Drug and Alcohol Dependence 192 (2018) 352–361

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Cost-effectiveness of naloxone kits in secondary schools

Lauren E. Cipriano[a,b,*], Gregory S. Zaric[a,b]

[a] Ivey Business School, Western University, London, ON, N6G 0N1, Canada
[b] Department of Biostatistics and Epidemiology, Schulich School of Medicine and Dentistry, Western University, London, ON, N6A 5C1, Canada

ARTICLE INFO

Keywords:
Cost effectiveness analysis
Opioid overdose
Opioid poisoning
Naloxone

ABSTRACT

Background: We seek to identify conditions under which a plan by the Toronto District School Board (TDSB) to equip high schools with naloxone kits would be cost-effective.
Methods: We developed a decision-analytic model to evaluate the costs, benefits, and cost-effectiveness of a school-based naloxone program. We estimated model inputs from the medical literature and used Toronto-specific sources whenever available. We present our results varying both the expected total number of opioid overdoses per year across all 112 TDSB high schools and the effectiveness of a school-based naloxone program in reducing mortality.
Results: A school naloxone program likely costs less than CAD$50,000 per quality-adjusted life-year gained if the overdose frequency is at least once each year and it reduces opioid poisoning mortality by at least 40% (from 10% to < 6.0%) or if the overdose frequency is at least two per year and the program reduces mortality by at least 20% (from 10% to < 8.0%). The results are sensitive to the intensity and cost of staff training, the lifetime costs and life-expectancy of overdose survivors, and the probability of an overdose being fatal in the absence of a school naloxone program.
Conclusions: School naloxone programs are relatively inexpensive, but that does not ensure that they are a cost-effective use of resources. While potentially cost-effective, if the risk of an overdose in a Toronto high school is low, then other programs aimed at improving the health and wellbeing of students may be better use of limited resources.

1. Introduction

Opioid poisoning can occur as a medical accident with commonly prescribed pain medications, through the use illicit opioids, or through the use of other non-opioid drugs (e.g., MDMA and cocaine) that have been contaminated with opioids (Howlett, 2017). From 2007–2015, hospitalizations for opioid poisoning increased by more than 30% for all Canadians and by 62% among 15 to 24-year-olds (Canadian Centre on Substance Abuse, 2016). Similarly, in the U.S., since 2004, the number of opioid-related hospital admissions among 12 to 17-year-olds has increased by approximately 8.7% each year (Kane et al., 2018). In 2017, 10.6% of Ontario students in grades 7–12 reported past-year use of opioid pain relievers to get high and not for medical purposes and 1% of students, approximately 5800 students, used fentanyl in the last year (Boak et al., 2017). News reports of high school aged children dying of opioid poisoning are uncomfortably common across North America (Craig, 2017; D'Amato, 2017; Hudes and Powell, 2017; Larsen, 2017; Luetzen, 2017; Postmedia News, 2017; Salvian, 2018; Smart, 2018; Tomassoni et al., 2017; Zussman and McArthur, 2018) and overdoses have been reported at U.S. schools (Bennett, 2018; Lake, 2014).

In response to the opioid crisis, naloxone is widely available to laypersons through pharmacies and public health departments (Canadian Pharmacists Association, 2017; Ontario Ministry of Health and Long-Term Care, 2017). Police officers in many Ontario cities as well as the Ontario Provincial Police carry naloxone (Howlett, 2017). The U.S. National Association of School Nurses recommends naloxone be incorporated into school emergency preparedness and response plans (King and Embrey, 2016). High schools in Connecticut, Delaware, Kentucky, Massachusetts, New York, New Mexico, and Pennsylvania have school-based naloxone programs (King, 2016; Pennsylvania Department of Health, 2018; The Recovery Village, 2018).

On February 8, 2018, several news outlets reported that the Toronto District School Board (TDSB) was planning to put naloxone nasal spray kits into all of its secondary schools (112 schools in total serving approximately 74,000 students (Toronto District School Board, 2018)) as part of a plan to combat the opioid crisis (Hamadi, 2018; Rizza, 2018). The total cost of the kits was estimated at $16,000-$20,000, which is small relative to the TDSB annual budget of approximately $3.1 billion

* Corresponding author at: Ivey Business School at Western University, 1255 Western Road, London, ON, N6G 0N1, Canada.
E-mail address: lcipriano@ivey.uwo.ca (L.E. Cipriano).

https://doi.org/10.1016/j.drugalcdep.2018.08.003
Received 1 May 2018; Received in revised form 2 August 2018; Accepted 4 August 2018
Available online 17 September 2018
0376-8716/

Table 1
Parameter values and sources.

Parameter	Estimate	Range	Source
Population			
Student age	16	13–18	Assumed
% Male	50%	24 – 76%	Boak et al. (2017); Special Advisory Committee on the Epidemic of Opioid Overdoses (2018)
Program effectiveness and patient outcomes			
Number of overdoses per year	Unknown	0.1–5.0	
Probability that an opioid overdose is fatal, status quo	10.1%[a]	1.8%–22%	Belz et al. (2006); City of Toronto (2018); Milloy et al. (2008)
Reduction in mortality from school-based programs: 4 Scenarios considered	15%		Rando et al. (2015)
	27%		Walley et al., (2013)
	46%		Walley et al. (2013)
	97%		Doe-Simkins et al. (2014)
Hospital admission	54.7%	30–70%	Yokell et al. (2014)[b]
School-based Naloxone Program Costs			
Program set-up costs			
Number of schools	112		Rizza (2018)
Initial Naloxone Inventory	$18,000	$16,000–$20,000	Rizza (2018)
Number of teachers or staff trained per school	3	2–4	Rizza (2018)
Training the trainers (seven 4-hour sessions)			
Training program cost	$1,123		Calculated[c]
Teacher/staff attendance	$26,651		Calculated[d]
Training additional staff (1-hour sessions for 3 staff in each school)	$19,988		
Total initial program costs	$65,762	50,000–100,000	Calculated[e]
Annual amortized cost of initial program set-up	$7,379	5,610–11,220	Calculated[f]
Program maintenance costs			
Annual naloxone inventory replacement	$9,000	7,000–10,000	North Carolina Harm Reduction Coalition, (2018)
Annual ongoing training costs	$20,697	16,000–24,000	Calculated[g]
Medical Care Costs			
Ambulance cost[h]	$929	750– 1500	City of Toronto (2017)
Hospital costs[i]			
Emergency department	$396	250– 750	CIHI (2016); Hsu et al. (2017); Yokell et al. (2014)
Inpatient care, survivors	$3,364	2,500–4500	CIHI (2016); Hsu et al. (2017); Yokell et al. (2014)
Inpatient care, fatality	$7,717	6,500–9000	CIHI (2016); Hsu et al. (2017); Yokell et al. (2014)
Physician costs			
Emergency department	$76.90		Ontario MOHLTC (2016)
Inpatient care, survivors	$354.96		Ontario MOHLTC (2016)
Inpatient care, fatality	$375.56		Ontario MOHLTC (2016)
Long-term outcomes			
One-year mortality after opioid overdose, incremental over age-specific mortality	9.95%	7.5%–12.5%	Weiner et al. (2017)
Chronic substance use disorder (SUD) in survivors	100%	0–100%	Assumed
Long-term, relative risk on age-specific mortality, SUD	14.68	3.6–18.8	Mathers et al. (2013)
Multiplier on baseline age-specific health care costs, SUD	1.64	1.3–2.4	Clark et al. (2009)
Multiplier on baseline age-specific utilities, SUD	0.80	0.73–0.90	Coffin and Sullivan (2013a)
Multiplicative modifiers for individual in drug treatment			
Mortality	0.42	0.32–0.56	Degenhardt et al. (2011)
Health care costs	0.71	0.60–1.20	Baser et al. (2011)
Utilities	1.07	1.0–1.20	Coffin and Sullivan (2013a)
Life-expectancy and health care costs for survivors			
100% SUD with 23% in drug-use treatment			
Lifetime discounted costs	96,679		Calculated[j]
Discounted life years	26.18		Calculated[j]
Discounted quality-adjusted life-years	19.90		Calculated[j]
Average-values for Canadian population (after year 1)			
Lifetime discounted costs	157,726		Calculated[j]
Discounted life years	37.53		Calculated[j]

(*continued on next page*)

Table 1 (*continued*)

Parameter	Estimate	Range	Source
Discounted quality-adjusted life-years	34.63		Calculated[j]
Discount rate	1.5%	0–5%	CADTH (2017)

[a] 1504 non-fatal overdoses and 111 fatal overdoses between August 7, 2017 and February 4, 2018 (26 weeks) with 518 naloxone administrations by either community members or paramedics (City of Toronto, 2018). We calculate the probability of death from overdose, when naloxone is not administered, given Toronto's current emergency response system services as 111/(1504 + 111–518) = 0.1012.

[b] Yokell et al. (2014) report that 45.3% are discharged from the emergency department directly. We assume all fatalities occur after admission.

