

Factors associated with drug shortages in Canada: a retrospective cohort study

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Abstract

Background: To monitor the magnitude of the drug shortage problem in Canada, since 2017, Health Canada has required manufacturers to report drug shortages. This study aimed to identify the factors associated with drug shortages in Canada.

Methods: We conducted a retrospective cohort study of all prescription drugs available on the market between Mar. 14, 2017, and Sept. 12, 2018, in Canada. All drugs of the same active ingredient, dosage form, route of administration and strength were grouped into a “market.” Our main outcome was shortages at the market level, determined using the Drug Shortages Canada database. We used logistic regression to identify associated factors such as market structure, route or dosage form, and Anatomic Therapeutic Chemical (ATC) classification.

Results: Among the 3470 markets included in our analysis, 13.3% were reported to be in shortage. Markets with a single generic manufacturer were more likely to be in shortage than other markets. Markets with oral nonsolid route or dosage form were more likely to be in shortage than those that were oral solid with regular release (odds ratio [OR] 1.66, 95% confidence interval [CI] 1.11 to 2.49). Markets for sensory organs were more likely to be in shortage than most other ATC classes. Markets with a higher proportion of drugs covered by public insurance programs were more likely to be in shortage (OR 1.03, 95% CI 1.00 to 1.05 per 10% increase).

Interpretation: Markets with a single generic manufacturer were most likely to be in shortage. To ensure the security of drug supply, governments should be vigilant in monitoring markets with a single generic manufacturer, with complex manufacturing processes, with higher demand from public programs or those that are in certain ATC classes.

Shortages of EpiPen for severe allergies,¹⁻³ opioid drugs⁴⁻⁶ and bupropion for mental illnesses⁷ have recently made headlines in Canada and globally. Such shortages can have severe, even life-threatening, consequences for patients.⁸ For example, shortages in generic intravenous norepinephrine are associated with increased mortality among patients with septic shock.⁹ Opioid shortages increase the risk for medication errors (e.g., delayed time to analgesia, adverse effects) when patients are administered a less familiar alternative, which leads to unnecessary patient suffering and longer hospital stays.^{4,10} In addition, drug shortages can aggravate the stress and burden on physicians and pharmacists and increase labour costs when they have to change their practices because of drug shortages.^{8,10}

Empirical studies of the causes of drug shortages have tended to use the longitudinal, high-quality drug shortage data provided by the US Food and Drug Administration¹¹ and American Society of Health-System Pharmacists.¹² These studies have identified manufacturing-quality problems for sterile injectable drugs,^{13,14} declines in the number of suppliers for

sterile injectable drugs¹⁴ and lower drug prices for vaccine and generic drugs¹⁵⁻¹⁷ as reasons for shortages in the United States.

Empirical evidence from Canada is sparse because of a lack of reliable data on drug shortages.¹⁸⁻²¹ Although Canadian drug manufacturers have voluntarily reported shortage data since 2011, these data were incomplete and unreliable for

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research purposes. On Mar. 14, 2017, manufacturers were required to report timely information on drug shortages to Health Canada.^{19,21-23} In this study, we aimed to identify the major factors associated with drug shortages in Canada using the drug shortage information available after such reporting was mandatory.

Methods

Study design

We conducted a retrospective cohort study of all prescription drugs available on the market between Mar. 14, 2017, and Sept. 12, 2018, in Canada.

Data sources

Manufacturers are required to report drug shortages on the Drug Shortages Canada website.²² A shortage is a situation in which a manufacturer is unable to meet the demand for a drug that has been approved in Canada.²² The drug shortage database, starting from Mar. 14, 2017 (start of mandatory reporting) to Sept. 12, 2018, was extracted from the website. All ongoing shortages as of Mar. 14, 2017, and all new shortages that occurred during the study period, were included in the study. The database contains information on the package size of each drug identification number (DIN) that was reported in shortage. The DIN uniquely identifies a drug's active ingredients, strength, dosage form, route of administration and manufacturer. More information on the shortage reporting and database, and other data sources (Health Cana-

da's Drug Product Database,²⁴ Canadian Institute for Health Information²⁵ and PharmaClik²⁶), can be found in Table 1 and Appendix 1, available at www.cmajopen.ca/content/8/3/E535/suppl/DC1.

Study sample and variables

Our study sample consisted of all prescription drugs marketed in Canada from Mar. 14, 2017, to Sept. 12, 2018. Each DIN was followed from Mar. 14, 2017 (already marketed) until the last day it was actively marketed during the study period. Following the methods of Danzon and Furukawa²⁷ and Dave and colleagues,¹⁷ we organized DINs of all products with the same active ingredients, dosage form, route of administration and strength into a group and called the group a "market."

