyl-involved deaths were observed after 6 months of follow-up (p=0.13). We were unable to complete an analysis of fentanyl-involved deaths using a 12 month follow-up due to a large number of counties with no deaths observed. These results suggests that, although the volume of fentanyl dispensing decreased after the P4P program was introduced, this had no measurable impact on overall rates of opioid-related deaths overall including those with fentanyl involvement.

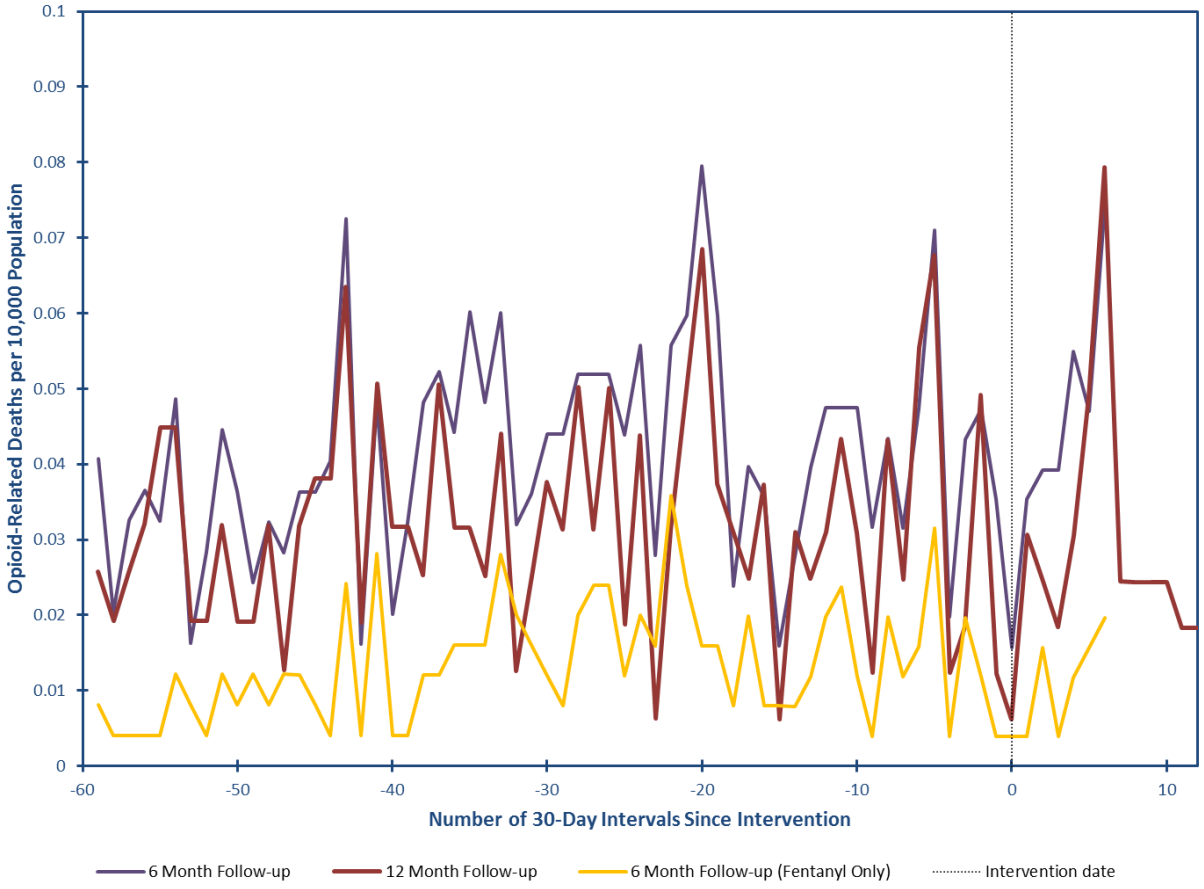
The results of the hospital and death analyses are important since a major concern of the P4P program is that limiting access to fentanyl may have negative consequences for those addicted to opioids. Opponents of the program state that there is a concern that as access is limited to fentanyl, those dependent on prescription opioids may turn to illicit opioid options. The lack of a significant increase in harm among the outcomes measured in this report should raise confidence in the safety of the P4P program. However, it is possible that the clinical impact would only be seen over longer follow-up as the volume of diverted fentanyl patches is reduced and patients are forced to seek out alternatives. Furthermore, these data are unable to specifically explore fentanyl-patch related hospital visits which would be a more sensitive measure. Future work should study whether there are any long-term impacts on patient outcomes broadly and fentanyl-patch related patient outcomes specifically. Note that these results are not available for the 24 month follow-up due to insufficient follow-up data to conduct this analysis.

