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Assessing the impact of a temporary class drug order on ethylphenidate-related infections among people who inject drugs in Lothian, Scotland: an interrupted time-series analysis

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ABSTRACT

Background and Aims: In April 2015, the UK government enacted a temporary class drug order (TCDO) on ethylphenidate in response to reported harms associated with its use, in particular an outbreak of infections among people who inject drugs (PWID) in Lothian, Scotland. This study assesses the effect that the TCDO had on reducing the most common infections identified during the outbreak; *Streptococcus pyogenes* (*S. pyogenes*) and *Staphylococcus aureus* (*S. aureus*).

Methods: The outbreak was split into a pre-intervention period (35 weeks) and a post-intervention period (26 weeks) based around the date of the TCDO. Segmented negative binomial regression models were used to compare trends in weekly counts of infections between the pre and post intervention periods.

Results: There were 251 *S. pyogenes* and/or *S. aureus* infections recorded among 211 PWID between February 2014 to December 2015 — 171 infections in the pre intervention period and 51 in the post-intervention period. Significant trend changes in weekly *S. pyogenes* and/or *S. aureus* infections following the TCDO were found (RR 0.88, 95% CI 0.82–0.94). PWID who self-reported using novel psychoactive substances (NPS) were at higher risk of acquiring these infections (RR 1.81, 95% CI 1.12–2.93), particularly when comparing the risk of infection with NPS use for a specific strain, *S. pyogenes emm*76.0, against the risk of infection with NPS use for *S. pyogenes* (*emm* types other than *emm*76.0) (RR 3.49, 95% CI 1.32–9.21).

Conclusions: The ethylphenidate temporary class drug order was effective in reducing infections among people who inject drugs during an outbreak situation in Lothian, Scotland. Legislative interventions aimed at decreasing accessibility and availability of particular substances can play an important role in the public health response to disease outbreaks linked to use of NPS.

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INTRODUCTION

The rapid rise in availability and diversity of Novel Psychoactive Substances (NPS) in recent years poses particular challenges for public health and policymakers. By 2014, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) were reportedly monitoring over 450 different NPS, including 101 new substances reported for the first time that year [1].

Historically, administration of NPS has been mainly via non-injecting routes [2], however evidence in recent years indicates a culture of NPS use among people who inject drugs (PWID) in addition to, or as a substitute for, traditional psychoactive substances such as heroin [1,3]. It has also been suggested that some NPS users have switched from snorting to injecting synthetic cathinones (e.g. mephedrone) [2].

NPS use by PWID is associated with high frequencies of injecting events and equipment sharing [2], and related morbidity and mortality [1,4,5]. Notably, increased frequency of injecting is associated with skin and soft tissue infections (SSTIs) at injecting sites [6]. A number of 'outbreaks' of NPS-related harm have occurred amongst PWID in recent years. In Dublin (Ireland), an outbreak of recent HIV infection among PWID was associated with a synthetic cathinone ('Snowblow'), with daily injectors being at highest risk [7]. Increases in HIV incidence among PWID in Hungary and Romania have also recently been reported, again related to emergence of NPS that require frequent injection [8,9].

In 2014, an outbreak of severe SSTIs, bacteraemias and infective endocarditis among PWID was identified in the Lothian region of Scotland. Specifically, the outbreak was identified following a rapid rise in individuals presenting with *Streptococcus pyogenes* (*S. pyogenes*) infections and *Staphylococcus aureus* (*S. aureus*) bacteraemia and soft tissue infections [10]. The former involved a number of presentations with the same strain (*emm*76.0). Enhanced surveillance of those affected at the onset of the outbreak identified those involved as mainly former heroin injectors and linked most cases to injection of an NPS known locally as 'Blue' or 'Burst'. Further investigation revealed Blue/Burst to contain ethylphenidate; a

stimulant NPS which shares chemical similarities to methylphenidate. Ethylphenidate use has been associated with intensive short 'rushes' and frequent injecting episodes [11].