The variables extracted from the Drug Shortages Canada website (D.G.), Health Canada's Drug Product Database (D.G.), PharmaClik and the Canadian Institute for Health Information are outlined in Table 1. The data to identify variables were not extracted from the source databases in duplicate.

Outcomes and factors

Our focus was on shortages at the market level, which occur when all manufacturers of the same interchangeable drug report shortages. We also evaluated shortages at the DIN level, indicating that some but not all manufacturers of the drug reported a shortage. Furthermore, we calculated the duration of shortages (total number of days in shortage during the study period) at the market and DIN levels.

Table 1: Data sources

Database	Data field extracted and used	Time period or extract version	Source
Drug Shortages Canada Database	DIN,* package size, actual shortage start date, shortage reasons (shortage of an active ingredient, shortage of an inactive ingredient or component, disruption of the manufacture of the drug, requirements related to complying with good manufacturing practices, delay in shipping of the drug, demand increase for the drug, or other), estimated shortage end date and actual shortage end date, if available	Mar. 14, 2017 to Sept. 12, 2018	Drug Shortages Canada website ²²
Drug Product Database	DIN, drug name, active ingredient(s), strength, dosage form, route of administration, manufacturer, package size, Active Ingredient Group number,† Anatomic Therapeutic Chemical classification, schedule (e.g., prescription, <i>Controlled Drugs and Substances Act</i> , biological, over-the-counter, "ethical" products‡), market status (marketed, cancelled, dormant) and status date	Data extracted were last updated by Health Canada on Apr. 12, 2019	Health Canada ²⁴
Formulary data for 9 provinces in Canada§	DIN; brand generic code that indicates whether a drug is a brand, generic or biologic; plan or program; formulary coverage start date and end date and the listed price, if available	April 2008 to Mar. 31, 2017	Canadian Institute for Health Information ²⁵
PharmaClik	DIN, package size¶	Catalogue downloaded on Oct. 10, 2018	McKesson Canada ²⁶

Note: DIN = Drug Identification Number.

*DIN uniquely identifies a drug's active ingredients, strength, dosage form, route of administration and manufacturer.

†A 10-digit number that identifies products that have the same active ingredient(s) and ingredient strength(s).

‡Drugs that do not require a prescription but are generally prescribed by medical practitioners for unscheduled professional use and emergency use.

§Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island and Saskatchewan.

¶Used to supplement the package code information obtained from the Drug Product Database.

We considered the following factors to be potentially associated with drug shortages at the market level, based on previous studies^{14–17} and our available data:

- market structure (branded manufacturers only, branded manufacturers and a single generic manufacturer, branded manufacturers and multiple generic manufacturers, biologic manufacturers, a single generic manufacturer only, and multiple generic manufacturers) at baseline, where baseline was defined as the first 30 days of the follow-up period;
- route of administration or dosage form (oral solid regular release, oral solid special release, injection, oral nonsolid, other route or form [such as topical cream or ointment, ophthalmic solution, inhalation solution, inhalation powder, transdermal patch or nasal spray]), in which injection, oral nonsolid and other route or form are more complex from a manufacturing viewpoint than oral solids;^{27,28}
- essential medicines or not, which refer to “those that satisfy the priority health care needs of the population”^{29,30} and were defined using the list from a report of the Patented Medicine Prices Review Board;³⁰
- proportion of DINs listed on formularies in at least 1 of the provinces (excluding Quebec); and
- Anatomic Therapeutic Chemical (ATC) classification.³¹

At the DIN level, we considered some additional factors, including DIN age (duration from when the DIN came to market to the start of follow-up), the number of provinces on formulary (the number of provincial formularies on which the DIN was listed weighted by the population size in each province), top 50 manufacturers (based on drug cost from public drug plans in Canada in 2017/18),³² manufacturer size (total number of DINs available in Canada) and type of manufacturers (proportion of branded DINs). Detailed definitions can be found in Appendix 2, available at www.cmajopen.ca/content/8/3/E535/suppl/DC1.

Statistical analysis

We used logistic regression to model shortages. We modeled shortage duration using a zero-truncated negative binomial regression model because of its skewed data distribution (Appendix 3, available at www.cmajopen.ca/content/8/3/E535/suppl/DC1), where the offset is the natural log of the follow-up time. Factors that were included in the final regression models were determined by their univariate analysis results ($p < 0.2$) and the Akaike information criteria.³³ Owing to the differences in terms of drug shortages and the factors between generic DINs and branded DINs, we conducted the analyses for generic and branded DINs separately. We also conducted a subgroup analysis among DINs that were listed on provincial formularies by considering their listing price²⁵ as an additional factor. We conducted sensitivity analyses by defining “market” by active ingredients, dosage form and route of administration. We conducted all the analyses using SAS version 9.4 (SAS Institute).

Ethics approval

Ethics approval was not required because our focus is on market-level data.