[c] Hourly wage for a nurse in Toronto was $38.50 in 2016 (Living in Canada, 2018). We adjusted for inflation to get $40.10/hour and calculate the total as = $40.10 per hour × 7 session × 4 h per session = $1123.

[d] The annual salary of a teacher in Toronto with 10-years of experience is about $92,327 with 192 8-hour work days (Statistics Canada, 2017; Ontario Secondary School Teachers' Federation, 2014). This results in an hourly wage of $59.49 [$92,327/(192 × 8) = 59.49]. We calculated the total as = $59.49 per hour × 4 h per session × 112 teachers = $26,651.

[e] Calculated as the sum of the training program cost (4-hour training led by a nurse, $1123) including the opportunity cost of 1 teacher per school attending the training to become a trainer ($26,651) plus the opportunity cost of 2 additional teachers (and the teacher-trainer) to participate in the 1-hour training within each school ($19,988).

[f] Calculated using 2.15% Ontario savings bond rate (Ontario Ministry of Finance, 2017) assuming a 10-year amortization period (Toronto District School Board, 2017).

[g] We assumed that all staff would require retraining every three years, consistent with Red Cross general first aid certification requirements (Canadian Red Cross, 2018) and an additional 10% of staff would need to be trained per year to account for retirements and staff turnover.

[h] Based on 220,667 patients transported in 2016 and total expenditures of $204,912,700; average cost per patient = 204,912,700/220,667 = $928.61 (City of Toronto, 2017).

[i] Among patients admitted to the hospital, we estimated the relative cost of fatal vs. non-fatal overdose using a US study of hospital costs (Hsu et al., 2017). We estimated the relative cost of patients discharged directly from the emergency department (compared to those admitted) from a report of US hospital charges (Yokell et al., 2014), applying cost-to-charge ratios. We assumed the proportion of emergency department discharges consistent with the latter US study (Yokell et al., 2014) and otherwise scaled the costs to be consistent with the average cost of CMG 778 (Poisoning/Toxic Effect of Drug) in a Canadian hospital.(Canadian Institute for Health Information, 2016).

[j] Calculated using Canadian life tables (Statistics Canada, 2015), the average age-specific costs of health care in Canada (Canadian Institute for Health Information, 2016), and median age-specific quality-of-life weights in Canada (Guertin et al., 2018). Incorporates one-year higher mortality after surviving opioid overdose (Weiner et al., 2017). After one-year, in individuals with SUD, increases in long-term mortality, costs, and decreases in quality-of-life were incorporated to account for life with untreated and treated SUD (Baser et al., 2011; Clark et al., 2009; Coffin and Sullivan, 2013a; Degenhardt et al., 2011; Mathers et al., 2013).

(Toronto District School Board, 2017). However, other treatment and harm reduction plans are in place in Toronto (Toronto Public Health, 2017) and the value of the investment by the TDSB depends on the incremental benefit of the school-based naloxone plan on top of existing services.

Although there have been no public reports of overdoses at Toronto or other Canadian schools, general concern regarding the opioid epidemic and reports of fatal overdoses in high school students have led to the implementation of school-based naloxone policies in other Ontario school districts as well as in at least some schools in British Columbia and Alberta (Campbell, 2017; Dangerfield, 2017; Ferguson, 2018; Michaels, 2018; Wells, 2017). Some Canadian school districts have decided against it (Outhit, 2018). The purpose of this article is to use the principles of cost-effectiveness analysis to understand the conditions under which a school-based naloxone program is a cost-effective use of resources not because the program is costly, but because targeting overdose fatality prevention at such a low-risk population has unclear value.

2. Materials and methods

We constructed a decision-analytic model to estimate the incremental costs, health effects, and cost-effectiveness ratio, of placing naloxone in high schools, relative to relying on existing emergency and public health resources. Costs are expressed in 2017 Canadian dollars (CAD); when necessary, costs were adjusted for inflation using the Canadian Consumer Price Index (Statistics Canada, 2018). We consider a societal perspective and a lifetime horizon for evaluating costs and benefits. Future costs and health benefits discounted at 1.5% consistent with the 2017 Canadian Guidelines for the Economic Evaluation of Health Technologies (Canadian Agency for Drugs and Technologies in Health (CADTH), 2017). Base case parameter values are shown in Table 1. Model documentation follows CHEERS[1] recommendations (Husereau et al., 2013). Cost-effectiveness was measured in incremental costs per quality-adjusted life-year (QALY) gained and we compare results to the common benchmark threshold of $50,000 per QALY-gained (Griffiths and Vadlamudi, 2016). We performed deterministic and probabilistic sensitivity analysis (probability distributions presented in Supplemental Table 1). We implemented the model in Microsoft Excel 2016 and we make the model available as online Supplemental Material. Institutional ethics review was not required for this study.

2.1. Program costs

Startup costs for the program include training and purchasing the initial supply of naloxone. We assumed that Toronto Public Health would train one staff member per school in four-hour group sessions consisting of 18 TDSB staff per session, consistent with descriptions of group training elsewhere (Devries et al., 2017). All subsequent training would be done by those TDSB staff to others at their schools in a "trainee-becomes-the-trainer" approach (Devries et al., 2017; Rizza, 2018). The cost of training was based on annual teacher salaries to reflect the opportunity cost of time devoted to training. We assumed that the initial cost of naloxone was $18,000, which was the mid-point of a published estimated cost range (Rizza, 2018). We assumed startup costs would be amortized over 10 years, consistent with the amortization duration the TDSB applies to the first-time equipping of schools (Toronto District School Board, 2017).

We assumed that all staff would require retraining every three years, consistent with Red Cross general first-aid certification requirements (Canadian Red Cross, 2018), and an additional 10% of staff would need to be trained per year to account for retirements and staff turnover. We assumed that naloxone kits would need to be replaced every two years (North Carolina Harm Reduction Coalition, 2018).

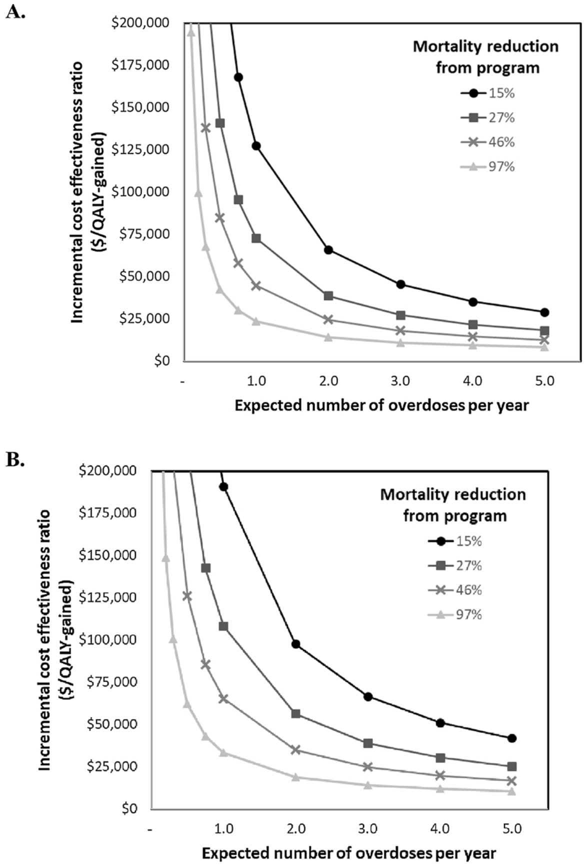

Fig. 1. Incremental cost-effectiveness ratio (ICER) as a function of number of overdoses per year (across all 112 TDSB high-schools) and program effectiveness. **(A)** Training costs based on a "trainee-becomes-the-trainer" model. **(B)** Training costs based on a half-day nurse-led training program.

2.2. Number of opioid poisonings in the school environment

The expected number of opioid overdoses per year that take place on or near school property is not known so model results are expressed in terms of this parameter. We varied this number from 0.1 (representing one overdose every 10 years across the entire school system) to 5.

2.3. Probability of fatal opioid overdose

There is uncertainty in the probability that an opioid overdose would be fatal in the absence of naloxone in high schools. One study of the number of overdose deaths potentially avoided by the Vancouver Supervised Injection Facility estimated, based on prior literature, a ratio of non-fatal to fatal overdoses ranging from 8.9 to 53.8 (Milloy et al., 2008), corresponding to probabilities of fatal overdose of 1.8% to 10.1%. Over a 26-week period from August 7, 2017 to February 4, 2018, the Toronto Overdose Information System reports that paramedics have responded to 1504 non-fatal and 111 fatal opioid overdoses (City of Toronto, 2018). Among non-fatal overdoses, 284 people received naloxone by a community member prior to Emergency Medical Services (EMS) arrival and approximately 234 received naloxone by EMS (City of Toronto, 2018). We used these numbers to estimate a probability of death given overdose of 10.1% [111/(1504 + 111-(284 + 234)) = 0.1012] in the base case and varied this in sensitivity analysis.