Figure 8: Average rate of hospital visits before and after the initiation of the P4P program at 6 and 12 months



Note: 6 and 12 month follow-up above only include counties with sufficiently long follow-up.

Figure 9: Average rate of opioid-related deaths before and after the initiation of the P4P program at 6 and 12 months



Note: 6 and 12 month follow-up above only include counties with sufficiently long follow-up.

Fentanyl-Patch related Police Incidents and Arrests

Table 3 reports the number and characteristics of fentanyl-patch related police incidents from 2008 to 2016. During the observation period there were 488 fentanyl-patch related OPP incidents with 494 individuals involved. Over half (57.6%) of the incidents resulted in an arrest. Individuals involved had a median age of 32 and close to three-quarters (71.5%) were male. The majority of incidents occurred at residences (43.6%), and the most serious violation was most often related to a possession–related charge (65.5%). There was little difference in the characteristics of incidents that occurred in counties with and without P4P programs. The only significant difference found was that individuals involved in incidents in P4P counties were more likely to be male (76.8% vs 66.9%, p=0.02) and slightly younger (31 vs 33, p=0.04).

Figure 10 reports the number of fentanyl-patch related police incidents by year and quarter over the entire observation period (2008 to 2016). There was a steady increase in the number of fentanyl-patch related police incidents in both counties with (1 in Q1-2008 to 13 in Q4-2016) and without (2 in Q1-2008 to 19 in Q4-2016) P4P programs. In all counties, the number of fentanyl-patch related police incidents appeared to accelerate in 2014. **Figure 11** reports the number of incidents before and after the intervention date among participating P4P counties zeroed on their intervention date. Overall, these results were highly variable with no clear indication of an immediate change in police incidents related to fentanyl-patches after the P4P program implementation. The results among a subset of counties with 6 months of follow-up show a potential spike in the 3rd month after the implementation of the P4P program, however this increase is largely driven by Sudbury County which had 10 fentanyl-patch related police incidents in that month.

Overall, the results from the analysis of police incidents are not definitive and require further follow-up. The findings may reflect a generally higher awareness of fentanyl by police officers and greater availability of diverted fentanyl patches in the community. Although the initial launch of the P4P program is more likely to lead to increased police incidents, because of the procedure for pharmacists to contact police as part of the P4P program, this was not clear from the results since increases in incidents were observed across the entire province regardless of participation in a P4P program.

Table 3: Number and characteristics of fentanyl-patch related police incidents from 2008 to 2016

	Total	Non-P4P Counties	Only P4P Counties	p-value
	N	N	N	
Total number of incidents	488	240	248	
Number of individuals involved	494	266	228	
Male individual involved (n, %)	353 (71.5%)	178 (66.9%)	175 (76.8%)	0.02*
Age of individuals involved (median, IQR)	32 (25, 42)	33 (27, 42)	31 (25, 41)	0.04*
Proportion of incidents with arrest (n, %)	281 (57.6%)	145 (60.4%)	136 (54.8%)	0.21
Incident Setting (n,%)				
Parking Lots	24 (4.9%)	12 (5.0%)	12 (4.8%)	0.92
Pharmacy	22 (4.5%)	7 (2.9%)	15 (6.0%)	0.10
Residence	213 (43.6%)	97 (40.4%)	116 (46.8%)	0.15
Streets/Roads/Highways/Transit	112 (23.0%)	62 (25.8%)	50 (20.2%)	0.14
Other	117 (24.0%)	62 (25.8%)	55 (22.2%)	0.35
Most Serious Violation				
Assault	5 (1.0%)	2 (0.8%)	3 (1.2%)	0.66
Break and Enter	61 (12.5%)	30 (12.5%)	31 (12.5%)	1.0
Fraud	8 (1.6%)	5 (2.1%)	3 (1.2%)	0.43
Importation	1 (0.2%)	0 (0%)	1 (0.4%)	0.33
Possession	79 (16.2%)	38 (15.8%)	41 (16.5%)	0.83
Possession Controlled Substance	109 (22.3%)	53 (22.1%)	56 (22.6%)	0.89
Robbery/Threat	19 (3.9%)	9 (3.8%)	10 (4.0%)	0.91
Trafficking Controlled Substance	132 (27.0%)	64 (26.7%)	68 (27.4%)	0.86
Other	74 (15.2%)	39 (16.3%)	35 (14.1%)	0.50