A key response by governments to the rise in NPS use and related harms has been the use of legislation, principally aimed at prohibiting availability and use of particular substances, and reducing associated harms. In the UK, temporary class drug orders (TCDOs) have been used to re-classify the legal status of a number of NPS including methoxetamine (February 2013) and benzofuran analogues (June 2013). In response to harms related to ethylphenidate use in the UK, in particular the Lothian outbreak, the UK Government enacted a TCDO against it and other derivatives of methylphenidate in April 2015. The TCDO made it illegal to sell or supply substances containing ethylphenidate from 10 April 2015 onwards. We aimed to determine whether the TCDO had contributed to a reduction in infections among PWID in Lothian. Another goal was to determine whether the TCDO had reduced the incidence of infections among NPS users identified within the outbreak. Specifically the aims were to:

- Evaluate the impact of the ethylphenidate TCDO on reducing the most common infections (*S. pyogenes* and/or *S. aureus* infections) among PWID or those with a connection to PWID during the Lothian outbreak in 2014/2015.

- Identify if there is an association between NPS-injecting and a specific subtype of causative bacteria. In particular, if there is a link between *S. pyogenes emm*76.0 infections with NPS-injecting.

METHODS

Setting

The Lothian health board region serves a population of around 800,000 people and incorporates Edinburgh, the capital city of Scotland (estimated population: 500,000). There are an estimated 10,000 problem drug users in Lothian [12] and over 3,000 PWID [13].

Data

Enhanced surveillance initiated during outbreak investigation involved microbiology laboratories in Lothian (Edinburgh Royal Infirmary and St John's hospital, Livingston) notifying all cases of *S. pyogenes* and/or *S. aureus* positive isolates that had a connection to PWID to the Health Protection Team in Lothian. All hospital and primary care microbiology samples from NHS Lothian are processed in these two laboratories. Data was collected consistently from both sites throughout the study period, ensuring that ascertainment of NPS associated infection across the whole of Lothian was as complete and comprehensive as possible. Hospital records for each case were reviewed to gather information on gender, age group, self-reported drug use, sample date and subtype of infection. For individuals whose samples cultured one or both of those organisms, the date of their first isolate within 2014/2015 was used in this analysis as representing the date of initial infection.

Analysis was performed on instances of different *S. pyogenes* and *S. aureus* infections. *S. pyogenes* infections were categorised as '*emm*76.0' and 'other *emm* type' depending on which *emm* type of *S. pyogenes* was identified or if the *emm* type was not known due to there being no *S. pyogenes* isolate available for *emm* typing. If a PWID sample cultured both *S. pyogenes* and *S. aureus* on the same date, then this was counted as a single coinfection. However if a PWID sample cultured *S. pyogenes* and *S. aureus* on different dates, these were counted as two separate infections. Furthermore, one PWID cultured different *emm* types of *S. pyogenes* on different dates and these were counted as two separate *S. pyogenes* infections.

Infection Groups

We wished to identify if the ethylphenidate TCDO was effective in reducing the incidence of infection due to specific bacteria (particularly *S. pyogenes emm*76.0 which through snapshot surveillance and *emm* typing for two weeks during the outbreak of all *S. pyogenes* isolates from all patients in Lothian, appeared to be only circulating in the PWID community or close contacts of PWIDs) or if it was only more generally effective in reducing the most common infections under consideration regardless of the causative bacteria. Therefore, the causative bacteria were grouped in the following ways:

1. *S. pyogenes* (all *emm* types) and/or *S. aureus* (n = 251)
2. *S. pyogenes* (*emm*76.0, n = 68) (*emm* types other than *emm*76.0, n = 40)
3. *S. aureus* (excluding coinfection with *S. pyogenes*) (n = 143)

The impact of the TCDO and the effect of NPS-injecting were evaluated against all three groups.