2.4. Effectiveness of a school-based naloxone program to reduce mortality

Naloxone is highly efficacious at reversing opioid poisoning and returning breathing (Doyon et al., 2014; Kim et al., 2009; Wermeling, 2015). Studies of community naloxone programs demonstrate that naloxone can be used effectively by laypersons and non-medical emergency personnel (Clark et al., 2014; Davis et al., 2014; Doyon et al., 2014; Lewis et al., 2016). For example, studies of naloxone programs targeting people who inject drugs achieve greater than 90% effectiveness when naloxone is administered (Doe-Simkins et al., 2014; Enteen et al., 2010). However, challenges in identifying a situation as one in which naloxone may help could result in missed opportunities and hence reduced effectiveness at reducing mortality from opioid poisoning (Fisher et al., 2016; Sumner et al., 2016). Despite these challenges, the introduction of programs to make naloxone broadly available to laypersons and non-medical first responders have demonstrated substantial impacts on the overall opioid overdose mortality rate ranging from 15% to 46% (Rando et al., 2015; Walley et al., 2013). We used this information to construct four scenarios representing the potential incremental effectiveness of a school-based program relative to existing services.

2.5. Survival and future healthcare costs

We assumed an average age of 16 and that half of all individuals suffering an opioid overdose were male consistent with equal rates of prescription opioid misuse by gender in Canadian youth (Boak et al., 2017). We assumed that all individuals experiencing opioid poisoning would be transported by ambulance to the emergency department as part of the first aid protocol used by schools. In the model, all overdose survivors have an elevated one-year mortality rate of 9.95% consistent with mortality rate observed in Massachusetts for individuals treated with naloxone (Weiner et al., 2017).

Canadian average age-specific future costs, life years, and quality-of-life weights were estimated from Statistics Canada, the Canadian Institute for Health Information (CIHI), and the Canadian Community Health Survey (Canadian Institute for Health Information, 2016; Guertin et al., 2018; Statistics Canada, 2015). In the base case, we assumed all overdose survivors have the higher-than-average mortality, higher-than-average costs, and lower-than-average quality-of-life associated with untreated and treated chronic substance use disorder (SUD).

Specifically, in the model, individuals with a history of overdose face a lifetime of higher mortality risk consistent with the standardized mortality ratios associated with opiate addiction (Mathers et al., 2013). We lowered these rates for individuals who participated in addiction treatment (risk ratio of 0.42) (Degenhardt et al., 2011). Baseline health care costs were increased by a factor of 1.64 consistent with multiplier observed in state Medicaid program for individuals with substance use disorders compared to those without a substance use disorder (Clark et al., 2009). We assumed 29% lower costs for individuals who participated in addiction treatment, resulting in a multiplier of 1.16 on baseline health care costs, as the substantial incremental costs associated with mediation-assisted addiction treatment are off-set by reductions in hospitalizations and emergency department visits (Baser et al., 2011). We assumed a multiplier on age-specific utilities of 0.8 in overdose survivors consistent with estimates associated with opioid addiction and a 7% improvement in quality of life for individuals who participate in addiction treatment (Coffin and Sullivan, 2013a). In sensitivity analysis, we varied these values significantly, including scenario analysis in which overdose survivors have the same future costs and benefits as the general population.

In the base case, we assumed that 23% of opioid poisoning survivors with SUD participate in drug-use related treatment, and going forward individuals transition between untreated and treated SUD health states maintaining 23% of the population in treatment consistent with the rate observed in the 2005–2013 National Surveys on Drug Use and Health (Wu et al., 2016).

Table 2
Minimum reduction in overdose mortality required for the school-based naloxone program to be cost-effective given the willingness-to-pay (WTP) threshold.

Across all TDSB high schools, on-campus opioid overdose occurs once every…	Training costs based on a "trainee-becomes-the-trainer" model		Training costs based on a half-day nurse-led training program	
	$50,000 /QALY-gained	$100,000 /QALY-gained	$50,000 /QALY-gained	$100,000 /QALY-gained
10 years	Not achievable	Not achievable	Not achievable	Not achievable
5 years	Not achievable	97%	Not achievable	Not achievable
3 years	Not achievable	57%	Not achievable	87%
2 years	82%	39%	Not achievable	59%
1 years	41%	20%	62%	30%
0.5 years	21%	10%	31%	15%
0.25 years	11%	5%	16%	8%

3. Results

3.1. Base case analysis

We varied the expected number of overdoses per year and the effectiveness of school-based naloxone in preventing mortality (Fig. 1a). The incremental cost-effectiveness ratio (ICER) is decreasing in the expected annual number of overdoses and decreasing in the effectiveness of the program in reducing mortality from overdose. When the total expected number of overdoses annually across all 112 high-school in the TDSB is more than two per year, then the program would cost less than $50,000 per QALY-gained if the program reduces opioid poisoning mortality by at least 20% (Table 2). However, at a lower frequency of overdose, the ICER becomes sensitive to program effectiveness. If there is less than one overdose every year, it is unlikely that a school-based naloxone program will be cost-effective unless the program reduces the mortality rate by at least 40% (from 10% to less than 6%).

This analysis highlights the range of assumptions under which a school-based naloxone program could be cost-effective (Table 3). In the most optimistic case, where a school-based program would nearly eliminate overdose mortality, the program would have an ICER of less than $50,000 per QALY-gained if the overdose frequency was 0.4 per year (approximately once every 2.5 years). In the least optimistic case, in which we assumed a 15% reduction in the mortality rate, as was seen after naloxone was provided to police services in one community (Rando et al., 2015), the program would achieve an ICER of $50,000 per QALY-gained if there were approximately 2.7 overdoses per year and an ICER of $100,000 per QALY-gained if there were approximately 1.3 overdoses per year.

Table 3
Annual number of overdoses required for the school-based naloxone program to be cost-effective given the willingness-to-pay (WTP) threshold.

WTP threshold	Naloxone Effectiveness in Reducing Mortality 15%	27%	46%	97%
	Training costs based on a "trainee-becomes-the-trainer" model			
$50,000 per QALY-gained	2.71	1.51	0.89	0.42
$100,000 per QALY-gained	1.29	0.72	0.42	0.20
	Training costs based on a half-day nurse-led training program			
$50,000 per QALY-gained	4.11	2.29	1.35	0.64
$100,000 per QALY-gained	1.96	1.09	0.64	0.31

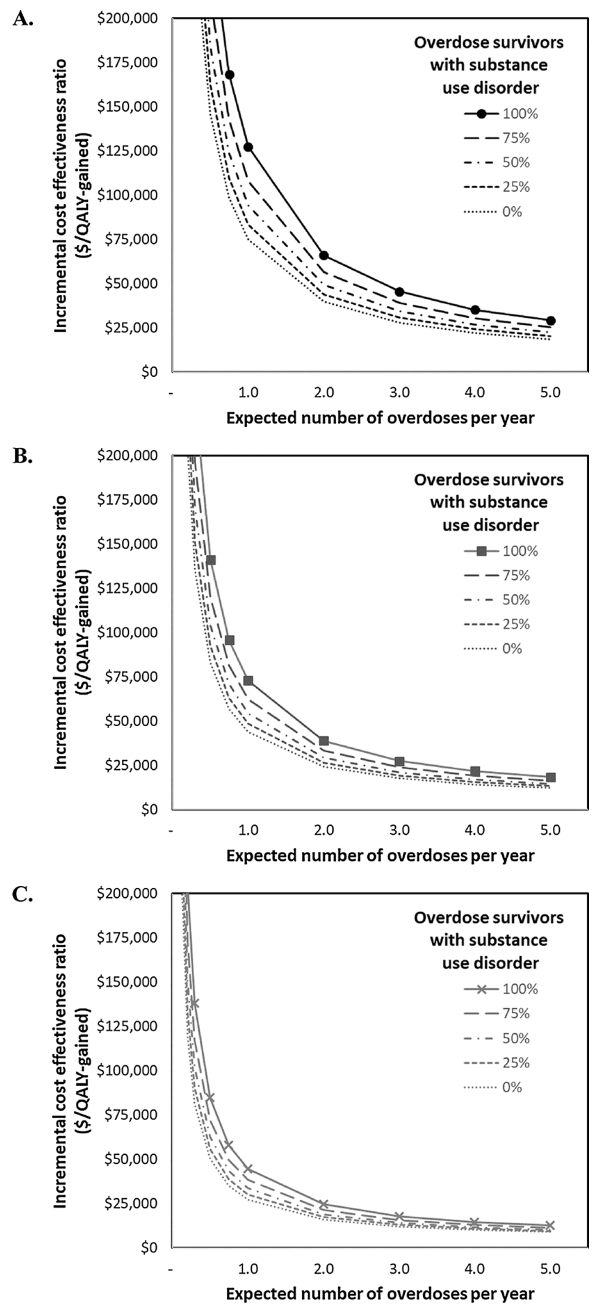

Fig. 2. Incremental cost-effectiveness ratio (ICER) as a function of number of overdoses per year (across all 112 TDSB high schools) and the proportion of overdose survivors with a chronic substance use disorder at various levels of program effectiveness: (A) 15% mortality reduction; (B) 27% mortality reduction; and (C) 46% mortality reduction compared to the status quo (10.1% mortality).