*denote any statistically significant finding (p-value <0.05). P-values compare P4P participating counties to non-P4P participating counties.

Figure 10: Number of fentanyl-patch related police incidents among counties with and without fentanyl P4P programs

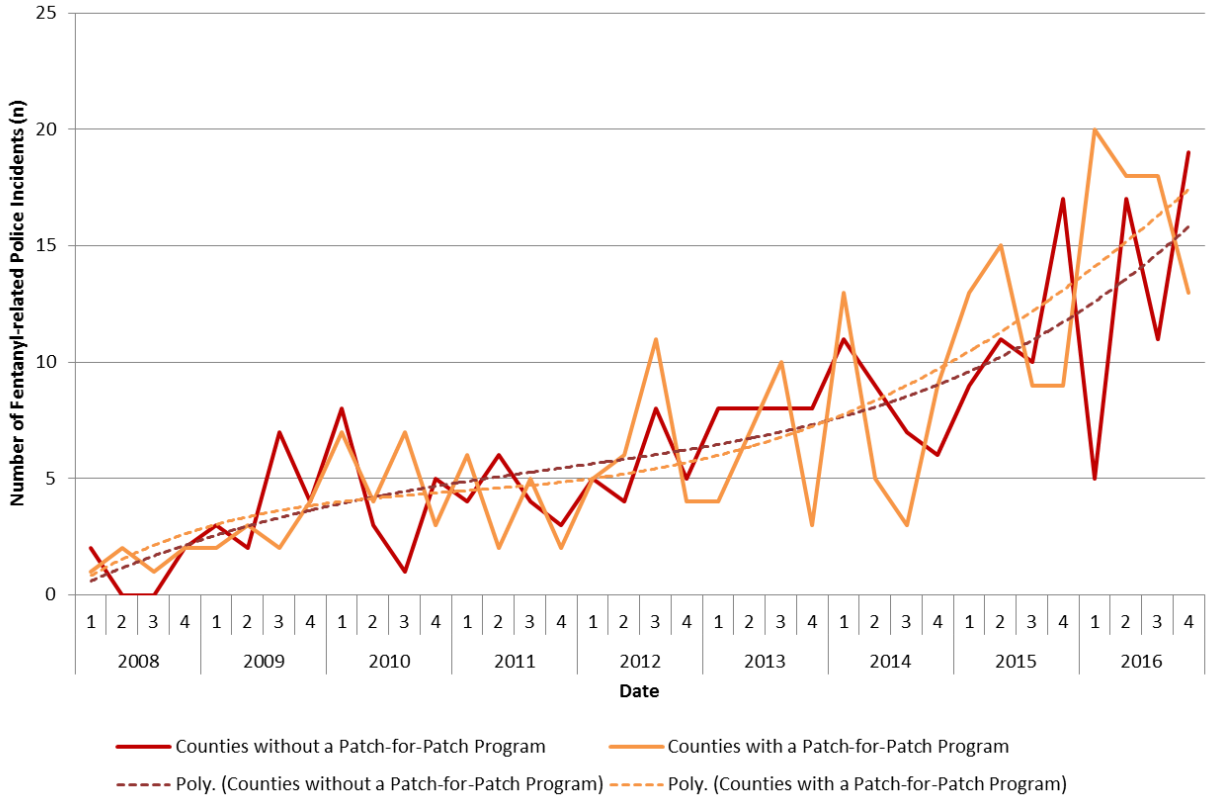
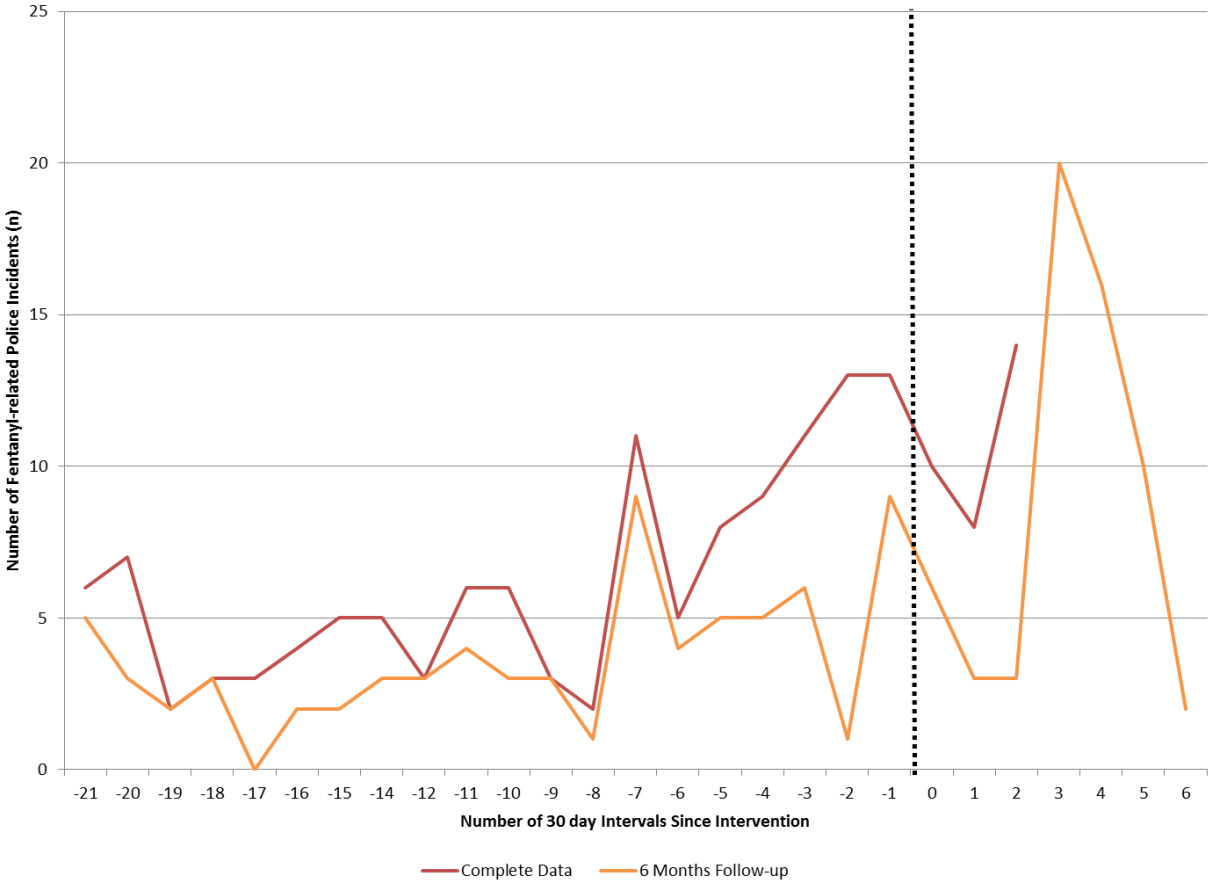


Figure 11: Number of fentanyl-patch related police incidents before and after the initiation of the fentanyl P4P program



Discussion

This report analyzed the impact of early P4P programs introduced across various counties in Ontario and found that the implementation of these programs reduced the number of fentanyl patches dispensed from pharmacies with no discernible impact on rates of other opioids dispensed, or on opioid-related hospital visits and deaths.

