Article details: 2019-0112	
Title	Opioid losses in terms of dosage and cost: a retrospective analysis of Health Canada data
Authors	Mark Fan BASc MHSc, Dorothy Tscheng BScPhm, Michael Hamilton MD MPH, Patricia Trbovich PhD
Reviewer 1	Dr. Brandon Zagorski
Institution	Faculty of Medicine, University of Toronto, Toronto, Ont.
General comments (author response in bold)	Thank you for the opportunity to review this manuscript, below are comments/questions. 1. Table 2. The units in the column totals are not consistent with the rest of the table. Change or properly label. Also, the estimates in each table can be expressed in '1000s (thousands) to reduce crowding in tables (for values of less than 1000 then the value can be expressed as "~0" or a value less than 1 (e.g 0.93 for injectable codeine OMEQ). **We thank the reviewer for noticing this. Since 1000 milligrams is simply grams, we debated simply changing the unit reported in our paper to grams rather than potentially confuse readers with Tables that state "per 1000" milligrams. Indeed this was what we did for Figures A1, A2 and A3 in the appendix. However, our current stance is that milligrams are a more meaningful context for clinicians and readers when discussing the scale of opioid losses. With the exception of fentanyl, which is typically prescribed in micrograms, most of these opioids are prescribed in milligrams, and so we have decided to retain the term milligrams throughout the paper.** **We have adjusted Tables 1, 2, 3, 4, A9 and A10 to report milligrams and OMEQs in 1000s as recommended. This change has also corrected the discrepancy between the column totals and the rest of the table in Table 2.** 2. Please provide all results for the year 2017 prorated up to a year so that comparisons to previous years can be easily made. Add this methodology in the methods section and change label each column to "2017" from "Sept 2017" **The presentation of a yearly trend is found in Table 4, Appendix Table A9, Appendix Table A10, and Figures A1, A2 and A3.** **For Tables 4, A9 and A10, we added a pro-rated column in an effort to address this request (but left the original 2017 data up to September 2017 for the reader's reference).** **For Figures A1, A3 and A3, we replaced the 2017 (up to September) with prorated data for 2017 so that the trend is not obscured by two data points for 2017.** **We did not prorate 2017 data in Tables 1, 2, and 3 because no yearly comparisons are being made in those tables.** **We have explained the pro-rating process in the methods section, data analysis, page 7: "For 2017, the HC dataset only contains data for January to September. We therefore provide a pro-rated estimate for a full year of 2017 only when data is presented by year. We averaged the milligram losses in the first three quarters of 2017 and added this value as the loss for the final quarter (October to December)."** 3. In the methods section and in each table that contain dollar values should be the units of currency (e.g. 2019 CAD). Since the data span multiple years please provide how inflation was accounted for (i.e. stating the specific inflation index). **Cost is only captured in Tables 1, A5 and A8 (Appendix). We have added "(CAD)" to the column header to denote the currency is being reported in Canadian dollars.** **We have added a limitation on page 14 indicating that wholesale drug costing was drawn from 2019 data without taking inflation into account.** **Additions are italicized:** **"Third, our estimates of wholesale costs and street value are simplified, as we applied**