Results

Shortage at the market level

Our analysis consisted of 3470 markets (9472 DINs, flow diagram in Appendix 4, Supplementary Figure 1, available at www.cmajopen.ca/content/8/3/E535/suppl/DC1). About 13.3% of markets ($n = 462$) were reported in shortage, and the average number of days in shortage was 136.6 (standard deviation [SD] 149.2) during our study period (Table 2; Appendix 4, Supplementary Table 1). Markets with a single generic manufacturer, oral nonsolid route or form, other complex route or form, or for sensory organs had a higher probability of being in shortage. More description is in Appendix 4.

The multivariable logistic regression results (Table 3) show that compared with markets with branded manufacturers and a single generic manufacturer, markets with a single generic manufacturer were more likely to be in shortage (odds ratio [OR] 1.99, 95% confidence interval [CI] 1.28 to 3.11), whereas markets with multiple generic manufacturers with or without branded manufacturers were 87% or 43% less likely to be in shortage, respectively, during our study period. Markets with oral nonsolid route or form were 66% more likely to be in shortage than those with oral solid regular release route or form. The markets with a higher proportion of DINs on formularies were more likely to be in shortage (OR 1.03, 95% CI 1.00 to 1.05 per 10% increase). The sensory organ ATC class was more likely to be in shortage than all other ATC classes except the class of antiparasitic products, insecticides and repellents. The results of pairwise comparisons are also presented in Appendix 5, available at www.cmajopen.ca/content/8/3/E535/suppl/DC1.

Using a different definition of “market” in the sensitivity analysis, our results were similar except that markets with injection ($p = 0.06$) and other complex route or form ($p < 0.01$) were also more likely to be in shortage than those with oral solid regular release route or form, and that the odds of being in shortage were not different between the sensory organ ATC class and several other classes (Appendix 6, available at www.cmajopen.ca/content/8/3/E535/suppl/DC1).

Shortage at the DIN level

Among all 9472 DINs (2322 branded DINs, 6527 generic DINs and 623 biologic DINs), 2212 (23.4%) were reported in shortage and their average number of days in shortage was 155.3 (SD 146.2). Generic DINs had a higher probability of being in shortage and having a longer shortage duration than branded DINs (26.5% v. 18.3% in shortage [$p < 0.01$] and 167.6 [SD 149.1] v. 99.9 [SD 111.7] days [$p < 0.01$]; (Table 2; Appendix 4, Supplementary Table 1).

Table 4 presents the factors associated with shortage at the DIN level. For both branded and generic DINs, DINs in the markets with branded manufacturers and a single generic manufacturer were significantly more likely to be in shortage than DINs in other market structures. The DINs with older age were more likely to be in shortage. DINs for sensory organs were more likely to be in shortage than DINs for most of other ATC classes. However, branded