3.2. Sensitivity analysis

The cost-effectiveness of a school-based naloxone program is sensitive to the intensity, and hence cost, and the training programs (Table 3). Individuals suffering from opioid poisoning may require and benefit from rescue breathing and cardiopulmonary resuscitation (American Heart Association, 2015). We considered the possibility of

Table 4
Deterministic Sensitivity Analysis. Incremental cost-effectiveness ratio ($/QALY gained) varying the effectiveness of a school naloxone program to reduce mortality and the expected number of overdoses (OD) per year for different values of other model inputs.

	Mortality reduction = 15%			Mortality reduction = 27%			Mortality reduction = 46%		
Parameter	0.5 OD/year	1 OD/year	2 OD/year	0.5 OD/year	1 OD/year	2 OD/year	0.5 OD/year	1 OD/year	2 OD/year
Base case	**250,200**	**127,400**	**66,000**	**141,000**	**72,800**	**38,700**	**84,700**	**44,700**	**24,700**
Student age (base case = 16)									
13 years	238,100	121,300	62,900	134,300	69,400	36,900	80,700	42,600	23,500
18 years	258,400	131,600	68,200	145,700	75,200	40,000	87,500	46,100	25,400
Overdose mortality rate (base case = 10.1%)									
Very low (1.8%)	1,385,000	694,800	349,700	771,500	388,100	196,400	454,700	229,700	117,200
Low (5%)	501,600	253,100	128,900	280,700	142,700	73,700	166,700	85,700	45,100
High (15%)	170,300	87,500	46,000	96,700	50,700	27,600	58,700	31,600	18,100
Very high (22%)	117,600	61,100	32,900	67,400	36,000	20,300	41,500	23,100	13,800
Long-term survival, costs, and quality-of-life									
1-year mortality after initial survival (base case = 9.95%)									
5%	237,600	121,100	62,900	134,000	69,400	37,000	80,600	42,600	23,600
7.5%	243,800	124,200	64,400	137,500	71,100	37,900	82,600	43,600	24,100
20%	280,400	142,500	73,600	157,900	81,200	42,900	94,600	49,600	27,100
Long-term hazard ratio on mortality (base case = 14.68)									
3.6x	201,300	103,700	55,000	114,600	60,400	33,300	69,800	38,000	22,100
8x	224,200	114,700	59,900	126,900	66,000	35,600	76,600	40,900	23,000
16x	254,700	129,600	67,100	143,500	74,000	39,300	86,100	45,300	25,000
Long-term multiplier on health care costs (base case = 1.64)									
1.3x	249,100	126,400	65,000	140,000	71,800	37,700	83,700	43,700	23,600
2.4x	252,400	129,600	68,300	143,300	75,100	41,000	86,900	46,900	26,900
Long-term quality-of-life weight (base case = 0.8)									
0.73	222,400	113,200	58,700	125,400	64,700	34,400	75,300	39,700	21,900
0.90	274,100	139,600	72,300	154,600	79,800	42,500	92,800	49,000	27,000
Combination scenarios									
Overdose survivors have Canadian average mortality, health-care costs, and utilities immediately (no elevated mortality even in year 1)	131,700	68,000	36,200	75,100	39,800	22,100	45,900	25,200	14,800
Overdose survivors have Canadian average mortality, health-care costs, and utilities after year 1	145,500	75,000	39,700	82,800	43,600	24,000	50,400	27,400	15,900
Overdose survivors have ‘low-intensity’ substance use disorder effects (7.5% one-year mortality, 3.6x long-term mortality, 1.3x long-term costs, 0.9x effect on utilities)	173,300	88,800	46,600	98,200	51,300	27,900	59,500	31,900	18,200
Drug treatment									
Uptake of drug treatment (base case = 23%)									
0%	262,300	133,600	69,300	147,900	76,400	40,700	88,900	46,900	25,900
50%	235,800	120,000	62,200	132,900	68,600	36,400	79,800	42,000	23,200
100%	207,800	105,800	54,800	117,100	60,500	32,100	70,300	37,100	20,400
Impact of drug treatment on long-term outcomes									
Low mortality benefit (0.56)	252,000	128,300	66,500	142,100	73,300	39,000	85,300	45,000	24,800
High mortality benefit (0.32)	248,800	126,700	65,700	140,300	72,500	38,600	84,300	44,500	24,600
Decreases net costs (0.6)	250,000	127,300	65,900	140,900	72,700	38,600	84,600	44,500	24,500
Cost neutral	250,500	127,700	66,400	141,400	73,200	39,100	85,000	45,000	25,000
Increases costs (1.2)	250,700	128,000	66,600	141,600	73,400	39,300	85,300	45,300	25,200
No impact on utilities (1.0)	254,200	129,400	67,100	143,300	74,000	39,400	86,100	45,400	25,100
High impact on utilities (1.2)	243,000	123,800	64,100	137,000	70,800	37,600	82,300	43,400	23,900
Combination scenario: Best-case drug treatment (low-cost, high-benefit)	241,600	123,000	63,700	136,100	70,300	37,300	81,700	43,100	23,700
Combination scenario: Worst-case drug treatment (high-cost, low-benefit)	256,700	131,000	68,100	144,900	75,100	40,200	87,300	46,300	25,800
Teachers trained per school (base case = 3)									
Fewer teachers trained per school (2)	226,100	115,400	60,000	127,700	66,200	35,400	76,800	40,700	22,700
More teachers trained per school (4)	274,200	139,400	72,000	154,400	79,500	42,100	92,500	48,600	26,600
Many more teachers trained per school (6)	322,400	163,500	84,100	181,200	92,900	48,800	108,200	56,400	30,500
Length of initial “train-the-trainer” session (base case = 4 h)									
Shorter initial training (2 h)	200,000	102,300	53,500	113,200	58,900	31,800	68,300	36,500	20,600
Longer initial training (8 h)	350,500	177,600	91,100	196,800	100,700	52,700	117,400	61,000	32,800
Re-training frequency (base case: complete re-training every 3 years; 10% of teachers re-trained annually)									
Lower re-training needs (5-years and 5%)	192,200	98,400	51,500	108,800	56,700	30,700	65,800	35,200	19,900
Higher re-training needs (2-years and 15%)	318,700	161,700	83,100	179,100	91,900	48,300	107,000	55,800	30,200
Initial naloxone inventory cost (base case = $18,000)									
$16,000	242,000	123,300	64,000	136,500	70,600	37,600	82,100	43,300	24,000
$20,000	258,300	131,400	68,000	145,500	75,100	39,900	87,300	46,000	25,300
$30,000; equivalent to 3 doses per school	298,800	151,700	78,200	168,100	86,400	45,500	100,600	52,600	28,600
Hospital costs (emergency and inpatient)									
Lower	250,200	127,400	66,000	141,100	72,900	38,800	84,700	44,700	24,700
Higher	250,100	127,400	66,000	141,000	72,800	38,700	84,700	44,700	24,600
Discount rate (base case = 1.5%)									
0%	185,700	95,400	50,200	105,400	55,300	30,200	64,000	34,500	19,800

(*continued on next page*)

Table 4 (*continued*)

Parameter	Mortality reduction = 15%			Mortality reduction = 27%			Mortality reduction = 46%		
	0.5 OD/year	1 OD/year	2 OD/year	0.5 OD/year	1 OD/year	2 OD/year	0.5 OD/year	1 OD/year	2 OD/year
3%	323,600	163,900	84,100	181,700	93,000	48,600	108,400	56,300	30,300
5%	432,100	217,900	110,900	241,700	122,800	63,300	143,500	73,700	38,800
Amortization period for training and naloxone inventory costs (base case = 10 years)									
1 year	646,100	325,400	165,000	361,000	182,800	93,700	213,800	109,200	56,900
5 years	294,100	149,400	77,000	165,400	85,000	44,800	99,000	51,800	28,200
25 years	224,000	114,300	59,500	126,500	65,600	35,100	76,200	40,400	22,500

all staff participating in a four-hour session led by a nurse (similar to the training session provided to the to-be "trainers") to ensure confidence in their preparation which significantly increased the incremental cost-effectiveness ratios (Fig. 1b). At these higher costs, the program is only cost-effective at a willingness-to-pay of $50,000 per QALY-gained if there are more than two overdoses per year and the program reduces overall overdose mortality by at least 31%.