Key Dates

A number of key dates were considered for analysis, particularly for defining the time periods before and after intervention.

- 04 April 2014 (Week 14 2014): First *S. pyogenes emm*76.0 isolate identified (retrospectively) in Lothian (from PWID).
- 29 September 2014 (Week 40 2014): Awareness of a cluster of PWIDs with *S. pyogenes* infections presenting to Edinburgh Royal Infirmary for surgical intervention and notification of the cluster to Public Health.
- 10 April 2015 (Week 15 2015): Introduction of UK-wide ethylphenidate TCDO.
- 22 October 2015 (Week 43 2015): Forfeiture Order under the General Product Safety Regulations 2005 granted. Edinburgh's head shops (shops selling drug-related paraphernalia) [14] and other retailers ceased trading NPS of all types from October 2015.

Note that week numbers refer to the *ISO-week* standard created by the Internal Organisation for Standardisation (ISO). This is a leap week calendar system where years have 52 or 53 weeks and are numbered in a standardised fashion. Specifically, week 1 is the first week in a new year where the majority of the days of that week fall in the new year.

Statistical Analysis

Segmented negative binomial regression on weekly counts of infections was used to evaluate the impact of the TCDO. Segmented regression is a robust modelling method for

analysing interrupted time series (ITS) data [15] and allows the data to be modelled by two time periods — a *pre-intervention* period and a *post-intervention* period. Note that the negative binomial model was favoured over a Poisson model as the data was overdispersed. Serial dependence in weekly infections was assessed by analysing the partial autocorrelation function (PACF) of the regression model residuals. In models where significant autocorrelation was identified, this was accounted for by using a GLARMA (generalised linear autoregressive moving average) model [16,17]. Model fits using different types of regression model were assessed using AIC (Table S1).

Although the TCDO came into effect on week 15 2015, a time delay was included to make the post-intervention period start in week 17. This delay is required as we assumed that individuals could have been sourcing NPS up until the TCDO but may not have consumed their drugs immediately, and therefore could have presented with infection later. Hence, any potential reduction in cases due to the TCDO would not be observed until after a delay. We decided that the post-intervention period could not run past the date of the forfeiture order because in following period, it is difficult to attribute impacts exclusively to the TCDO.

The start of the pre-intervention period (week 34 2014) was chosen based on when PWID were presenting with infections almost every week. This period lasted until the end of week 16 2015 (19 April); 35 weeks in total. The post-intervention period started on week 17 2015 (20 April) and up to the end of the week closest to the forfeiture order (week, 42 2015; 18 October); 26 weeks in total.

Separate models were used for different groups of causative bacteria (*S. pyogenes* and/or *S. aureus*, *S. pyogenes* and *S. aureus*). All models had four explanatory variables in common — number of weeks since the start of the pre-intervention period, a variable indicating pre and post-intervention weeks, number of weeks since the start of the post-intervention period and a variable to identify individuals who reported NPS use. The *S. pyogenes* model also included a variable to discern *S. pyogenes emm*76.0 infections and an interaction between NPS use and *S. pyogenes emm*76.0 infections. These models enable the change in level and trend pre and post intervention to be investigated and also allows NPS use to be

considered. The interaction term allows the risk of infection for NPS users to be compared between *S. pyogenes emm*76.0 infections and *S. pyogenes* (*emm* types other than *emm*76.0). A 5% value was used to test for statistical significance.

RESULTS

There were 211 individuals who had a total of 251 *S. pyogenes* and/or *S. aureus* infections between February 2014 and the end of 2015. Most of these occurred between, and including, week 34 2014 and week 20 2015 (a few weeks after the TCDO — Figure 1). Cases were predominantly male and aged between 26–50; almost two-thirds of cases identified themselves as NPS users (Table 1). The 'NPS user' group comprised those who self-reported to be NPS users without current heroin use (*n* = 27) and those who reported that they were currently using both NPS and heroin (*n* = 106) (data not shown).