Table 2: Markets and DINs in drug shortage and shortage duration

Variable	Markets			Branded DINs			Generic DINs		
	Total, <i>n</i>	Markets in shortage, <i>n</i> (%)	Shortage duration,* mean days ± SD	Total, <i>n</i>	DINs in shortage <i>n</i> (%)	Shortage duration,* mean days ± SD	Total, <i>n</i>	DINs in shortage <i>n</i> (%)	Shortage duration,* mean days ± SD
All	3470	462 (13.3)	136.6 ± 149.2	2322	426 (18.3)	99.9 ± 111.7	6527	1730 (26.5)	167.6 ± 149.1
Market structure									
B and G single	208	31 (14.9)	134.5 ± 131.2	235	64 (27.2)	120.4 ± 124.7	214	73 (34.1)	163.2 ± 160.9
B and G multiple	620	13 (2.1)	126.5 ± 142.3	681	131 (19.2)	100.0 ± 109.9	4423	1169 (26.4)	162.5 ± 144.9
G single	454	124 (27.3)	187.2 ± 169.2				464	127 (27.4)	188.2 ± 169.3
G multiple	387	36 (9.3)	130.0 ± 158.1				1426	361 (25.3)	177.9 ± 152.2
BIO	484	49 (10.1)	192.1 ± 184.6						
B only	1317	209 (15.9)	95.6 ± 112.7	1406	231 (16.4)	94.1 ± 108.7			
Route of administration or form									
Injection	991	119 (12.0)	168.5 ± 170.3	323	59 (18.3)	105.3 ± 108.1	640	151 (23.6)	181.8 ± 163.1
Oral nonsolid	189	44 (23.3)	159.4 ± 170.8	123	23 (18.7)	108.6 ± 123.2	134	40 (29.9)	188.4 ± 164.7
Oral solid regular release	1513	154 (10.2)	132.6 ± 149.8	1195	198 (16.6)	104.3 ± 119.2	4789	1239 (25.9)	165.3 ± 145.7
Oral solid special release	238	25 (10.5)	84.0 ± 108.8	254	39 (15.4)	75.2 ± 108.3	526	144 (27.4)	179.6 ± 160.0
Other	539	120 (22.3)	112.5 ± 115.1	427	107 (25.1)	95.8 ± 97.9	438	156 (35.6)	156.0 ± 147.4
Essential medicine									
No	2981	388 (13.0)	136.5 ± 149.0	1945	361 (18.6)	103.3 ± 114.7	4923	1277 (25.9)	167.5 ± 149.6
Yes	489	74 (15.1)	137.2 ± 151.1	377	65 (17.2)	80.9 ± 91.5	1604	453 (28.2)	167.9 ± 147.9
On formulary†									
No	878	107 (12.2)	153.6 ± 168.0	512	83 (16.2)	116.8 ± 131.7	1171	222 (19.0)	154.8 ± 142.6
Yes	2592	355 (13.7)	131.5 ± 142.9	1810	343 (19.0)	95.8 ± 106.1	5356	1508 (28.2)	169.5 ± 150.0
DIN age, yr									
< 3				250	8 (3.2)	102.4 ± 105.7	1154	193 (16.7)	183.1 ± 153.7
≥ 3				2072	418 (20.2)	99.8 ± 111.9	5373	1537 (28.6)	165.7 ± 148.5
Top 50 manufacturers‡									
No				520	85 (16.3)	119.2 ± 105.8	1942	358 (18.4)	173.7 ± 149.1
Yes				1802	341 (18.9)	95.1 ± 112.8	4585	1372 (29.9)	166.1 ± 149.2
Manufacturer size§									
Small				731	78 (10.7)	115.8 ± 111.3	322	43 (13.4)	189.6 ± 186.8
Medium				682	143 (21.0)	112.4 ± 128.3	636	146 (23.0)	135.6 ± 119.5
Large				909	205 (22.6)	85.0 ± 97.1	5569	1541 (27.7)	170.1 ± 150.2

Note: B = branded manufacturer, BIO = biologic manufacturer, DIN = Drug Identification Number, G = generic manufacturer, SD = standard deviation.

*Shortage duration among those in shortage.

†On provincial formulary in at least 1 of the included provinces.

‡Top 50 manufacturers by drug cost from public drug plans in Canada in 2017/18.

§Manufacturer size was defined by the total number of DINs. Small: 1–40, Medium: 40–99, Large: 100+.

Table 3: Association between drug shortage and factors and its duration at the market level