In our base case analysis, we assumed that all overdose survivors would experience long-term health care costs, life expectancy, and quality-of-life consistent with a chronic substance use disorder (SUD). Our results are sensitive to this assumption (Fig. 2). In a scenario in which we assumed overdose survivors have 'low-intensity' SUD (modelled using the low values from the sensitivity analysis range for one-year mortality, long-term mortality, and cost and the high value for quality-of-life), the ICER of a school-based naloxone program decreased by approximately 30% (Table 4). In a scenario in which we assumed survivors immediately had Canadian average health care costs, life-expectancy, and quality-of-life resulted in ICERs that were nearly half those in the base case analysis. For example, if there is one overdose per year and a school-based naloxone program reduces mortality by 27%, then the ICER is $72,800 per QALY-gained if overdose survivors have chronic SUD, $51,300 per QALY-gained if overdose survivors have a 'low-intensity' SUD, and $39,800 per QALY-gained if overdose survivors go on to have average Canadian life outcomes (Table 4).

Our results are also sensitive to the *status quo* mortality rate. If the current mortality rate from opioid overdose is higher than in our base case (22%, as observed in Belz et al., 2006), then a school naloxone program appears dramatically more cost-effective. However, if current care in response to an overdose at a Toronto high school results in a mortality rate less than 5%, then it is unlikely a school naloxone program will reduce mortality enough to be cost-effective even if there are more than two overdoses per year.

Probabilistic sensitivity analysis indicated that at a willingness-to-pay of $50,000 per QALY-gained, the probability that a school-based naloxone program is cost-effective only exceeds 50% if there are more than two overdoses per year and the program reduces mortality by more than 27% or if there is more than one overdose per year and the program reduces mortality by more than 46% (Fig. 3). Even at a higher willingness-to-pay of $100,000 per QALY-gained, the probability that a school-based naloxone program is cost-effective is highly dependent on the expected number of overdoses per year and the program's effectiveness. If there is only one overdose every other year, the probability that the program is cost-effective is 0.1%, 2.9%, and 16.7% if the program reduces the probability of a fatal overdose by 15%, 27%, and 46%, respectively. If there is greater than one overdose per year, then the probability that a school-based naloxone program is cost-effective is 23%, even if the program only reduces mortality by 27%; the probability of being cost-effective increases to over 50% if the program reduces mortality by 46% or if the number of overdoses per year is greater than 2.

4. Discussion

We constructed a model to evaluate the cost-effectiveness of a school-based naloxone program in Toronto secondary schools. Distributing naloxone to individuals who are likely to be present at the time of the overdose (as with laypersons who are family or friends of a person with a known addiction to opioids) or whose response time can be extremely short because of relative ubiquity (as with police and fire services—and, in a school environment, teachers—compared to advanced life support paramedic services) aims to reduce the time from opioid exposure to naloxone administration, which increases the chances of survival. High schools present a comparably low-risk setting and so we performed our cost-effectiveness analysis not because the program is costly, but because it has unclear value.

We find that a school-based naloxone program is cost-effective at a willingness-to-pay of $50,000 per QALY-gained under the following conditions: if it reduces opioid poisoning mortality by at least 40% and there is at least one overdose per year; or, if it reduces mortality by at least 20% and there are at least two overdoses per year. A program with a modest effect on the mortality rate of 15%, as was seen in the first year after naloxone was provided to police services in one community (Rando et al., 2015), has an ICER less than $50,000 per QALY-gained only if there are, on average, 2.7 opioid overdoses across all 112 high schools in the TDSB each year. If the frequency of overdose is less than once every 2 years, then the program is not likely to be cost-effective (the mortality reduction needs to exceed 82%). While relatively low-cost on a per-school basis and relative to the total budget of the school board, low-cost alone does not make a program such as this a good use of resources. Several school-based prevention and harm reduction programs have been estimated to be cost-saving (e.g., sexually transmitted infections and pregnancy prevention programs (Wang et al., 2000); tobacco-use prevention program (Wang et al., 2001); and an asthma treatment program (Noyes et al., 2013)) and others appear to be more cost effective than a school-based naloxone program (e.g., childhood obesity prevention program (Ekwaru et al., 2017); an eating disorder screening program (Wright et al., 2014); and a cannabis-use prevention program (Deogan et al., 2015)).

Despite decreasing non-medical opioid drug use (Boak et al., 2017), the risk of overdose among young people is increasing due to an increase in fentanyl use, fentanyl contamination, and counterfeit drugs (Coroners Service of British Columbia, 2018a, b; Salvian, 2018; Special Advisory Committee on the Epidemic of Opioid Overdoses, 2018). However, the frequency of overdose in a school setting is unknown and the ability of teachers to recognize the appropriate signs and symptoms is uncertain. It is known that response time is critical to survival and programs that have equipped non-medical first responders and laypeople with naloxone improve survival outcomes (Giglio et al., 2015). In Toronto, approximately 10% of overdoses that emergency medical services responded to resulted in death when naloxone had not been administered (City of Toronto, 2018). For a school-based naloxone program to be cost-effective, the expected number of opioid poisonings occurring within Toronto high-schools needs to exceed one each year and trained staff need to effectively recognize and respond to opioid poisoning rapidly in order to reduce overdose mortality by more than 40% (from 10% to < 6%).

Naloxone is safe, even when administered to an individual who has not been exposed to opioids, with few, extremely rare adverse effects

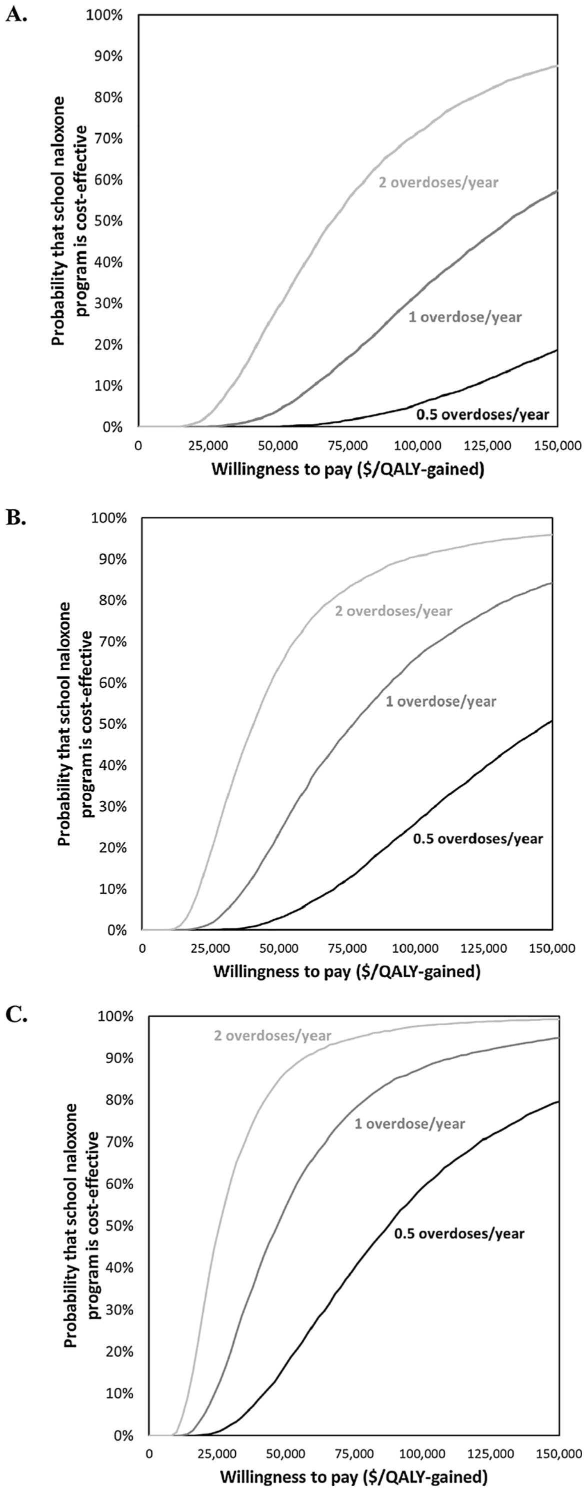

Fig. 3. Probabilistic sensitivity analysis. The probability that a school-based naloxone program is cost effective for different expected number of opioid poisonings per year for a program with (A) 15% mortality reduction; (B) 27% mortality reduction; and (C) 46% mortality reduction compared to the status quo (10.1% mortality). All input parameters were varied simultaneously with 5000 replications using distributions described in Supplemental Table 1.

(Cressman et al., 2017; Doyon et al., 2014; Kerensky and Walley, 2017; Wheeler et al., 2015). However, uncertainty in the nature of a medical emergency or the stress of an emergency situation may cause a bystander to hesitate, as has been observed with bystander resuscitation and AEDs in public spaces (Chan et al., 2014; Swor et al., 2013, 2006). For individuals with prior exposure to overdose, training may take as little as five minutes to one hour (Devries et al., 2017) but with individuals who have less exposure, training may be longer in duration to ensure confidence in preparedness (Panther et al., 2017). If higher intensity training is required to ensure high school staff are prepared and ready to use naloxone when a situation arises, then our analysis indicates that the frequency of overdose will need to be at least two per year for the program to be cost-effective.