[Insert Table 1 about here]

There were no significant differences by age and gender between individuals with *S. pyogenes* infections compared to those with *S. aureus* infections. A higher proportion of cases infected with *S. aureus* reported heroin use (25.2%, *n* = 36/143) compared with cases infected with *S. pyogenes* (15%, *n* = 16/107), however the difference was not significant (χ^2 = 3.3, *p* = 0.07). Conversely, a larger proportion of PWIDs infected with *S. pyogenes* reported use of NPS (68.2%, *n* = 73/107) compared to those infected with *S. aureus* (63.6%, *n* = 91/143) but this difference was not significant (χ^2 = 0.4, *p* = 0.535). Of those with *S. pyogenes* infections, 63.6% (*n* = 68/107) were due to *emm*76.0.

TCDO Impact

There were marked reductions in the incidence of weekly infections due to the groups of causative bacteria following the TCDO (Table 2). The largest reduction was in *S. pyogenes emm*76.0 infections where the weekly incidence was 4 times larger in the pre-intervention period (1.6 infections per week) compared with the post-intervention period (0.4 infections per week) and which continued to appear only to be affecting the PWID

population throughout the outbreak. In contrast, the incidence of weekly infections of *S. pyogenes* with *emm* types other than *emm*76.0 remained similar before (0.6 infections per week) and after the TCDO (0.4 infections per week). Table 2 also shows that only a small number of infections in 2014 and 2015 occurred at times outwith the time periods chosen for analysis, in particular for *S. pyogenes emm*76.0 infections. This gives assurance that the chosen time periods are appropriate for the research questions under investigation.

[Insert Table 2 about here]

The relative risks (RRs) and corresponding 95% confidence intervals (CIs) in Table 3 show that the trend in weekly infections was significantly lower following the TCDO for all causative bacteria under consideration. These trend changes are illustrated in Figure 1. Note that only two models (*S. pyogenes* and/or *S. aureus* and *S. aureus* alone) accounted for first-order autocorrelation and the *S. pyogenes* model did not as no significant autocorrelation was detected there. Furthermore, NPS-injecting significantly increased the risk of infections due to *S. pyogenes* (all *emm* types) and/or *S. aureus* (RR 1.81, 95% CI 1.12–2.93) but not due to *S. aureus* alone (RR 1.58, 95% CI 0.94–2.68). In the *S. pyogenes* model, an interaction term between NPS use and *S. pyogenes emm*76.0 infections was included and this shows that NPS-injecting increased the risk of infection due to *S. pyogenes emm*76.0 much more than for *emm* types other than *emm*76.0 (RR 3.49, 95% CI 1.32–9.21).

[Insert Table 3 about here]

[Insert Figure 1 about here]

DISCUSSION

To date, few quantitative studies have attempted to assess the effectiveness of policies that legislate against the availability of NPS. This study differs from those that have been conducted previously [18–21] as it is the first to examine the impact of a TCDO that was enacted in response to a disease outbreak. The ethylphenidate TCDO enacted in April 2015 was highly effective in reducing incidence of *S. pyogenes* and *S. aureus* infections among PWID during an outbreak in Lothian, Scotland. Many of these PWID self-reported using NPS

which was associated with an increased risk of acquiring infection, especially those due to *S. pyogenes emm*76.0. Dramatic reductions in infections due to *S. pyogenes* and *S. aureus* following the TCDO were observed among individuals that reported NPS use.

Introducing policies that prohibit the availability and/or use of certain psychoactive substances may result in immediate positive public health impacts but also lead to adverse and unintended consequences [22,23]. Opponents to the use of legislative prohibition measures argue they are overly simplistic and often ineffective, either because prohibition will move a particular NPS to the black market or that particular NPS will be replaced by new drugs [22,24–26]. To counter these criticisms, it is essential to make assessments of how successful these measures have been in achieving intended outcomes.