	single point-in-time estimates (without discounting costs over the dataset timespan) from select provincial formularies or police services to the whole dataset. Wholesale costs were drawn from 2019 formularies and police services data reflect average pricing across geographies and the database timeframe of 2012 to 2017." 4. Table 3: Can be improved by providing marginal (column and row) grand totals. **Thank you for the suggestion. We have now added marginal totals to Table 3.** 5. Table 4: Some numbers are missing commas (e.g. incidents of loss). **Thank you for bringing this to our attention. We have amended Table 4 so that the missing commas have been added.** 6. Table 4. R-sq values are reported however there is no details in the methods on what this statistic is attempting to represent nor how it was calculated. Please provide specific details on this statistic, such as the how it was calculated, description of the X and Y vars, units of analysis, time period (e.g. Is 2017 included and if so, it is prorated for a partial year - if years is the unit?). If this is a model fit statistic for a linear regression model regressing on calendar time(year), please provide regression diagnostic statistics, including how non-stationarity was addressed. Or simply remove it from the table as it is not mentioned anywhere else in manuscript. **We have removed the R-sq values from the manuscript.** 7. Please confirm that Table A7 for BC 2017 value of "72" is the intended value. Compared to previous values and being close to 0 (zero) might suggest that its not full reporting. I understand that BC has attempted to address this with time-delayed safes and could explain some decrease. **We can confirm this is intended value and is what is present in the Health Canada dataset. It seems unlikely that the level of disclosure/reporting from organizations has decreased, although it is a possibility. Such a limitation would apply equally to any of the other cells in the table. We have no evidence to comment on whether this is the case and so have left the data as is without additional commentary. By reporting milligrams per thousand as per Reviewer 1's suggestion (point 1), this cell now appears as ~0.** 8. Please provide justification for presenting the results of the database scan, especially Table A2. **We have included the database scan to highlight that Health Canada provides the most accurate source of drug loss and theft data compared to potential alternatives. The database scans compares numerous sources of information none of which have comparable volume to Health Canada's dataset. We hope that showing the database scan helps justify our use of Health Canada data for the article. We are unaware of any other source of data that would offer a superior means of performing this analysis.** **We believe our statement (now moved to the second paragraph of the introduction on page 4) may explain this to readers. It states:** **"Pilot work by the authors suggests that HC data represents the best source of data on the incidence of Canadian opioid losses (see Appendix)."** **We have also added our justification to the Appendix on page 2 in a rationale section to help clarify its inclusion. We are happy to make further amendments if the reviewer believes more information is needed for why we included this in the Appendix.** **The Appendix (page 2) addition reads:** **"Rationale** **The database scan was conducted to assess what database provides the most comprehensive data on opioid losses, such that analyses are conducted on the best data available."**

9. Please add the proportion of records excluded from the HC database due to restricting to the 5 opioids. This will give context to the study and importance of opioids to the problem.
Our dataset consisting of 5 common opioids is 64,963 rows. The original dataset from Health Canada consisted of all drugs, including benzodiazepines, cannabis, anabolic steroids, barbiturates etc. and was 142,420 rows. Therefore our dataset represents 45.6% of the line items in the Health Canada data.
We have now added this statement to page 6, under the 'Inclusion Criteria and Constraints' subheading in the Methods:
"Restricting our analysis to these five opioids results in 64,963 reports, which is 45.6% of the reports in the original HC dataset, which contains 142,420 reports."

10. The authors are suggesting that the milligram based metrics are superior (in accuracy) to the incidence or dosage unit based metrics there needs to be data to support this. That the annual trends of each metric are not similar do not support this notion as each metric measures different aspects of loss. Secondly, all metrics have limitations and might be inaccurate to similar magnitudes. Removing comments that suggest superior accuracy should be removed unless the authors provide data to support it. If authors feel that the use of milligram based metrics are superior to better support wholesale/street value estimation, then there is no need for extra data analysis.
The reviewer is correct – our contention is that milligram based metrics are superior for wholesale/street value estimation. However, we recognize the reviewer's comment that there are limitations with all measures.
Counting the number of loss reports acts as a better measure of reporting frequency, but does not support an analysis of whether the actual amount of milligrams of loss is increasing, which is the primary question we are seeking to answer. Similarly, reports of dosage units lost does not address whether we are losing more or less drug year to year. To address this comment, we have repositioned our statements in the paper to focus on the complementary benefit of including milligram measures to existing measures in future reporting.
We have added a statement in the introduction (top of page 5) so that the 'reliability' or accuracy of the milligram data is no longer the primary advantage it provides (changes italicized):
- **From: "Given that both Canadian and US reports of opioid losses are based on 'dosage units', policy makers have not yet had reliable data to accurately assess or compare losses year to year, nor can they accurately estimate costs of the lost drug based on dosage units alone."**
- **To: "Given that both Canadian and US reports of opioid losses are based on 'dosage units', policy makers have not yet seen analyses that directly estimate losses in dose (e.g., milligrams), which may confer advantages in comparing losses year to year, and also offer the opportunity to estimate the cost of lost drug by milligram"**

We have also amended the discussion on page 10, changing the following:
- **From: "Based on this data, we suggest that losses as measured by dosage units or incidents of loss can mischaracterize the severity of the opioid loss; a dose based metric (e.g., milligrams, OMEQs) provides a more accurate means of assessing loss trends over time within and between facility types or provinces."**
- **To: "Based on this data, we suggest that losses as measured by dosage units or incidents of loss alone can mischaracterize the severity of the opioid loss; a dose based metric (e.g., milligrams, OMEQs) provides an important complementary means of assessing loss trends over time within and between facility types or provinces."**

As well as on page 13 of the discussion:
- **From: "As described previously, our findings show that milligram losses provide a**

more accurate representation of opioid loss trends than either dosage units or incidents of loss."