Previous cost-effectiveness analyses, two based on US data, one on UK data, and one on Russian data, have evaluated the costs and benefits of distributing naloxone to individuals at high risk of opioid overdose via illicit injection drug use (Coffin and Sullivan, 2013a, b; Langham et al., 2018; Uyei et al., 2017). These analyses find that distributing intramuscular naloxone kits to individuals with an annual risk of overdose ranging from 7% to 20%, results in reducing the overall number of overdose deaths by about 6% (13% in the highest risk population) and is highly cost-effective with an incremental cost-effectiveness ratio below $2000 per QALY gained (USD). As these studies focused on distributing naloxone to populations at high risk of overdose, the results may not be immediately transferable to a secondary school setting where the frequency of overdose is expected to be low.

Our analysis has limitations including many simplifications. However, extensive sensitivity analysis reveals that our results are robust to uncertainty in most model parameters. Our model only considers whether or not naloxone in high schools is cost-effective compared to the status quo—it does not consider increasing access to drug use education (Golonka et al., 2017), harm reduction programs targeting youths (Toumbourou et al., 2007), or other social programs which may effectively prevent unsafe drug use, overdose, or overdose mortality. Youths are often especially at risk because they experiment with mixing drugs and increasing doses but are often not tied into harm reduction programs in which they may learn safer use practices including naloxone programs for drug users (Jenkins et al., 2017; Marshall et al., 2016; Toumbourou et al., 2007).

5. Conclusions

If the risk of an overdose in a Toronto high school is low, then other programs aimed at improving the health and wellbeing of students may be better use of limited resources. However, our analysis demonstrates that making naloxone available in TDSB secondary schools is likely to be cost-effective if there are at least two overdoses every year. High school students have relatively lower rates of opioid use for medical purposes than the general population, but have relatively high rates of non-medical use resulting in increasing rates of hospitalization (Boak et al., 2017; Canadian Centre on Substance Abuse, 2016; Canadian Centre on Substance Use and Addiction, 2017). If it is not yet cost-effective to equip high school staff with naloxone, it may be in the future. Naloxone can reverse opioid poisoning, but not the opioid crisis. Additional programs are necessary to reduce the number of opioid overdoses among Canadians overall and in youth specifically.

Contributors

GSZ conceived of the project; LEC and GSZ designed the model, implemented the model, acquired inputs, performed analyses, interpreted results, drafted and revised the article, and give final approval of the version submitted for review.

Conflict of interest

The authors declare no competing interests.

Acknowledgements

The authors thank Dr. Andrea Sereda, MD, London Intercommunity

Health and the Medical Director of the Western University Student Emergency Response Team, for her assistance with model assumptions. LEC is supported by the David G. Burgoyne Faculty Fellowship. GSZ is supported by the J. Allyn Taylor and Arthur H. Mingay Chair in Management Science.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2018.08.003.

References

American Heart Association, 2015. Part 10: Special Circumstances of Resuscitation. Available at: https://eccguidelines.heart.org/index.php/circulation/cpr-ecc-guidelines-2/part-10-special-circumstances-of-resuscitation/ (Accessed February 18 2018).

Baser, O., Chalk, M., Fiellin, D.A., Gastfriend, D.R., 2011. Cost and utilization outcomes of opioid-dependence treatments. Am. J. Manag. Care 17 (Suppl. 8), S235–S248.

Belz, D., Lieb, J., Rea, T., Eisenberg, M.S., 2006. Naloxone use in a tiered-response emergency medical services system. Prehosp. Emergy Care 10, 468–471.

Bennett, S., 2018. Teen's Alleged Overdose at School Highlights Citywide Opioid Abuse Increase. Available at: https://katv.com/news/local/teens-alleged-overdose-at-school-highlights-citywide-opioid-abuse-increase (Accessed February 8, 2018).

Boak, A., Hamilton, H.A., Adlaf, E.M., Mann, R.E., 2017. Drug Use Among Ontario Students, 1977-2017: Detailed Findings From the Ontario Student Drug Use and Health Survey (OSDUHS). CAMH Research Document Series No. 46. Centre for Addiction and Mental Health, Toronto, ON.

Campbell, M., 2017. LDSB [Limestone District School Board] Putting Naloxone Kits in High Schools Across the District. Available at: https://globalnews.ca/news/3873404/ldsb-putting-naloxone-kits-in-high-schools-across-the-district/ (Accessed: November 21, 2017).

Canadian Agency for Drugs and Technologies in Health (CADTH), 2017. Guidelines for the Economic Evaluation of Health Technologies: Canada (4th edition). Available at:. Ottawa. https://www.cadth.ca/about-cadth/how-we-do-it/methods-and-guidelines/guidelines-for-the-economic-evaluation-of-health-technologies-canada.

Canadian Centre on Substance Abuse, 2016. Hospitalizations and Emergency Department Visits Due to Opioid Poisoning in Canada. Canadian Institute for Health Information. Available at: https://secure.cihi.ca/free_products/Opioid%20Poisoning%20Report%20%20EN.pdf.

Canadian Centre on Substance Use and Addiction, 2017. Prescription Opioids, Canadian Drug Summary. Available at. http://www.ccsa.ca/Eng/Pages/default.aspx.

Canadian Institute for Health Information (CIHI), 2016. National Health Expenditure Trends, 1975 to 2016. Available at:. . https://secure.cihi.ca/free_products/NHEX-Trends-Narrative-Report_2016_EN.pdf.

Canadian Pharmacists Association, 2017. Environmental Scan: Access to Naloxone Across Canada. Available at: https://www.pharmacists.ca/cpha-ca/assets/File/cpha-on-the-issues/Environmental%20Scan%20-%20Access%20to%20Naloxone%20Across%20Canada_Final.pdf (Accessed: November 2017).

Canadian Red Cross, 2018. Standard Child Care First Aid and CPR. Available at: http://www.redcross.ca/training-and-certification/course-descriptions/first-aid-at-home-courses/standard-child-care-first-aid—cpr (Accessed February 16 2018).

Chan, P.S., McNally, B., Tang, F., Kellermann, A., Group, C.S., 2014. Recent trends in survival from out-of-hospital cardiac arrest in the United States. Circulation 130, 1876–1882.

City of Toronto, 2017. Analyst Notes - Operating Budget - Toronto Paramedic Services. Available at: https://www.toronto.ca/legdocs/mmis/2017/ex/bgrd/backgroundfile-100586.pdf (Accessed February 12 2018).

City of Toronto, 2018. Toronto Overdose Information System. Available at: https://www.toronto.ca/community-people/health-wellness-care/health-inspections-monitoring/toronto-overdose-information-system/ (Accessed February 12 2018).

Clark, R.E., Samnaliev, M., McGovern, M.P., 2009. Impact of substance disorders on medical expenditures for medicaid beneficiaries with behavioral health disorders. Psychiatr. Serv. 60, 35–42.

Clark, A.K., Wilder, C.M., Winstanley, E.L., 2014. A systematic review of community opioid overdose prevention and naloxone distribution programs. J. Addict. Med. 8, 153–163.

Coffin, P.O., Sullivan, S.D., 2013a. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. Ann. Intern. Med. 158, 1–9.

Coffin, P.O., Sullivan, S.D., 2013b. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal in Russian cities. J. Med. Econ. 16, 1051–1060.

Coroners Service of British Columbia, 2018a. Fentanyl-Detected Illicit Drug Overdose Deaths (2012-2018) [last Updated May 10, 2018], Statistical Reports Into B.C. Fatalities. British Columbia. Available at:. . https://www2.gov.bc.ca/gov/content/safety/public-safety/death-investigation/statistical-reports.

Coroners Service of British Columbia, 2018b. Illicit Drug Overdose Deaths in BC: January 1, 2008 – May 31, 2018 (Accessed July 28 2018). Available at:. https://www2.gov.bc.ca/assets/gov/public-safety-and-emergency-services/death-investigation/statistical/illicit-drug.pdf.

Craig, M., 2017. It Rips a Part of You Away': Grieving Saskatoon Father Speaks Out Against Fentanyl (Accessed: June 14, 2017). Available at:. https://globalnews.ca/news/3529021/it-rips-a-part-of-you-away-grieving-saskatoon-father-speaks-out-against-fentanyl/.

Cressman, A.M., Mazereeuw, G., Guan, Q., Jia, W., Gomes, T., Juurlink, D.N., 2017. Availability of naloxone in Canadian pharmacies: a population-based survey. CMAJ Open 5, e779–e784.

D'Amato, L., 2017. Grieving Mom Has No Answers After 14-year-old Son Dies From Fentanyl Overdose (Accessed: October 28, 2017). Available at:. https://www.therecord.com/opinion-story/7689792-grieving-mom-has-no-answers-after-14-year-old-son-dies-from-fentanyl-overdose.