The outbreak arose due to the increasing prevalence of injecting ethylphenidate in Lothian combined with a change in injecting behaviour associated with injection of this drug. Changes included sharing of needles (which occurred as communal injecting in unhygienic conditions was not uncommon [11]), use of dirty injecting paraphernalia, injection of non sterile drug diluents, preferential injecting into anatomical sites known to harbour bacteria associated with causing severe SSTIs, poor personal hygiene and hand hygiene in conjunction with multiple necrotic, ulcerating or discharging skin lesions and compulsive, repetitive redosing associated with ethylphenidate use [27] (some individuals reported injecting up to 30 times daily), with each repeated skin puncture raising the possibility of infection [28]. In this predicament where NPS-injecting clearly had high addictive potential and was causing serious harm, availability of the implicated NPS (here, ethylphenidate based) is an important factor (as evidenced previously by the experiences of NPS users in Ireland [29] and Scotland [30]) and the urgency at which a TCDO could be executed was crucial in preventing individuals from easily obtaining ethylphenidate. As a consequence of reduced availability, risky NPS associated injecting behaviours and consequently infective complications of injecting NPS were positively influenced.

Enhanced surveillance facilitated the collection of richer data including information on individual drug use and laboratory testing. The initial dominance of *S. pyogenes emm*76.0 was striking as prior to the outbreak it was an uncommon *emm* type in the United Kingdom

and even rarer in Scotland [31,32]. The discovery early in the outbreak that *emm*76.0 *S. pyogenes* was being transmitted solely within the PWID community (or their immediate contacts) allowed investigators to more easily identify links between cases and that the common factor between many of the cases was likely to be NPS-injecting.

One of the strengths of this study is that it measured the impact of the TCDO against a defined and patient-centred clinical outcome (infective complications of injecting). This is in a similar vein to the study by Wood *et al.* [21] which measured impact against numbers of emergency department visits for acute toxicity from patients with self-reported mephedrone use. In contrast, previous studies have assessed effectiveness of legislative prohibition using measures with perhaps, greater degrees of uncertainty with respect to their ability to measure public health impacts. For instance, Hill *et al.* [18] and Loeffler *et al.* [33] measured the impact of the temporary bans by examining numbers of calls to information services for substance toxicity. Here, the uncertainty comes from some enquiries being for information only rather than being related to actual cases and also fluctuating levels of knowledge regarding NPS by members of the public and health professionals over time.

Another strength of this study is the decision to use segmented regression in a GLARMA model [16,17] to analyse the data split into pre and post-intervention time periods. In the absence of randomisation or clinical trial data, segmented regression has been suggested by Kontopantelis *et al.* [34] as the 'next best' approach for analysing the effect of interventions. Furthermore, the method has been suggested to be powerful, robust and allows substantial flexibility in controlling how the intervention effect is modelled and interpreted [15,35,36]. In this analysis, the flexibility of the approach allowed for trends in numbers of infections pre and post-intervention to be modelled while accounting for self-reported NPS use and serial dependence in the time series data.

The time-series analysis undertaken in this study is confined to a local area (Lothian), therefore the application of the findings to other territories, particularly those at a national population level, should be done with caution. Further, we were unable to determine whether the results were confounded by the rate of drug use or drug injecting over time

due to an absence of relevant data. The most recent prevalence estimates available for Lothian date back to 2012/13 (problem drug use) [12] and 2006 (PWID) [13].

Despite a programme of enhanced surveillance undertaken during the outbreak, it is possible that eligible cases were not identified and therefore not included within our analysis. However, extensive efforts were made to coordinate data collection between secondary care, laboratories and public health during the outbreak meaning that the extent of missing data is likely to be minimal. A further potential limitation in our methodology is the use of self-reported data on drug use and the potential for social desirability bias in responses. Prior research has concluded that drug user self-reports offer a "sufficiently reliable and valid" method for describing drug use [37] and related harms and we thus assume similar levels of validity and reliability in this study.