- **To: "As described previously, our findings show that milligram losses provide an important complementary metric of opioid loss trends over time, alongside dosage units and incidents of loss."**

We have also amended the appendix (section 4, page 17)

- **From: "However, literatures suggests that street pricing accurately reflects equianalgesic potency, which supports our contention that reporting losses in terms of dose (e.g., milligrams) or potency (e.g., oral morphine equivalents) is superior to alternative forms of measurement (e.g., dosage units, incidents of loss)."**
- **To: "However, literatures suggests that street pricing accurately reflects equianalgesic potentcy, which supports our contention that reporting losses in terms of dose (e.g., milligrams) or potency (e.g., oral morphine equivalents) is a useful addition to complement existing measures (e.g., dosage units, incidents of loss)."**

11. The milligram based metrics have one notable limitation the others do not, its the phenomena of anomalous reports (p 38 line 23). That the MG metric is a major focus of the study, quantifying the degree of imputation would provide the audience with an upward bound of the results. The following is requested:

A. Calculate the frequency(and %) of records and cumulative MG of loss (estimated min value) imputed (proportion of the total) overall and for each of the 5 drugs.

We have added Table A4 to page 11 and 12 of the Appendix to describe the frequency and percentage of records and cumulative milligrams of loss imputed from anomalous and non-anomalous records:

Drug	Total Number of records	Total Milligram loss	Number of non-anomalous reports	Non-anomalous Milligram loss	Number of Anomalous records (% of total reports in the dataset)	Anomalous Milligram loss (conservative) ($ of total milligrams in dataset)
Codeine	20,786	47,304,765	20,749	47,005,756	37 (0.18%)	299,009 (6.32%)
Fentanyl	3,189	264,193	3,037	184,930	152 (4.75%)	79,263 (30.0%)
Hydromorphone	15,182	12,723,946	14,987	9,372,740	195 (1.28%)	3,351,206 (26.34%)
Morphine	9,880	15687907	9739	15,389,434	141 (1.43%)	298,473 (1.9%)
Oxycodone	15,926	36546878	15,884	285,65,419	42 (2.64%)	7,981,459 (21.84%)
Total	64,963	112,525,448	64,397	100,518,280	567 (8.71%)	12,007,168 (10.67%)

We have added the Table A4 to the appendix because we wish to reserve the word count in the manuscript for the additional methodological details and limitations we have added from other points in the suggested revisions.

In order to clarify this point in the body of the manuscript, we have added the following sentence to the last sentence of the limitations on page 14:
"Finally, 567 reports (0.87% of the HC data) were ambiguous or anomalous, requiring assumptions to complete our analysis. The anomalous reports were responsible for ~10% of the milligram losses in the dataset and are described further in the Appendix (Table A4)."

B. Estimate the impact if a non-conservative approach was taken to the imputation. No additional estimates need to entered in the tables/figures, simply providing a statement in the

results (following p.6 of 19 line 55) as follows would suffice: "These estimates are the result of a conservative approach when imputing anomalous records. When a more liberal approach was used the results increased XX% MG and XX% street/wholesale value". If the resources do not allow for this, a random sample of the imputed records can be used. Add these methods to the manuscript's methods section.

We have added the suggested sentence to the Results section (page 8) as suggested by the reviewer, but because we used a sample of the anomalous reports we opted to explain the impact of a non-conservative approach in absolute values rather than a percentage increase to the original dataset.

"These estimates are the result of a conservative approach when imputing anomalous reports. When a more liberal approach was used on a sample of anomalous reports, the milligram losses increased by 7.4 kilograms, the wholesale value increased $886,670, and the street value of the losses increased by $9,695,290."

Due to resource limitations, we were unable to conduct a non-conservative analysis of the milligram losses for all anomalous reports.

On page 6 and 7 of the Methods, under the "Data Analysis" subheading, we have described our strategy for estimating the impact of a non-conservative approach:

"To estimate the impact of a non-conservative approach, we recalculated the losses for the top 40% of anomalous reports most affected by our conservative approach, for each of the five opioids (see Appendix section 2 for additional details)."