Parameter or level	Shortage		Shortage duration*	
	OR (95% CI)	Coefficient (SE)	p value	Average marginal effect (95% CI)‡
Market structure (Ref.: B and G single)				
B and G multiple	0.13 (0.06 to 0.25)	-0.18 (0.38)	0.639	-23.5 (-121 to 80.6)
B only	1.15 (0.76 to 1.76)	-0.17 (0.23)	0.465	-22.0 (-104 to 32.0)
G single	1.99 (1.28 to 3.11)	0.51 (0.24)	0.034	95.9 (11.4 to 169.0)
G multiple	0.57 (0.34 to 0.97)	-0.19 (0.29)	0.502	-25.1 (-112 to 51.0)
BIO	1.13 (0.65 to 1.97)	0.34 (0.32)	0.283	58.2 (-57.9 to 167.4)
Overall p value†	< 0.001	< 0.001		
Route of administration or form (Ref.: oral solid regular release)				
Injection	1.14 (0.82 to 1.59)	0.05 (0.21)	0.831	7.2 (-58.2 to 75.7)
Oral nonsolid	1.66 (1.11 to 2.49)	0.27 (0.21)	0.204	47.1 (-22.7 to 130.1)
Oral solid special release	1.05 (0.66 to 1.68)	0.04 (0.27)	0.896	5.6 (-96.0 to 150.1)
Other	1.31 (0.89 to 1.91)	-0.01 (0.21)	0.942	-2.3 (-65.7 to 76.6)
Overall p value†	0.151	0.758		
Proportion of DINs on formulary				
Per 10% increase	1.03 (1.00 to 1.05)	-0.02 (0.01)	0.071	-3.8 (-8.3 to 0.5)§
Anatomic Therapeutic Chemical Classification (Ref.: sensory organs)				
Alimentary tract and metabolism	0.20 (0.10 to 0.38)	-0.40 (0.35)	0.255	-70.4 (-210 to 56.0)
Blood and blood-forming organs	0.08 (0.03 to 0.22)	-0.64 (0.56)	0.258	-100 (-262 to 100.9)
Cardiovascular system	0.51 (0.28 to 0.90)	-0.31 (0.29)	0.281	-57.5 (-204 to 56.1)
Dermatologicals	0.36 (0.20 to 0.64)	-0.07 (0.29)	0.803	-14.7 (-135 to 108.8)
Genitourinary system and sex hormones	0.55 (0.31 to 0.98)	-0.36 (0.30)	0.230	-64.2 (-196 to 46.1)
Systemic hormonal preparations, excluding sex hormones and insulins	0.30 (0.15 to 0.59)	-0.41 (0.38)	0.287	-71.2 (-216 to 67.5)
Anti-infectives for systemic use	0.43 (0.25 to 0.74)	-0.33 (0.31)	0.287	-59.7 (-194 to 51.9)
Antineoplastic and immunomodulating agents	0.18 (0.10 to 0.34)	-0.53 (0.37)	0.148	-88.3 (-232 to 54.7)
Musculoskeletal system	0.35 (0.17 to 0.73)	-0.01 (0.37)	0.970	-2.9 (-155 to 144.7)
Nervous system	0.35 (0.21 to 0.59)	-0.23 (0.28)	0.399	-44.5 (-170 to 65.4)
Antiparasitic products, insecticides and repellents	0.55 (0.10 to 2.89)	-1.03 (0.85)	0.225	-137 (-282 to -2.5)
Respiratory system	0.58 (0.34 to 0.99)	-0.44 (0.28)	0.111	-75.8 (-191 to 12.6)
Various	0.22 (0.11 to 0.47)	-0.18 (0.44)	0.676	-35.4 (-189 to 144.4)
Overall p value†	< 0.001	0.955		
Model fit statistics				
C-statistic	0.73			
AIC	2487.90	5540.4		
Log-likelihood	-1219.95	-2745.2		
<p>Note: AIC = Akaike information criteria, B = branded manufacturer, BIO = biologic manufacturer, CI = confidence interval, DIN = Drug Identification Number, G = generic manufacturer, OR = odds ratio, Ref. = reference category (0 or 1 as appropriate), SE = standard error. *Results were based on truncated negative binomial regression models among markets in shortage. †Based on type III Wald Test for shortage and type III likelihood ratio test for shortage duration. ‡The average marginal effect of a variable was evaluated as the average of predicted differences (from the reference group) at observed values of covariates for each observation; 95% CI were the bootstrap confidence intervals based on 2000 bootstrap samples. §For an increase from 80% to 90%.</p>				

DINs from branded manufacturers and top 50 manufacturers were less likely to be in shortage than those from other manufacturer types. Generic DINs from large or medium manufacturers irrespective of whether they were in the top

50 manufacturers, were all more likely to be in shortage than small manufacturers.

Essential medicines were marginally significantly associated with higher odds of being in shortage for generic DINs

Table 4: Association between drug shortage and factors at the DIN level		
Parameter or level	Branded DINs OR (95% CI)	Generic DINs OR (95% CI)
Market structure (Ref.: B and G single)		
B and G multiple	0.65 (0.45 to 0.94)	0.68 (0.49 to 0.93)
B only	0.68 (0.48 to 0.95)	
G single		0.65 (0.45 to 0.93)
G multiple		0.62 (0.45 to 0.86)
Overall <i>p</i> value*	0.048	0.036
DIN age (every year increase)		
DIN age, yr (Ref.: < 3)	1.02 (1.02 to 1.03)	
≥ 3		1.85 (1.55 to 2.21)
Route of administration or form (Ref.: oral solid regular release)		
Injection	1.16 (0.80 to 1.70)	1.29 (1.00 to 1.66)
Oral nonsolid	1.12 (0.67 to 1.89)	1.09 (0.73 to 1.65)
Oral solid special release	0.87 (0.59 to 1.28)	1.17 (0.94 to 1.45)
Other	1.28 (0.84 to 1.94)	1.23 (0.87 to 1.72)
Overall <i>p</i> value*	0.603	0.165
Interaction of manufacturer type and top 50 manufacturer (Ref.: branded = yes, top 50 = yes)		
Branded = no, top 50 = no	3.22 (1.91 to 5.44)	
Branded = no, top 50 = yes	2.23 (1.50 to 3.31)	
Branded = yes, top 50 = no	1.59 (1.13 to 2.25)	
Overall <i>p</i> value*	< 0.001	
Interaction of manufacturer size and top 50 manufacturer (Ref.: small)		
Large, top 50 = no		1.82 (1.25 to 2.64)
Large, top 50 = yes		2.40 (1.71 to 3.38)
Medium, top 50 = no		2.16 (1.45 to 3.23)
Medium, top 50 = yes		2.41 (1.39 to 4.17)
Overall <i>p</i> value*		< 0.001
Essential medicine (Ref.: no)		
Yes		1.13 (0.99 to 1.30)
Number of provinces on formulary (weighted)		
		1.09 (1.07 to 1.11)
Anatomic Therapeutic Chemical Classification (Ref.: sensory organs)		
Alimentary tract and metabolism	0.40 (0.20 to 0.81)	0.30 (0.18 to 0.50)
Blood and blood-forming organs	0.35 (0.14 to 0.86)	0.12 (0.05 to 0.30)
Cardiovascular system	0.57 (0.30 to 1.10)	0.35 (0.22 to 0.56)
Dermatologicals	0.51 (0.28 to 0.94)	0.37 (0.22 to 0.64)
Genitourinary system and sex hormones	0.45 (0.23 to 0.85)	0.42 (0.25 to 0.71)
Systemic hormonal preparations, excluding sex hormones and insulins	0.22 (0.10 to 0.51)	0.35 (0.18 to 0.70)
Anti-infectives for systemic use	0.31 (0.15 to 0.62)	0.41 (0.25 to 0.67)
Antineoplastic and immunomodulating agents	0.22 (0.11 to 0.45)	0.36 (0.21 to 0.63)
Musculoskeletal system	0.63 (0.27 to 1.43)	0.27 (0.16 to 0.45)
Nervous system	0.43 (0.23 to 0.79)	0.40 (0.25 to 0.64)
Antiparasitic products, insecticides and repellents	0.60 (0.10 to 3.60)	0.28 (0.08 to 0.92)
Respiratory system	0.64 (0.34 to 1.21)	0.48 (0.29 to 0.81)
Various	0.30 (0.09 to 0.97)	0.46 (0.17 to 1.23)
Overall <i>p</i> value*	0.004	< 0.001
Model fit statistics		
C-statistic	0.68	0.64
AIC	2126.38	7278.45
Log-likelihood	-1038.19	-3611.23
<p>Note: AIC = Akaike information criteria, B = branded manufacturer, CI = confidence interval, DIN = Drug Identification Number, G = generic manufacturer, OR = odds ratio, Ref.= reference category. *Based on type III Wald Test.</p>		