Dangerfield, K., 2017. Canadian Schools Stock up on Naloxone Kits in Wake of Growing Opioid Crisis (Accessed: September 5, 2017). Available at:. https://globalnews.ca/news/3718201/canadian-schools-stock-up-on-naloxone-kits-in-wake-of-growing-opioid-crisis.

Davis, C.S., Ruiz, S., Glynn, P., Picariello, G., Walley, A.Y., 2014. Expanded access to naloxone among firefighters, police officers, and emergency medical technicians in Massachusetts. Am. J. Public Health 104, e7–e9.

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M., McLaren, J., 2011. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction 106, 32–51.

Deogan, C., Zarabi, N., Stenstrom, N., Hogberg, P., Skarstrand, E., Manrique-Garcia, E., Neovius, K., Mansdotter, A., 2015. Cost-effectiveness of school-based prevention of cannabis use. Appl. Health Econ. Health Policy 13, 525–542.

Devries, J., Rafie, S., Polston, G., 2017. Implementing an overdose education and naloxone distribution program in a health system. J. Am. Pharm. Assoc. 57, S154–S160.

Doe-Simkins, M., Quinn, E., Xuan, Z., Sorensen-Alawad, A., Hackman, H., Ozonoff, A., Walley, A.Y., 2014. Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: a retrospective cohort study. BMC Public Health 14, 297.

Doyon, S., Aks, S.E., Schaeffer, S., 2014. Expanding access to naloxone in the United States. J. Med. Toxicol. 10, 431–434.

Ekwaru, J.P., Ohinmaa, A., Tran, B.X., Setayeshgar, S., Johnson, J.A., Veugelers, P.J., 2017. Cost-effectiveness of a school-based health promotion program in Canada: a life-course modeling approach. PLoS One 12, e0177848.

Enteen, L., Bauer, J., McLean, R., Wheeler, E., Huriaux, E., Kral, A.H., Bamberger, J.D., 2010. Overdose prevention and naloxone prescription for opioid users in San Francisco. J. Urban Health 87, 931–941.

Ferguson, E., 2018. Alberta Schools Adding Anti-overdose Kits, Training Teachers to Use (Accessed: March 21, 2018). Available at:. https://calgaryherald.com/news/local-news/alberta-schools-adding-anti-overdose-kits-training-teachers-to-use.

Fisher, R., O'Donnell, D., Ray, B., Rusyniak, D., 2016. Police officers can safely and effectively administer intranasal naloxone. Prehosp. Emerg. Care 20, 675–680.

Giglio, R.E., Li, G., DiMaggio, C.J., 2015. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. Injury Epidemiol. 2, 10.

Golonka, M.M., Peairs, K.F., Malone, P.S., Grimes, C.L., Costanzo, P.R., 2017. Natural peer leaders as substance use prevention agents: the Teens' Life Choice Project. Prev. Sci. 18, 555–566.

Griffiths, E.A., Vadlamudi, N.K., 2016. Abstract PHP278: CADTH's $50,000 cost-effectiveness threshold: fact or fiction? Value Heatlh 19, A488–A489.

Guertin, J.R., Feeny, D., Tarride, J.E., 2018. Age- and sex-specific Canadian utility norms, based on the 2013-2014 Canadian Community Health Survey. CMAJ 190, E155–E161.

Hamadi, R., 2018. TDSB Approves Plan to Stock Naloxone Kits in High Schools. Available at: http://www.cbc.ca/news/canada/toronto/tdsb-naloxone-high-schools-1.4526114 (Accessed February 12 2018).

Howlett, K., 2017. Canada's Black Market for Illicit Drug Fentanyl Booming. Available at: https://www.theglobeandmail.com/news/national/canadas-black-market-for-drug-fentanyl-booming/article34116506/ (Accessed February 16 2018).

Hsu, D.J., McCarthy, E.P., Stevens, J.P., Mukamal, K.J., 2017. Hospitalizations, costs and outcomes associated with heroin and prescription opioid overdoses in the United States 2001-12. Addiction 112, 1558–1564.

Hudes, S., Powell, B., 2017. 2 Teens Found Dead in Etobicoke Highrise. Available at: https://www.thestar.com/news/gta/2017/08/02/2-women-found-dead-in-etobicoke-high-rise.html (Accessed: August 2, 2017).

Husereau, D., Drummond, M., Petrou, S., Carswell, C., Moher, D., Greenberg, D., Augustovski, F., Briggs, A.H., Mauskopf, J., Loder, E., 2013. Consolidated health economic evaluation reporting standards (CHEERS) statement. Value Health 16, e1–5.

Jenkins, E.K., Slemon, A., Haines-Saah, R.J., 2017. Developing harm reduction in the context of youth substance use: insights from a multi-site qualitative analysis of young people's harm minimization strategies. Harm Reduct. J. 14, 53.

Kane, J.M., Colvin, J.D., Bartlett, A.H., Hall, M., 2018. Opioid-related critical care resource use in US children's hospitals. Pediatrics 141 e20173335.

Kerensky, T., Walley, A.Y., 2017. Opioid overdose prevention and naloxone rescue kits: what we know and what we don't know. Addict. Sci. Clin. Pract. 12, 4.

Kim, D., Irwin, K.S., Khoshnood, K., 2009. Expanded access to naloxone: options for critical response to the epidemic of opioid overdose mortality. Am. J. Public Health 99, 402–407.

King, R., 2016. Science over stigma: saving lives–implementation of naloxone use in the school setting. NASN Sch. Nurse 31, 96–101.

King, R., Embrey, M., 2016. Naloxone use in the school setting–the role of the school nurse: position statement. NASN Sch. Nurse 31, 119–120.

Lake, H., 2014. Three Teens Overdose on Prescription Drugs in the Middle of the School. Available at: https://katu.com/news/local/three-teens-overdose-on-prescription-drugs-in-the-middle-of-the-school-day (Accessed: January 16, 2014).