In Appendix 2 we have added a following on page 12:

"Our current approach to estimating the milligram losses of anomalous reports is to use a conservative approach and use the lowest reasonable loss based on the information available (see the resolution column in Table A3, rows 2, 5 and 6). However, it is important to assess how our conservative approach may have impacted our estimate of milligram losses, as well as drug costs.

As a result, we repeated our calculations with a non-conservative approach to estimate the impact on our findings. Due to resource limitations, we did not repeat our calculations for all anomalous reports, but instead selected a subset of the anomalous reports for analysis. The subset was based on several criteria.

First, we limited our non-conservative analysis to the two types of anomalous reports affected by our assumptions. These are:

- **reports where the loss was reported as a "package", and**
- **reports where no drug concentration was provided.**

This reduced our sample for analysis from 567 to 440 reports.

Second, we removed any anomalous reports from this subset where the unit of loss was grams, milligrams, or micrograms, as these reports do not require any assumptions on our part. This reduced our sample for analysis from 440 to 358 reports.

Further, to conduct the analysis within our resource constraints, we sampled roughly 40% of the reports for each drug. To avoid bias, we first organized the reports from largest to smallest milligram loss, and selected the top milligram losses for analysis using a non-conservative approach. The change in milligram losses, wholesale cost, and street value, is summarized in Table A5."

Table A5. Change in Milligram Loss when Anomalous Reports Analyzed Conservatively Versus Non-Conservatively

Drug	Number of Sampled Anomalous Reports / Total Subset of Anomalous Reports	Milligram Loss (Conservative)	Wholesale Cost (CAD) (Conservative)	Street Value (CAD) (Conservative)	Milligram Loss (Non-Conservative) (% increase from conservative approach)	Wholesale Cost (CAD) (Non-Conservative) (% increase from conservative approach)	Street Value (CAD) (Non-Conservative) (% increase from conservative approach)

Codeine	10/23	18,824	$525	$21,648	179,675 (854%)	$5,020 (856%)	$206,626 (854%)
Fentanyl	32/80	231	$6,335	$305	544 (135%)	$11,301 (78%)	$1,957 (541%)
Hydromor-phone	52/132	443,330	$147,732	$664,994	2,238,464 (405%)	$728,842 (393%)	$3,357,696 (405%)
Morphine	42/105	93,935	$57,107	$77,966	347,800 (270%)	$163,352 (186%)	$288,674 (270%)
Oxycodone	8/18	352,280	$12,657	$440,350	5,636,480 (1500%)	$202,511 (1500%)	$7,045,600 (1500%)
Total	144/358	908,599	$224,356	$1,205,263	8,402,963 (825%)	$1,111,026 (395%)	$10,900,553 (804%)

12. Figures: Fitting a bivariate linear regression model to non-linear data is not good statistical practice. In additional, comparing R-square and/or slope between models to identify correlation between metrics its not an appropriate approach (if that is the intention). Please remove the linear slopes from all figures. Providing other statistical measures of correlation are encouraged if the authors feel that a statistical comparison is necessary.
We have removed the R^2 model and all linear slopes from the figures.

Reviewer 2	Dr. James Ted McDonald
Institution	Department of Economics, University of New Brunswick, Fredericton, NB
General comments (author response in bold)	1. More information should be provided about what the reporting requirements are. From the tables these losses include spillage and breakage which are not losses as such since I assume the product is accounted for and so not subject to illicit use. Similarly, for drugs lost to manufacturer's shortage and under-shipment, is there the potential for double counting? Presumably these under-shipments would be communicated back to the dispensing supplier but are supplier losses also required to be reported to Health Canada? This leads to another question about what company losses mean – are companies wholesalers and/or manufacturers? **We have provided additional details regarding the reporting requirements in our response to the editors above, point 2.** **We wish to retain the reporting of milligram losses for spillage and breakage since it is possible that these reports could still be used to disguise diversion (see our response to the editors' comments, point 9).** **Additionally, while we suggest that some hospital losses may result in diversion and illicit use, we also wish to highlight the overall rate of opioid losses regardless of their eventual destination. Should there be a high degree of spillage and breakage, such a finding would suggest further research may be useful to understand how to prevent unintended and accidental loss of opioids through these means. We would advocate for these types of losses to be incorporated into annual reporting from Health Canada, as we allude to in the last paragraph of our discussion (page 14).** **With regards to the potential for double counting (e.g., under-shipment and manufacturer's shortage), we acknowledge this is a possibility. In general, there are processes for transfer of accountability (e.g., the healthcare facility signs that they have received a drug shipment, it is technically within their control and not the distributor's), which are likely to influence who is responsible for reporting the loss. However, a duplicate report is possible if both parties become aware that the manifest was not accurate. The reviewer is correct in assuming that supplier losses would be required to be reported to Health Canada, as suppliers would be licensed dealers (as we have defined in our response to the editors, point 2, above). We do not have a means to assess whether duplicate reports were recorded with the information currently in the dataset. 'Companies' may be manufacturers or distributors, as a license is required to manufacture or transport opioid inventory.**