but not for branded DINs. Generic DINs listed on more provincial formularies were more likely to be in shortage. The subgroup analysis among DINs being listed on formularies shows that a lower listing price was marginally significantly associated with the shortage of branded DINs ($p = 0.06$) but not with the shortage of generic DINs (Appendix 7, available at www.cmajopen.ca/content/8/3/E535/suppl/DC1).

Shortage duration among markets and DINs

At the market level, markets with a single generic manufacturer tended to have a longer shortage duration (OR 95.9, 95% CI 11.4 to 169.0 more days) than those with branded manufacturers and a single generic manufacturer (Table 3). At the DIN level, disruption of the manufacturer, shortage of ingredients, delay in shipping not being the shortage reason, business reason, older DIN age, not being listed on formulary and smaller manufacturer size were associated with a longer shortage duration for branded DINs (Table 5). For generic DINs, disruption of the manufacturer, demand increase not being the shortage reason, business reason and being in sensory organs ATC class were associated with a longer shortage duration.

Interpretation

Our main finding is that markets with a single generic manufacturer were the most vulnerable to shortage during our study period. This did not occur for markets with a single branded manufacturer, suggesting that markets with a single supplier and relatively lower profit margins (related to the lower reimbursement price for generic drugs^{34,35}) may lead to shortages. Markets with complex routes or formulations were more susceptible to shortage, although generic pricing regulations have allowed a higher reimbursement price for non-oral solid drugs.^{34,35} Markets for sensory organs ATC class or with more demand from public insurance programs were more likely to be in shortage.

At the DIN level, when generic DINs or branded DINs were in the markets with branded manufacturers and a single generic manufacturer, they were the most likely to be in shortage. This might be driven by the combined impact of the generic competition, lower reimbursement price from public insurance programs^{34,35} and small market size that can accommodate only a single generic entrant. In addition, the newer branded or generic DINs were less likely to be in shortage. Possible reasons included the restriction of price increases for drugs by provincial governments,³⁶ the pan-Canadian tiered pricing framework for new generic drugs implemented on Apr. 1, 2017,^{34,35} large loss of market share for older branded DINs after generic entry³⁷⁻³⁹ or that manufacturers might pay more attention to the supply of the relatively newer products.

Some of our study findings are consistent with those from the US Government Accountability Office, which identified factors (a decline in the number of suppliers and drugs with sales of a generic version) that were strongly associated with shortages of sterile injectable anti-infective and cardiovascular drugs in 2012–2014 in the US.¹⁴ Dave

and colleagues found that special formulations, such as solutions and extended-release capsules, were associated with higher risks of generic drug shortages in the US.¹⁷ Donelle and colleagues were the first to assess the drug shortage problem using the Drug Shortages Canada database.²¹ However, their analyses were based on the data reported between 2010 and 2017 (before the mandatory reporting), which were incomplete.