Another possible confounder was the discovery latterly during the outbreak that some heroin being injected by the PWID community was adulterated with ethylphenidate-based NPS resulting in heroin injectors manifesting the infections due to causative bacteria associated with NPS-injecting. This point may help to explain one of our findings. Although *S. pyogenes emm*76.0 infections were strongly linked to NPS-injecting, we did not find a significant difference in the change in mean level of *S. pyogenes emm*76.0 infections following the TCDO between those with and without self-reported NPS use. This may have been because the individuals who acquired *S. pyogenes emm*76.0 infections but did not report NPS use may have in fact been NPS users unknowingly or direct contacts of those PWIDs with *S. pyogenes* skin infections. This could be explained if the *emm*76.0 *S. pyogenes* was transmitted between individuals by a mechanism other than through injecting NPS such as close contact in unhygienic conditions.

The study was not able to evaluate the impact of the TCDO on all infections associated with the outbreak. For example, incidence of *S. aureus* endocarditis, an infection which had one of the largest impacts on the health service during the outbreak and was characterised by severe morbidity and, in some cases, mortality, reduced dramatically post TCDO. However, the relatively small numbers of these infections in the pre-intervention period precluded evaluation using a modelling approach.

It is challenging to isolate the effect of the TCDO from the impact of other ongoing public health responses to the outbreak that were happening simultaneously. For instance, prior to the introduction of the TCDO in April 2015, several head shops across Lothian were identified as trading ethylphenidate. A letter from the Director of Public Health (DPH) was sent to 24 head shops on 19 March 2015 requesting that they cease selling these substances, highlighting the significant health impact of their use at both an individual and population level. In addition, proactive communication raising awareness of this outbreak was targeted to the 'at risk' population and those services/agencies in contact with the at risk population. It is possible that these communications contributed to a reduction in ethylphenidate use and associated infections in Lothian. However, the timing of the abrupt drop in incidence of infective complications of injecting and significant change in trend following the TCDO point to the TCDO being the crucial intervention above all others in impacting availability, use and related infection(s).

In this study, the TCDO was enacted on 10 April 2015 but a decision was made to start the post-intervention period on 20 April 2015 (week 17). This is because we hypothesised that individuals could source ethylphenidate up to April 10 but purchased drugs would not all be consumed immediately. Here, the choice of how much lag-time to include is subjective. For this reason, the sensitivity of results to the chosen start date for the post-intervention period was tested by also starting the period on 13th and 27th April (weeks 16 and 18). Under all alternative scenarios, the results were similar (Tables S2–S3) and conclusions drawn were largely consistent with our original choice of 20th April. Only one notable difference was found, which occurred when using 27th April — the trend change in the *S. pyogenes* model was no longer significant. The is understandable as the results from that model are more sensitive to changes due to there being less infections (compared with the other two models) and the inclusion of an interaction between NPS use with *S. pyogenes emm*76.0 infections.

CONCLUSION

NPS use and its related harm continue to pose risks for public health internationally, including in the UK [38]. Before legislation can be enacted to prohibit NPS, sufficient evidence must be accumulated. In the situation where these NPS are causing severe harm to individuals, urgent action is needed and the strict requirements for implementing legislation may need to be circumvented; this is the where TCDOs offer most value. This study demonstrates that the TCDO for ethylphenidate was effective in disrupting the transmission of infection among PWID in Lothian, Scotland.