These results are similar to those described in other evaluations of policies and programs that have been designed to reduce misuse and abuse of prescription opioids. In particular, this work has suggested that these policies and programs can significantly impact patterns of prescribing and have limited impact on opioid-related harms (Gilson, Fishman, Wilsey, Casamalhuapa, & Baxi, 2012; T. Gomes, D. Juurlink, et al., 2014; Pradel et al., 2009; Reifler et al., 2012). This is likely influenced by the broad availability of both prescription and illicit opioids that allow people to readily seek alternatives after the introduction of new deterrent policies. Therefore, the demand for prescription opioids does not necessarily decline as the supply of diverted prescription opioids decreases. Rather, this reduction in supply increases the value of these products, without changing demand. Therefore, it is imperative that programs such as the P4P program be accompanied with increased access to addiction therapy, such as opioid maintenance therapy and other harm-reduction programs, as it is the combination of these interventions that is likely to have the largest impact on reducing opioid-related harms. Furthermore, front-line healthcare workers, including pharmacists, need to be better trained to both enforce policies and to provide information and support to patients wishing to access harm-reduction programs and addiction therapy.

A general upward trend in the number of fentanyl-patch related police incidents in both participating and non-participating counties suggests that the P4P program did not directly influence this outcome. Instead, these trends are likely driven by a growing awareness and concern by police enforcement across Ontario of the misuse and abuse of fentanyl patches. In particular, we see the most growth in the number of incidents from 2014 to 2016, aligning with the launch of the first P4P programs which were associated with large political and media attention. Further, the growing number of incidents in recent years may also be reflective of a general increase in the abuse of fentanyl patches more broadly across Canada over this period (Canadian Centre on Substance Abuse, 2015).

The finding of no change in measured outcomes is reassuring and supports the notion that such programs are generally safe. This is particularly important, since there has been concern that as access is limited to fentanyl, those dependent on opioids may turn to heroin or illicitly manufactured fentanyl products that may have higher risks of overdose since they do not meet any standards of dosing, potency or manufacturing. Therefore, the lack of a significant increase in harm among the outcomes measured in this report should raise confidence in the use of the P4P program in other jurisdictions across Canada, as a means to reduce unintended diversion of patches funded by drug payers without increasing harm. However, given the relatively short duration of follow-up (6 to 12 months) captured in this analysis, future studies confirming this finding using more data when available are needed.

The contrast in the findings related to rates of fentanyl and non-fentanyl opioid dispensing is interesting. Specifically, although there was a significant reduction in the dispensing of fentanyl patches associated with the launch of P4P programs, this did not significantly influence prescribing of non-fentanyl opioids in these regions. This suggests that the P4P program may have been successful in reducing the volume of prescription opioids that were dispensed and diverted for sale illicitly. While it is possible that some of this declining fentanyl dispensing could

have impacted patients legitimately using fentanyl for pain, it is unlikely that the P4P program would affect this group of individuals since there would be no barriers to continued access to fentanyl if all patches were being used appropriately. Furthermore, it is possible that the reduction in fentanyl dispensing was not mirrored by rising use of non-fentanyl opioids because of the emergence of illicit fentanyl powder near the end of the study period in 2016. In this case, restricted fentanyl patches may have been replaced with illicit fentanyl powder instead of alternative prescription opioids.