Compared with previous studies, one of our study's strengths is that we focused on shortages at the market level rather than at the DIN or drug product-level only. This perspective is more relevant as it speaks to real shortage scenarios as opposed to a situation in which one manufacturer is not supplying but others are. In addition, we considered all active drugs in Canada that can be used in both community and hospital settings instead of focusing on generic drugs for outpatient use only¹⁷ or drugs for certain diseases.¹⁴⁻¹⁶ The subgroup analysis among DINs listed on provincial formularies represented those used mainly in community settings (dispensed in community pharmacies).

Limitations

One of our study limitations is that we could evaluate the association between drug price and drug shortage only among DINs listed on formularies because of a lack of price data for all DINs. Although lower prices have been found to be associated with shortages of generic drugs,^{15,17} we did not find such an association in generic DINs but a marginally significant association among branded DINs. Prices for branded and generic drugs are typically regulated by different pricing policies. In Canada, prices of generic drugs covered under publicly funded insurance programs have been regulated by the pan-Canadian tiered pricing framework or by provincial price-cap policies,^{34,35} under which generic prices are capped at specified percentages of the associated branded drug's price. The percentages vary from 10% to 35% for existing generic drugs and 25% to 85% for new generic drugs (since Apr. 1, 2017), depending on the number of suppliers.^{34,35} The prices of patented branded drugs are regulated by the Patented Medicine Prices Review Board,⁴⁰ assessed for cost-effectiveness by the Canadian Agency for Drugs and Technologies in Health⁴¹ and negotiated by the pan-Canadian Pharmaceutical Alliance.⁴² Owing to the fact that the price varies widely between the branded and generic DINs, we were not able to consider price at the market level.

In addition, we did not have utilization data for each DIN. To mitigate this limitation, we considered the formulary listing in different provinces, market structure and essential medicines, which might indicate different levels of utilization. Another limitation is regarding the main shortage reason options given on the Drug Shortages Canada website. These reasons might not be mutually exclusive; e.g., "shortage of an active ingredient" or "shortage of an inactive ingredient or component" could overlap with "demand increase for the drug." In addition, the stated reasons are simply those that the manufacturers chose to report, but they may or may not reflect what is actually happening.

Table 5: Association between duration of drug shortage and factors at the DIN level among those in shortage