2. Please define what is meant by daily defined doses and pilferage. Is pilferage shoplifting?
Daily defined doses are defined by the WHO as the "assumed average maintenance dose per day for a drug used for its main indication in adults."11 Daily defined doses (DDDs) were created to facilitate international comparisons between countries. We have added this definition to the manuscript in the 'Data Analysis' section within 'Methods', page 7. With regards to the definition of pilferage, we have added definitions based on Health Canada's guidance document for reporting controlled drug losses.3 We have repasted this word for word in Table A11 in the Appendix to ensure its accessibility for readers, and made references to Table A11 in Table 3, Table A9 and Table A10 (where loss descriptions are listed). It is of note that several loss descriptions in the dataset (e.g., spillage, breakage, impersonation, manufacturer's defect) are not present in the definition list in Health Canada's guidance document. We have chosen to retain these reports so as to minimally alter the dataset.

3. In the appendix with results by province the authors note 'an astonishing downward trend' in break and enter/armed robbery losses in BC pharmacies, but at the same time unexplained losses surge. This suggests at least some of the reduction might be due to differences in how losses are recorded. Nevertheless, a more general comment is that the provincial yearly numbers show a lot of volatility so caution needs to be used in drawing any conclusions about trend.
The reviewer's comment here is well taken. We have added a statement to the discussion where BC pharmacies are discussed (end of page 11 and page 12): "However, there are increases in other loss categories (e.g., unexplained losses), so interpretation of provincial trends should taken with caution."

4. The discussion speculates about how some of the provincial results might reflect the introduction of different rules covering inspections and reporting, or in the use of loss reduction methods such as time delay safes. Could the authors do more with the large amount of interprovincial data available and consider policy impacts more formally? This could certainly be the subject of future work, though again careful attention would need to be given to the impact of outliers.
We are not sure what interprovincial data the reviewer is referring to. We have highlighted possible contributors to differences in provincial trends, but this is drawn mostly from our familiarity with some of the literature and discussion in regulatory circles. A more formal analysis of provincial differences would likely require a new research project.
We are happy to recommend this as future work, but believe that our primary recommendation for Health Canada to begin reporting these metrics on an annual basis (without the need for individual groups to request data through Access to Information legislation) is the most practical and 'within reach' recommendation we can make at this time to facilitate future research of the kind suggested here.

5. Since the authors have coded the details for every report, it would be interesting to see more analysis of what is underpinning these numbers in terms of behavior. Could an analysis of disaggregated loss data, even by incident, consider how the level and nature of losses vary by rural/urban status, area-level socioeconomic status, etc? This could also be the subject of future work. The authors could mention future work in their discussion or conclusion.
The loss reports provided by Health Canada are anonymized, so we are unable to determine rural/urban status, socioeconomic status etc. Provincial location and date of report are the most precise details available in the current dataset, and this does not provide sufficient background for the analysis suggested. Health Canada does have more details of the loss reports, but this data requires a separate Access to Information request and a manual qualitative analysis of free-text incident descriptions, which is beyond the