Langham, S., Wright, A., Kenworthy, J., Grieve, R., Dunlop, W.C.N., 2018. Cost-effectiveness of take-home naloxone for the prevention of overdose fatalities among heroin users in the United Kingdom. Value Health 21, 407–415.
Larsen, K., 2017. B.C. Teen Who Died of an Overdose Thought She Was Taking MDMA. Available at: http://www.cbc.ca/news/canada/british-columbia/16-year-old-overdose-victim-thought-she-was-taking-mdma-1.4136010 (Accessed: May 30, 2017).
Lewis, D.A., Park, J.N., Vail, L., Sine, M., Welsh, C., Sherman, S.G., 2016. Evaluation of the overdose education and naloxone distribution program of the baltimore student harm reduction coalition. Am. J. Public Health 106, 1243–1246.
Living in Canada, 2018. Registered Nurse Salary Canada. Available at: https://www.livingin-canada.com/salaries-for-registered-nurses.html.
Luetzen, K., 2017. Montana High School Student Dies After Prescription Drug Overdose. Available at: http://www.kbzk.com/story/36997188/montana-high-school-student-dies-after-prescription-drug-overdose (Acessed: December 5, 2017).
Marshall, B.D., Green, T.C., Yedinak, J.L., Hadland, S.E., 2016. Harm reduction for young people who use prescription opioids extra-medically: obstacles and opportunities. Int. J. Drug Policy 31, 25–31.
Mathers, B.M., Degenhardt, L., Bucello, C., Lemon, J., Wiessing, L., Hickman, M., 2013. Mortality among people who inject drugs: a systematic review and meta-analysis. Bull. World Health Organ. 91, 102–123.
Michaels, L., 2018. Naloxone Kits Coming to Lambton-Kent High Schools. Available at: http://blackburnnews.com/sarnia/sarnia-news/2018/02/01/naloxone-kits-coming-lambton-kent-high-schools/ (Accessed: February 1, 2018).
Milloy, M.J., Kerr, T., Tyndall, M., Montaner, J., Wood, E., 2008. Estimated drug overdose deaths averted by North America's first medically-supervised safer injection facility. PLoS One 3, e3351.
Postmedia News, 2017. Chloe Had a Spark of Life in Her That Was Pure Sunshine': Ottawa-area School Mourns Death of Teen in Apparent Overdose. Available at: http://nationalpost.com/news/canada/chloe-had-a-spark-of-life-in-her-that-was-pure-sunshine-kanata-school-mourns-death-of-teen-in-apparent-overdose (Acceessed: February 16, 2017).
North Carolina Harm Reduction Coalition, 2018. Naloxone 101. Available at: http://www.nchrc.org/programs-and-services/naloxone-101/ (Accessed February 16 2018).
Noyes, K., Bajorska, A., Fisher, S., Sauer, J., Fagnano, M., Halterman, J.S., 2013. Cost-effectiveness of the school-based asthma therapy (SBAT) program. Pediatrics 131, e709–e717.
Ontario Ministry of Finance, 2017. Ontario Savings Bonds (2017 Series, Fixed rate, 10 year). Available at:. https://ontariosavingsbonds.com/en/index.html.
Ontario Ministry of Health and Long-Term Care (Ontario MOHLTC), 2016. OHIP Schedule of Benefits and Fees (version Amended April 1, 2016). Available at. Ontario Health Insurance Plan. http://www.health.gov.on.ca/en/pro/programs/ohip/sob.
Ontario Ministry of Health and Long-Term Care (Ontario MOHLTC), 2017. Ontario Public Drug Programs: Naloxone. Available at:. http://www.health.gov.on.ca/en/pro/programs/drugs/naloxone.
Ontario Secondary School Teachers' Federation, 2014. Collective Agreement Between the Toronto District School Board and the Ontario Secondary School Teachers Federation. Available at:. https://osstftoronto.ca/wp-content/uploads/2014/01/2014-2019-OSSTF-Collective-Agreement-Final-1.pdf.
Outhit, J., 2018. Public Board Schools Won't Stock Life-saving Naloxone Kits. Available at: https://www.therecord.com/news-story/8132019-public-board-schools-won-t-stock-life-saving-naloxone-kits/ (Accessed: February 13, 2018).
Panther, S.G., Bray, B.S., White, J.R., 2017. The implementation of a naloxone rescue program in university students. J. Am. Pharm. Assoc. 57, S107–S112 e102.
Pennsylvania Department of Health, 2018. Naloxone Program for Schools. Available at: https://www.health.pa.gov/topics/school/Pages/Naloxone%20Program.aspx (Accessed May 23 2018).
Rando, J., Broering, D., Olson, J.E., Marco, C., Evans, S.B., 2015. Intranasal naloxone administration by police first responders is associated with decreased opioid overdose deaths. Am. J. Emerg. Med. 33, 1201–1204.
Rizza, A., 2018. Toronto District School Board High Schools to Get Opioid Overdose Kits. Available at: https://www.thestar.com/news/gta/2018/02/08/toronto-district-school-board-high-schools-to-get-opioid-overdose-kits.html (Accessed: February 8 2018).
Salvian, H., 2018. Kitchener Mom Who Lost Her Son to Fentanyl on a Mission to Tell His Story. Available at: https://www.cbc.ca/news/canada/kitchener-waterloo/zion-farrell-fentanyl-death-opiod-crisis-panel-1.4564239 (Accessed: March 6, 2018).
Smart, A., 2018. Victoria Teen's Accidental Overdose Started With Prescription Drugs, Parents Say. Available at: http://www.cbc.ca/news/canada/british-columbia/elliot-eurchuk-victoria-overdose-death-1.4630297 (Accessed: April 21, 2018).
Special Advisory Committee on the Epidemic of Opioid Overdoses, 2018. National Report: Apparent Opioid-related Deaths in Canada (January 2016 to September 2017) Web-based Report. Available at:. Public Health Agency of Canada; Ottawa. https://www.canada.ca/en/public-health/services/publications/healthy-living/national-report-apparent-opioid-related-deaths-released-march-2018.html#a2.2.
Statistics Canada, 2015. Life Tables, Canada, Provinces and Territories 2009 to 2011 (Product 84-537-X). Available at:. http://www.statcan.gc.ca/pub/84-537-x/84-537-x2013005-eng.htm.
Statistics Canada, 2017. Table D.2.1 Annual Statutory Teachers' Salaries in Public Institutions, by Level of Education Taught and Teaching Experience, Canadian Dollars, Canada, Provinces and Territories, 2014/2015 Education Indicators in Canada: an International Perspective Catalogue no. 81-604-X. Available at:. http://www.statcan.gc.ca/pub/81-604-x/81-604-x2017001-eng.htm.
Statistics Canada, 2018. Consumer Price Index, Historical Summary (1998 to 2017). CANSIM, Table 326-0021 and Catalogue nos. 62-001-X, 62-010-X and 62-557-X. Available at:. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/econ46a-eng.htm.
Sumner, S.A., Mercado-Crespo, M.C., Spelke, M.B., Paulozzi, L., Sugerman, D.E., Hillis, S.D., Stanley, C., 2016. Use of naloxone by emergency medical services during opioid drug overdose resuscitation efforts. Prehosp. Emerg. Care 20, 220–225.
Swor, R., Khan, I., Domeier, R., Honeycutt, L., Chu, K., Compton, S., 2006. CPR training and CPR performance: do CPR-trained bystanders perform CPR? Acad. Emerg. Med. 13, 596–601.
Swor, R., Grace, H., McGovern, H., Weiner, M., Walton, E., 2013. Cardiac arrests in schools: assessing use of automated external defibrillators (AED) on school campuses. Resuscitation 84, 426–429.
The Recovery Village, 2018. Narcan in Schools | Narcan Policy and Procedure for Schools. Available at: https://www.therecoveryvillage.com/narcan-addiction/narcan-in-schools/#gref (Accessed July 28 2018).
Tomassoni, A.J., Hawk, K.F., Jubanyik, K., Nogee, D.P., Durant, T., Lynch, K.L., Patel, R., Dinh, D., Ulrich, A., D'Onofrio, G., 2017. Multiple fentanyl overdoses - New Haven, Connecticut, June 23, 2016. MMWR Morb. Mortal. Wkly. Report 66, 107–111.
Toronto District School Board, 2017. Consolidated Financial Statements of the Toronto District School Board. Available at: http://www.tdsb.on.ca/Portals/0/docs/TorontoDistrictSchoolBoardIAR0817FinalOriginalSigned.pdf (Accessed February 12 2018).
Toronto District School Board, 2018. Our Students. Available at: http://www.tdsb.on.ca/About-Us/Students (Accessed April 5 2018).
Toronto Public Health, 2017. Toronto Overdose Action Plan: Prevention and Response. Available at: https://web.toronto.ca/wp-content/uploads/2017/08/968f-Toronto-Overdose-Action-Plan.pdf (Accessed February 12 2018).
Toumbourou, J.W., Stockwell, T., Neighbors, C., Marlatt, G.A., Sturge, J., Rehm, J., 2007. Interventions to reduce harm associated with adolescent substance use. Lancet 369, 1391–1401.
Uyei, J., Fiellin, D.A., Buchelli, M., Rodriguez-Santana, R., Braithwaite, R.S., 2017. Effects of naloxone distribution alone or in combination with addiction treatment with or without pre-exposure prophylaxis for HIV prevention in people who inject drugs: a cost-effectiveness modelling study. Lancet Public Health 2, e133–e140.
Walley, A.Y., Xuan, Z., Hackman, H.H., Quinn, E., Doe-Simkins, M., Sorensen-Alawad, A., Ruiz, S., Ozonoff, A., 2013. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ 346, f174.
Wang, L.Y., Davis, M., Robin, L., Collins, J., Coyle, K., Baumler, E., 2000. Economic evaluation of Safer Choices: a school-based human immunodeficiency virus, other sexually transmitted diseases, and pregnancy prevention program. Arch. Pediatr. Adolesc. Med. 154, 1017–1024.
Wang, L.Y., Crossett, L.S., Lowry, R., Sussman, S., Dent, C.W., 2001. Cost-effectiveness of a school-based tobacco-use prevention program. Arch. Pediatr. Adolesc. Med. 155, 1043–1050.
Weiner, S., Baker, O., Bernson, D., Schuur, J., 2017. One-year mortality of opioid overdose victims who received naloxone by emergency medical services. 402. Annal. Emerg. Med. 70, S158.
Wells, N., 2017. B.C. School Trustee Pushes for Province-wide Naloxone Kits. Available at: https://www.ctvnews.ca/health/b-c-school-trustee-pushes-for-province-wide-naloxone-kits-1.3606173 (Accessed: September 26, 2017).
Wermeling, D.P., 2015. Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. Ther. Adv. Drug Saf. 6, 20–31.
Wheeler, E., Jones, T.S., Gilbert, M.K., Davidson, P.J., 2015. Opioid overdose prevention programs providing naloxone to laypersons - United States, 2014. MMWR Morb. Mortal. Wkly. Rep. 64, 631–635.
Wright, D.R., Austin, S.B., LeAnn Noh, H., Jiang, Y., Sonneville, K.R., 2014. The cost-effectiveness of school-based eating disorder screening. Am. J. Public Health 104, 1774–1782.
Wu, L.T., Zhu, H., Swartz, M.S., 2016. Treatment utilization among persons with opioid use disorder in the United States. Drug Alcohol Depend. 169, 117–127.
Yokell, M.A., Delgado, M.K., Zaller, N.D., Wang, N.E., McGowan, S.K., Green, T.C., 2014. Presentation of prescription and nonprescription opioid overdoses to US emergency departments. JAMA Intern. Med. 174, 2034–2037.
Zussman, R., McArthur, A., 2018. After a 15-year-old's Opioid Overdose Death, B.C. Looks at Giving Parents More Rights. Available at: https://globalnews.ca/news/4031222/bc-opioid-overdose-parents-rights/ (Accessed: February 16, 2018).