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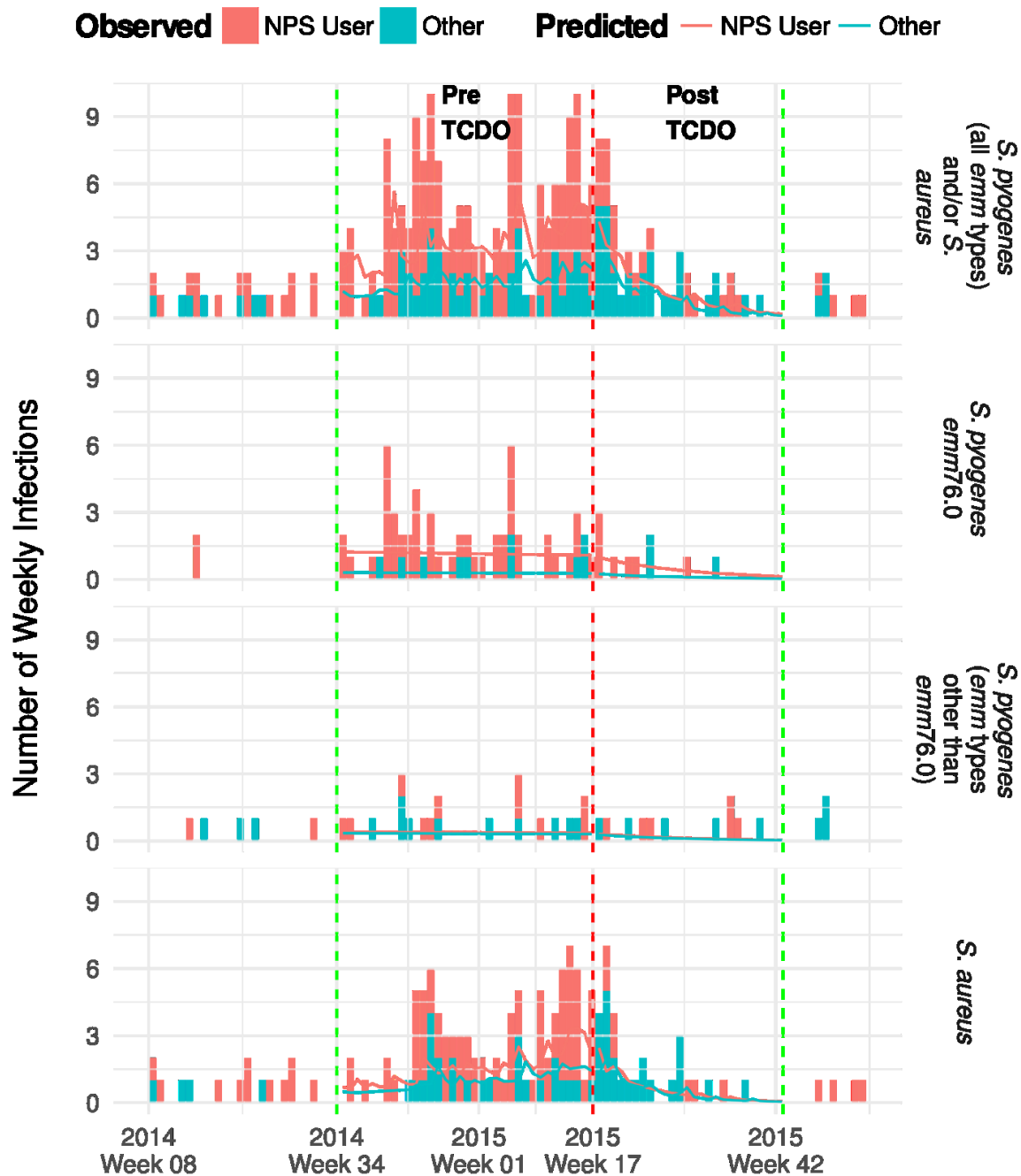
Figure 1 Observed and predicted weekly infections for groups of causative bacteria split by PWID with/without NPS use (those without are 'Other'). Predictions were made using segmented negative binomial regression. The *S. pyogenes* and/or *S. aureus* model and *S.aureus* alone model accounted for first-order autocorrelation. The green dashed lines show the start of the pre-intervention period and the end of the post-intervention period. The red dashed line shows the changeover date (20 April 2015) from pre to post-intervention which occurs later than the date the TCDO was enacted (10 April 2015) due to the inclusion of a delay.