Limitations

Given the nature of data available for this evaluation, there are several limitations to these analyses that warrant discussion. First, during the study period, the P4P program was not mandated by law. Therefore, pharmacies were participating in the program voluntarily and not all pharmacies in a county were required to participate. Therefore, it is possible that significant impacts of the P4P program were not observed in some regions due to low pharmacy participation rates. The sensitivity analyses, limited to counties that had a statistically significant reduction in fentanyl dispensing, serves to explore outcomes among counties with high levels of participation. These analyses yielded consistent results, with no evidence of significant impacts of the P4P program on the outcomes measured. Second, since not all counties initiated their P4P programs at the same time, and because it was not a mandatory program, some people may have gone to pharmacies in neighboring counties where no program was present to access fentanyl for the purposes of misuse and diversion. However, the analysis among non-participating counties suggests that there was no important rise in fentanyl dispensing in non-participating counties, and, in fact, there may have been a diffusion of the P4P program into non-participating counties as evidenced by reductions in fentanyl dispensing in some of these regions. Future research is needed to explore the impact of the P4P program after province-wide implementation in October 2016. Third, the analysis was limited to only publically-funded prescription drugs and does not account for shifts in use of opioids paid for by other means (cash and private insurance) or use of illicit forms of opioids. Future research is required that leverages broader drug data such as the Narcotic Monitoring System when available to update these models. Fourth, this analysis only evaluated opioid prescribing outcomes, opioid-related hospital visits and deaths and may not account for other risks and benefits such as other healthcare utilization (i.e. doctor visits), use of other pharmacologic agents, and uptake of opioid-maintenance therapy. Additionally, the use of administrative claims data has limited ability to assess other important factors such as quality of life and mental health status. Importantly, it is possible that these programs have a longer-term clinical impact, as the volume of diverted fentanyl patches is reduced in these regions and patients are forced to seek alternatives. This study evaluated the initial impact of the program at 6 and 12 months. Future work is needed to follow dispensing patterns for a longer duration to evaluate longer-term impacts on patient outcomes. The police data used was limited to only OPP data and do not include specific city police services. Therefore, these data do not account for all fentanyl-patch related police incidents in Ontario as some counties have both city police services and OPP, and thus are an underestimate of the true number of police incidents involving fentanyl-patches across the province. In a sensitivity analysis (see **Appendix E)** limited to only counties without specific city policy services, the trends remained generally consistent in both participating and non-participating counties. Finally, the police data was limited to only those incidents where police flagged fentanyl patch involvement. It is likely that earlier in the observation period, police were less aware of the potential for fentanyl patch misuse and were therefore not flagging it in their reports. As a result, our findings may be more reflective of shifts in police awareness than actual increases in fentanyl abuse and misuse.

Conclusions

The joint OPP-public health P4P program appears to have helped reduce the dispensing of fentanyl patches that may have been diverted. There were no measurable adverse consequences for patients in terms of opioid-related hospital visits and deaths. This study also found that the number of fentanyl-patch related police incidents has been increasing across the province, with no tangible differences between participating or non-participating P4P counties. Our findings may be reflective of a shift in police awareness.

Overall, the findings of this report supports the use of P4P programs as part of a larger opioid-abuse reduction strategy rather than a stand-alone solution. Given the concern that limiting access may turn patients to heroin or illicitly manufactured fentanyl products, the lack of a significant increase in harm raises confidence in the use of the P4P program. Importantly, programs such as the P4P program should be accompanied with increased access to addiction therapy and other harm-reduction programs.

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Appendices

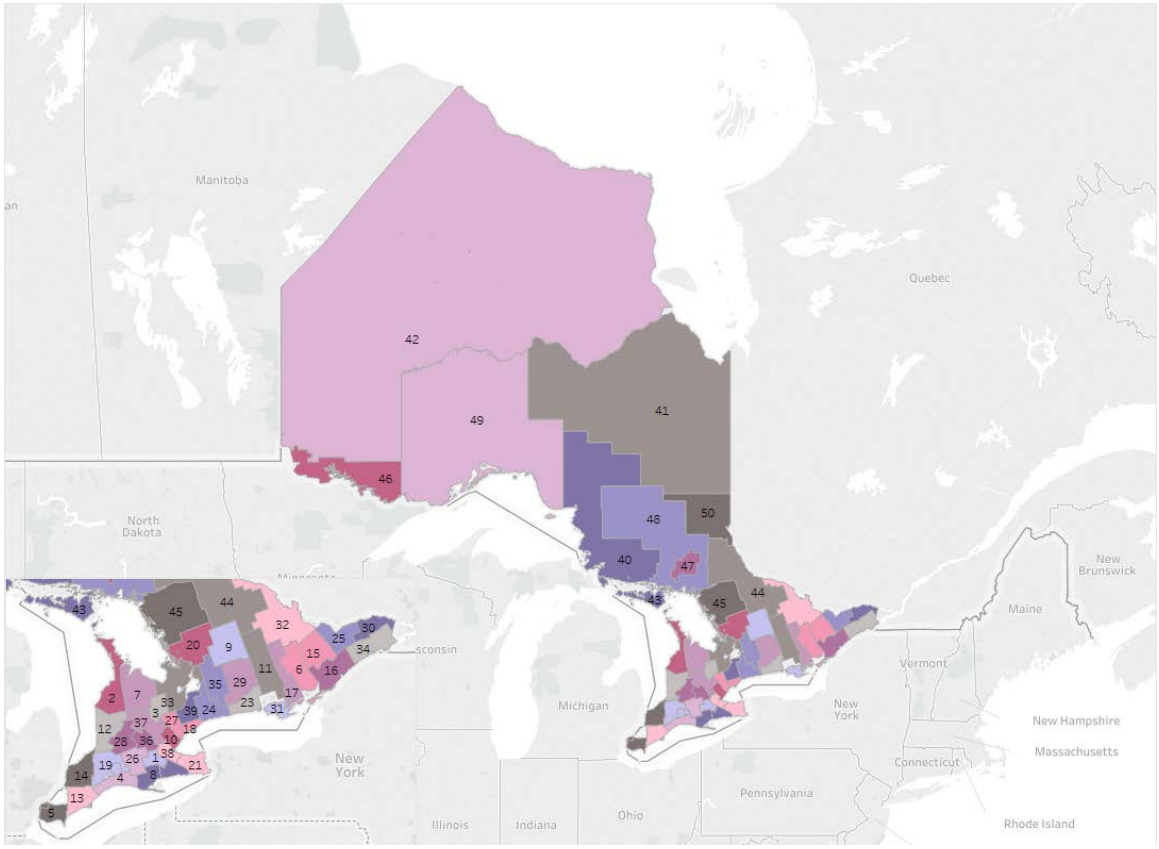
Appendix A: Opioid drugs used to define opioid recipients and prescriptions in the ODB database, by type of opioid