Parameter or level	Branded DINs			Generic DINs		
	Coefficient (SE)	p value	Average marginal effect (95% CI)‡	Coefficient (SE)	p value	Average marginal effect (95% CI)‡
Market structure (Ref.: B and G single)						
B and G multiple	0.01 (0.17)	0.958	1.4 (-57.7 to 59.2)	-0.24 (0.12)	0.049	-47.5 (-103 to 5.5)
B only	-0.46 (0.17)	0.007	-58.1 (-117 to -8.6)			
G single				-0.09 (0.14)	0.507	-20.2 (-81.8 to 36.7)
G multiple				-0.10 (0.13)	0.433	-21.1 (-77.2 to 33.8)
BIO						
Overall p value*	0.002			0.040		
Route of administration or form (Ref.: oral solid regular release)						
Injection	-0.03 (0.21)	0.882	-3.5 (-49.3 to 50.0)	0.15 (0.10)	0.135	28.9 (-7.2 to 66.2)
Oral nonsolid	0.15 (0.26)	0.576	18.0 (-46.1 to 103.6)	0.30 (0.17)	0.070	64.9 (6.8 to 137.9)
Oral solid special release	-0.68 (0.20)	0.001	-56.6 (-88.5 to -24.6)	0.12 (0.08)	0.163	22.7 (-7.3 to 56.3)
Other	0.55 (0.23)	0.014	85.4 (10.6 to 189.8)	-0.19 (0.15)	0.223	-31.0 (-79.1 to 25.4)
Overall p value*	0.001			0.067		
Reason for shortage						
Disruption of manufacture (Ref.: no)	0.49 (0.14)	< 0.001	62.5 (26.2 to 106.7)	0.28 (0.08)	< 0.001	48.8 (26.2 to 72.1)
Shortage of ingredient (Ref.: no)	0.90 (0.24)	< 0.001	161.6 (68.7 to 324.7)			
Delay in shipping (Ref.: no)	-0.46 (0.16)	0.004	-47.9 (-78.6 to -13.6)	-0.15 (0.08)	0.074	-26.4 (-51.0 to 1.5)
Demand increase (Ref.: no)	-0.12 (0.15)	0.429	-14.3 (-46.1 to 31.0)	-0.49 (0.1)	< 0.001	-74.4 (-95.2 to -49.3)
Business reason (Ref.: no)	1.65 (0.33)	< 0.001	494.0 (264.2 to 959.0)	0.78 (0.18)	< 0.001	213.1 (127.3 to 313.0)
Compliance† (Ref.: no)				-0.08 (0.12)	0.526	-13.7 (-53.3 to 29.6)
Anatomic Therapeutic Chemical Classification (Ref.: sensory organs)						
Alimentary tract and metabolism	0.58 (0.36)	0.108	66.1 (-20.4 to 167.7)	-0.61 (0.20)	0.003	-175 (-341 to -60.9)
Blood and blood-forming organs	0.18 (0.48)	0.708	16.7 (-53.2 to 135.5)	-1.02 (0.39)	0.009	-243 (-433 to -92.9)
Cardiovascular system	0.56 (0.30)	0.068	62.5 (-1.2 to 123.8)	-0.70 (0.19)	0.000	-192 (-359 to -84.5)
Dermatologicals	0.35 (0.27)	0.193	35.6 (-11.9 to 92.9)	-0.45 (0.19)	0.020	-139 (-263 to -47.9)
Genitourinary system and sex hormones	0.22 (0.29)	0.452	20.8 (-49.8 to 77.1)	-0.81 (0.22)	0.000	-211 (-383 to -94.7)
Systemic hormonal preparations, excluding sex hormones and insulins	0.19 (0.42)	0.652	17.5 (-51.5 to 105.8)	-0.54 (0.28)	0.056	-159 (-340 to -24.6)
Anti-infectives for systemic use	0.59 (0.36)	0.102	67.6 (-14.0 to 177.1)	-0.76 (0.20)	0.000	-203 (-373 to -90.0)
Antineoplastic and immunomodulating agents	0.45 (0.38)	0.242	47.5 (-43.3 to 161.9)	-1.07 (0.23)	< 0.0001	-251 (-421 to -139)
Musculoskeletal system	0.81 (0.38)	0.032	104.6 (-4.9 to 235.3)	-1.06 (0.21)	< 0.0001	-249 (-416 to -139)
Nervous system	0.33 (0.30)	0.269	33.3 (-29.0 to 90.2)	-0.78 (0.19)	< 0.0001	-206 (-371 to -101)
Antiparasitic products, insecticides and repellents	-0.22 (0.80)	0.787	-16.4 (-87.5 to 70.2)	-1.31 (0.50)	0.009	-278 (-457 to -152)
Respiratory system	0.04 (0.30)	0.890	3.5 (-45.2 to 48.2)	-0.39 (0.19)	0.035	-124 (-255 to -28.9)
Various	-0.40 (0.61)	0.511	-27.8 (-93.2 to 48.4)	-1.40 (0.41)	0.001	-287 (-456 to -146)
Overall p value*	0.445			< 0.001		
DIN age, yr	0.01 (0.004)	0.001	1.6 (0.6 to 2.5)§			
On formulary (Ref.: no)	-0.59 (0.15)	< 0.001	-88.8 (-151 to -45.8)			
Manufacturer size (Ref.: large)						
Small	0.86 (0.16)	< 0.001	118.2 (63.0 to 188.0)			
Medium	0.45 (0.13)	< 0.001	50.2 (17.8 to 85.0)			
Overall p value*	< 0.001					
Model fit statistics						
AIC	4778.4			21251.2		
Log-likelihood	-2359.2			-10598.6		

Note: AIC = Akaike information criteria, B = branded manufacturer, BIO = biologic manufacturer, CI = confidence interval, DIN = Drug Identification Number, G = generic manufacturer, Ref. = reference category, SE = standard error.
 Results were based on truncated negative binomial regression models.
 *Based on type III likelihood test.
 †Requirement related to compliance with good manufacturing practices.
 ‡The average marginal effect of a variable was evaluated as the average of predicted differences (from the reference category) at observed values of covariates for each observation; 95% CI were the bootstrap confidence intervals based on 2000 bootstrap samples.
 §For an increase from 20 years to 21 years.

Conclusion

Markets with a single generic manufacturer, oral nonsolid route or form, larger proportion of drugs on provincial formularies and in sensory organs ATC class were more likely to be in shortage. Policy-makers trying to balance cost-containment with security of drug supply should pay extra attention to markets with relatively tight profit margins and that are under pressure of price-capping policies, which may result in a market with a single generic supplier. In addition, they should be vigilant in monitoring markets with complex manufacturing processes, with higher demand from public insurance programs or those that are in certain ATC classes.

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Data sharing: The complete dataset used in our study is not available to others. However, data on drug shortages may be extracted from the Drug Shortages Canada website (www.drugshortagescanada.ca). The Drug Product Database of Health Canada can be accessed from www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product

[-database/what-data-extract-drug-product-database.html](#). Formulary data can be accessed by request from the Canadian Institute for Health Information (www.cihi.ca/en/national-prescription-drug-utilization-information-system-metadata). More detailed data access information can be found in Appendix 1.

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