Table 1 Characteristics of cases of infection split into *S. pyogenes* (all *emm* types) and/or *S. aureus*, *S. pyogenes* (all *emm* types), and *S. aureus* (excluding coinfection with *S. pyogenes*).

		S. pyogenes and/or *S. aureus*		*S. pyogenes*		*S. aureus*	
		n	*%*	*n*	*%*	*n*	*%*
Gender	Female	58	27.5	31	29.0	41	28.7
	Male	153	72.5	76	71.0	102	71.3
Age	20 and under	1	0.5	0	0.0	1	0.7
	21–25	9	4.3	4	3.7	6	4.2
	26–30	29	13.7	14	13.1	22	15.4
	31–35	59	28.0	35	32.7	37	25.9
	36–40	49	23.2	20	18.7	33	23.1
	41–45	36	17.1	21	19.6	27	18.9
	46–50	23	10.9	9	8.4	16	11.2
	51+	5	2.4	4	3.7	1	0.7
Drug Use (Self-Reported)	NPS User	133	63.0	73	68.2	91	63.6
	Heroin User	48	22.7	16	15.0	36	25.2
	ex-PWID	18	8.5	9	8.4	12	8.4
	Other	9	4.3	7	6.5	3	2.1
	PWID (unknown type)	2	0.9	2	1.9	0	0.0
	No recent information	1	0.5	0	0.0	1	0.7
S. pyogenes emm Type	*emm*76.0			68	63.6		

Table 2 Numbers and weekly rate of infections within the pre and post-intervention periods by infection group. Rates were estimated using a pre-intervention period of 35 weeks and a post-intervention period of 26 weeks.

Infection Group	Pre-TCDO		Post-TCDO		Outwith Period
	n	Weekly Rate	*n*	Weekly Rate	*n*
S. pyogenes (all *emm* types) and/or *S. aureus*	171	4.9	51	2.0	29
S. pyogenes (*emm*76.0)	56	1.6	10	0.4	2
S. pyogenes (*emm* types other than *emm*76.0)	21	0.6	11	0.4	8
S. aureus (excluding coinfection with *S. pyogenes*)	94	2.7	30	1.2	19

Table 3 Relative risks and 95% confidence intervals estimated from segmented negative binomial regression models for three groups of infections. The *S. pyogenes* and/or *S. aureus* model and *S.aureus* alone model accounted for first-order autocorrelation.

	RR	95% CI	p
S. pyogenes* (all *emm* types) and/or *S.aureus			
Intercept	1.12	0.59 – 2.11	0.728
Trend: Pre-TCDO	1.02	0.99 – 1.05	0.229
Level change following TCDO	1.11	0.46 – 2.70	0.820
Trend change following TCDO	0.88	0.82 – 0.94	<0.001
NPS User	1.81	1.12 – 2.93	0.016
S. pyogenes			
Intercept	0.36	0.18 – 0.72	0.004
Trend: Pre-TCDO	1.00	0.97 – 1.02	0.762
Level change following TCDO	0.97	0.39 – 2.45	0.956
Trend change following TCDO	0.93	0.87 – 1.00	0.037
NPS User	1.14	0.55 – 2.35	0.726
*S. pyogenes emm*76.0	0.86	0.40 – 1.87	0.708
Interaction: NPS User with *emm*76.0	3.49	1.32 – 9.21	0.012
S. aureus			
Intercept	0.41	0.19 – 0.88	0.022
Trend: Pre-TCDO	1.05	1.01 – 1.08	0.004
Level change following TCDO	0.87	0.40 – 1.91	0.736
Trend change following TCDO	0.83	0.77 – 0.90	<0.001
NPS User	1.58	0.94 – 2.68	0.087