Opioid Drug Groups	*Products Included (Brand and Generic Names)*
Fentanyl Patches	APO-FENTANYL MATRIX
	CO FENTANYL
	DURAGESIC
	DURAGESIC MAT
	MYLAN-FENTANYL MATRIX
	PMS-FENTANYL MTX
	RAN-FENTANYL
	RAN-FENTANYL MATRIX
	SANDOZ-FENTANYL MTX
	TEVA-FENTANYL
Other Long-Acting Opioids	
Long-Acting Codeine	CODEINE CONTIN
Long-Acting Hydromorphone	HYDROMORPH CONTIN
	PALLADONE XL
Long-Acting Morphine	KADIAN
	M.O.S.-SR
	M-ESLON
	MS CONTIN
	ORAMORPH SR
	PMS-MORPHINE SULFATE SR
	SANDOZ-MORPHINE SR
	TEVA-MORPHINE SR
Long-Acting Oxycodone	OXYCONTIN
	OXYNEO

Appendix B: ICD-10 CA codes used to identify opioid poisonings

Code	Description
T40.0	Opium
T40.1	Heroin
T40.2	Codeine/Morphine
T40.3	Methadone
T40.4	Synthetic
T40.6	Other/Unspecified

Appendix C: Map of all Ontario counties by county number



- 1. Brant County
- 2. Bruce County
- 3. Dufferin County
- 4. Elgin County
- 5. Essex County
- 6. Frontenac County
- 7. Grey County
- 8. Haldimand-Norfolk Regional Municipality
- 9. Haliburton County
- 10. Halton Regional Municipality
- 11. Hastings County
- 12. Huron County
- 13. Chatham-Kent Division
- 14. Lambton County
- 15. Lanark County
- 16. Leeds and Grenville United Counties
- 17. Lennox and Addington County
- 18. Toronto Division
- 19. Middlesex County
- 20. Muskoka District Municipality
- 21. Niagara Regional Municipality
- 23. Northumberland County
- 24. Durham Regional Municipality
- 25. Ottawa Division
- 26. Oxford County
- 27. Peel Regional Municipality
- 28. Perth County
- 29. Peterborough County
- 30. Prescott and Russell United Counties
- 31. Prince Edward Division
- 32. Renfrew County
- 33. Simcoe County
- 34. Stormont, Dundas and Glengarry United Co..
- 35. Kawartha Lakes Division
- 36. Waterloo Regional Municipality
- 37. Wellington County
- 38. Hamilton Division
- 39. York Regional Municipality
- 40. Algoma District
- 41. Cochrane District
- 42. Kenora District
- 43. Manitoulin District
- 44. Nipissing District
- 45. Parry Sound District
- 46. Rainy River District
- 47. Greater Sudbury Division
- 48. Sudbury District
- 49. Thunder Bay District
- 50. Timiskaming District