	scope of the current paper. 6. I would like to see more discussion of the 'loss unexplained' category. Are pharmacies, hospitals and companies allowed to classify a loss as unexplained at their discretion, or would it actually reflect that the reason for the missing drugs really is unknown? **We have now included a definition of the loss unexplained category in Appendix Table A11. Pharmacies, companies and hospitals can classify reports at their discretion, and therefore, there is not a guarantee that the losses have been classified correctly. This is discussed briefly in our response to the editors, point 9 (risk of misclassification). The main safeguard against this is the threat of inspection by Health Canada or other regulatory bodies (depending on the province/territory); accounting records must be maintained for 2 years so that they can be reviewed if an inspection is initiated.**
Reviewer 3	Natalie McCormick PhD
Institution	Post-Doctoral Research Fellow, Mongan Institute, Department of Medicine, Massachusetts General Hospital, Boston, Mass.
General comments (author response in bold)	Thank you for your efforts in preparing this manuscript reporting on the extent and costs of opioid losses from Canadian healthcare facilities. I appreciate your efforts in cleaning and standardising what seems like a 'messy' dataset, but what your Database Scan suggests is currently the best source of data available to address this question on a national scale. The Appendix contained much detail about the database scan and available data sources, Milligram Calculation procedures, and choice of conversion factors and street pricing. However, I think readers would benefit from additional background information about the opioid tracking and reporting process. This may help in understanding why there were some ambiguities in the reporting and how it could be improved. For example, there were a lot of Unexplained Losses – are the penalties less severe for Unexplained Losses (vs. pilferage)? Do facilities have sufficient resources to fully investigate all losses and report them comprehensively? Which is worse – the loss having occurred (which could result in some losses going unreported), or the reason for the loss? Please see some specific questions and suggestions below: **Thank you for your review!** **The reviewer has raised two important questions, which we will address in turn.** **First, on the question of 'penalties' for types of losses: At the present time, there are no penalties depending on loss categories. Although we are not aware of how Health Canada uses this data, we can presume that Health Canada may be motivated to inspect certain healthcare facilities if there are indications that they not be compliant with controlled drug legislation. Health Canada might consider the number reports, and the types of loss categories reported, to determine whether they should inspect a healthcare facility, but this is not the same as a penalty per se. Unlike the Drug Enforcement Agency in the U.S., Health Canada does not issue fines for non-compliance.** **Second, on the question of whether facilities have sufficient resources to fully investigate all losses and report them: We suspect most healthcare facilities do not have sufficient resources or motivation to fully investigate losses and report all loss incidents. In literature on hospital drug thefts and losses, the resources required to detect theft are very high. Often manual reconciliation is required between prescribing, dispensing, administration and waste records to detect discrepancies. This level of scrutiny is often only undertaken when there is already considerable cause for suspicion. Therefore, there is likely a large degree of under-detected cases of drug theft or loss to begin with; the question of whether such incidents are reported once discovered is a separate topic on which we do not currently have sufficient evidence to comment on, but we suspect most facilities do report when they become aware of losses. We have touched on the difficulty of detection briefly already in the second last paragraph of the discussion on page 13.**

On the third question regarding which is 'worse' – the loss having occurred or the reason for the loss: We believe the reviewer is commenting on which is worse from the standpoint of a healthcare facility being penalized. For example, is it better to not have any losses at all, or is it okay to have some losses if they are due to certain types of loss? As we have commented in the first of the reviewer's questions, given that fines or penalties are not issued in the Canadian context, there is not currently any incentive for facilities to prefer one approach versus another.

Major Comments

1. Introduction, page 3, paragraph 2: Could you please provide more information about which facilities are required to report opioid losses, a bit more about the reporting process (i.e. submitted electronically? By a manager?), and the procedures/penalties in place to ensure these losses are reported in the first place, within the required timeframe, and as accurately as possible?

We have addressed this in our response to the editors, point 2, and hope this sufficiently answers the reviewer's comment.

2. Results, page 7, paragraph 2: Either here, or in the Introduction or Methods, it would help to define pilferage, especially as it was a major source of opioid losses. Does this refer to thefts by employees? How does it differ from "grab theft"?

The definitions provided by the Health Canada guidance document specifies the following:

- **Grab Theft means the theft from a site during working hours without warning. The person conducting the theft 'grabs' the product and escapes.**
- **Pilferage means the theft from a site by authorized personnel.**

In other words, pilferage typically refers to thefts by employees, whereas grab theft is non-specific and could include non-employees (e.g., patients, family members, visitors, external contractors). Given that it is often unclear how drug was lost or stolen, it is currently unclear how respondents are deciding between these two categories.

These definitions are now incorporated into the Appendix in Table A11 word for word, and readers are pointed to this table in the notes for Tables 3, A9 and A10. In addition, we have added a reference to these definitions in the Methods under the 'Data Analysis' section on page 7:

"We have included the definitions from Health Canada for the various loss categories (e.g., unexplained loss, pilferage) in the dataset in the Appendix (Table A11)."