Appendix D: List of Counties and overlapping Ontario Provincial Police Precincts

#	*County*	*Overlapping OPP Precincts (Code)**
1	Brant County#	Brant County (6B)
2	Bruce County	South Bruce (6I), Bruce Peninsula (6R)
3	Dufferin County	Dufferin (1N)
4	Elgin County#	Elgin County (6P)
5	Essex County#	Essex County (6E)
6	Frontenac County#	Frontenac (3R)
7	Grey County#	Collingwood (1O), Mount Forest (6K), Grey County (6L)
8	Haldimand-Norfolk Regional Municipality	Haldimand County (6C), Norfolk County (6O)
9	Haliburton County	Haliburton Highlands (1E)
10	Halton Regional Municipality#	HSD-Burlington (5C), HSD-HWY 407 (5L)
11	Hastings County#	Bancroft (3C), Napanee (3J), Central Hastings (3Q), Quinte West (3U)
12	Huron County	Huron (6G)
13	Kent County#	Chatam-Kent (6D)
14	Lambton County#	Lambton (6M)
15	Lanark County#	Lanark County (3N)
16	Leeds and Grenville United Counties#	Leeds County (3D), Grenville County (3P)
17	Lennox and Addington County	--
18	Toronto Metropolitan Municipality#	HSD-Toronto (5F)
19	Middlesex County#	London (6J), Middlesex (6Q)
20	Muskoka District Municipality#	Bracebridge (1C), Huntsville (1G), Southern Georgian Bay (1K)
21	Niagara Regional Municipality	HSD-Niagara (5G)
23	Northumberland County#	Northhumberland (1F)
24	Durham Regional Municipality#	HSD-Whitby (5K)
25	Ottawa-Carleton Regional Municipality#	Ottawa (3K)
26	Oxford County#	Oxford (6S)
27	Peel Regional Municipality	Caledon (1S), Caledon (5D), HSD-Port Credit (5I)
28	Perth County#	Perth County (6N)
29	Peterborough County#	Peterborough County (1I)
30	Prescott and Russell United Counties	Russell County (3E), Hawkesbury (3S)
31	Prince Edward County	Prince Edward (3O)
32	Renfrew County#	Arnprior (3B), Upper Ottawa Valley (3M), Renfrew (3T)

33	Simcoe County#	Barrie (1B), Huronia West (1H), Nottawasaga (1L), Orillia (1M), Chippewas of Rama (1P)
34	Stormont, Dundas and Glengarry United Counties#	Stormont, Dundas and Glengarry (3I)
35	Kawartha Lakes#	City of Kawartha Lakes (1J)
36	Waterloo Regional Municipality#	HSD-Cambridge (5E)
37	Wellington County#	Wellington County (6T)
38	Hamilton-Wentworth Regional Municipality	--
39	York Regional Municipality#	HSD-Aurora (5B)
40	Algoma District	East Algoma (4B), Sault Ste. Marie (4K), Superior East (4O)
41	Cochrane District	Cochrane (4D), Kapuskasing (4F), James Bay (4P)
42	Kenora District	Dryden (2C), Kenora (2F), Pickle Lake (2J), Red Lake (2K), Sioux Lookout (2L)
43	Manitoulin District	Manitoulin (4H)
44	Nipissing District#	Killaloe (3F), Temiskaming (4E), North Bay (4I), Noelville (4M)
45	Parry Sound District	Almaguin Highlands (4C), West Parry Sound (4J)
46	Rainy River District	Rainy River District (2D)
47	Sudbury Regional Municipality#	Sudbury (4N)
48	Sudbury District#	South Porcupine (4L)
49	Thunder Bay District#	Armstrong (2B), Greenstone (2E), Marathon (2G), Nipigon (2H), Thunder Bay (2M)
50	Timiskaming District	Kirkland Lake (4G)

*Notes: Precincts that overlapped with multiple counties were placed in counties that had the earlier launch of the P4P program. If none of the counties were P4P counties they were placed in the county that makes up the majority of the counties area. HSD= Highway Safety Division. # denotes counties with city police services within their limits.

Appendix E: Sensitivity analysis of the number of fentanyl-patch related police incidents limited to counties without city police services from 2008 to 2016