3. Conclusion, page 12, final sentence: Do you think the reporting process also needs to be made more streamlined or straightforward, to help improve the quality of the reports? If so, maybe the final sentence should be modified to something like: "Ensuring that reports of controlled drug loss unambiguously capture the dose (e.g.,milligrams) of the loss, as well as more streamlined reporting procedures, and transparent and standardized methods of making this data available…"

The reporting process is fairly straightforward currently (e.g., fill out the form and submit it). The issue is more likely that healthcare facilities' lack the ability to identify and detect discrepancies when they occur, and the fact that they may not be strictly audited for compliance with the Health Canada's reporting mandate. We have not implemented the reviewer's suggestion at the present time, but are open to further discussion and dialogue if the reviewer feels that the reporting process itself is one of the key issues at play.

4. Appendix 2, Table A3: Thank you for your thorough description of the Milligram Calculation Procedures. I realise there were ambiguities and inconsistencies in the data, and for the most

part, you took a conservative approach when addressing these. However, I noticed you did not make any corrections when the units of loss or quantities seemed higher than expected. How often did this occur? Do your findings change much when these rows are removed altogether, or modified to lower, more typical units/quantities?
We hope that the new sensitivity analysis, which is now reported in Section 2 of the Appendix, helps address the reviewer's concern. We describe this analysis in more detail in our response to reviewer 1, point 11.
With respect to answering the reviewer's question, there are 26 reports where the quantity was unexpectedly large. These 26 reports are responsible for 10,706,355mg of loss, which is 9.5% of the total milligrams lost in our dataset. Seven of these 26 reports are addressed by our sensitivity analysis discussed in section 2 of the Appendix.
Nineteen of the 26 reports are not discussed in our sensitivity analysis because our calculation assumptions did not apply to them (e.g., the milligram calculation was straightforward). If we were to alter these reports, it would be unclear how we would decide to arbitrarily lower the amount.

Minor Comments
1. Methods, page 6, paragraph 2, sentence 1: Did you use information from the Ontario Drug Benefit Database for each calendar year (and adjust for inflation), or just for 2017? Your reference to "single point-in-time estimates" (Discussion, top of page 12) would suggest it was from a single calendar year.
That is correct, we used a single calendar year for the Ontario Drug Benefit database (2019). We have added the year 2019 to our description of the Wholesale costing section in the Methods on page 8 and in the limitations on page 15. We did not adjust for inflation over the timespan of our dataset.

2. Methods, page 6, paragraph 2 "see Supplemental file for wholesale pricing information": I could not locate this supplemental file, but did locate the supplemental file about the street pricing – is that what you intended to refer to?
This data is in the excel sheet which we were unable to attach along with our submission as it contains our complete dataset (the submission process required all documents to be converted to PDF). Given that our dataset contained several tabs and over 64,963 rows it was infeasible to add to the submission website. We will submit this file separately to the editors so they can append it to this response letter. We hope the reviewer can review this excel file to see the wholesale pricing information assembled from the Ontario Drug Benefit database and other provincial formularies when needed. Our calculation formulas will also be present.

3. Results, top of page 7: It makes sense to focus on the top-three facility types, but the reader is left curious about the other facility types. I know this is reported in Table 2, but if space permits, could you please list the others here?
We have now made several additions while addressing the feedback from other reviewers. We are happy to incorporate this if the editors allow it, but have not made this addition presently to adhere to the journal's word limit restrictions as best we can. As the reviewer has acknowledged, this data is present in Table 2, so this may not be a significant barrier to the reader's comprehension.

4. Did the prevalence of missing/ambiguous data in the Health Canada dataset differ by facility type?
We report on the number of anomalous reports by facility type below.

Facility Type	Number of reports	Number of	Percentage of

	in total	anomalous reports	anomalous reports out of the total reports
Community Pharmacy	58,442	219	0.4%
Companies	2,501	45	1.8%
Hospital	3,880	288	7.4%
Long term care facility	51	4	7.8%%
Nurse station	38	3	7.9%
Canadian Forces Base	27	3	11.1%
Ambulatory services	24	5	20.8%
Total	64,963	567	8.8%

We have not presently decided to add this Table to the manuscript or appendix given the number of other additions already made to the manuscript, but are happy to discuss with the reviewer if they feel it is required after they have reviewed the new version. The availability of the dataset for readers to review themselves may also reduce the need to include this in the manuscript or appendix.

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