

Syndromic surveillance of *Norovirus* using over-the-counter sales of medications related to gastrointestinal illness

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OBJECTIVE: To assess whether over-the-counter (OTC) sales of gastrointestinal illness (GI)-related medications are associated with temporal trends of reportable community viral, bacterial and parasitic infections.

METHODS: The temporal patterns in weekly and seasonal sales of nonprescription products related to GI were compared with those of reportable viral, bacterial and parasitic infections in a Canadian province.

RESULTS: Temporal patterns of OTC product sales and *Norovirus* activity were similar, both having highest activity in the winter months. In contrast, GI cases from both bacterial and parasitic agents were highest from late spring through to early fall.

CONCLUSIONS: Nonprescription sales of antidiarrheal and anti-nauseant products are a good predictor of community *Norovirus* activity. Syndromic surveillance through monitoring of OTC product sales could be useful as an early indicator of the *Norovirus* season, allowing for appropriate interventions to reduce the number of infections.

Key Words: Gastroenteritis; Gastrointestinal illness; *Norovirus*; Over-the-counter medications; Syndromic surveillance

Monitoring trends of gastrointestinal illness (GI) in the community using over-the-counter (OTC) sales of relevant medications (ie, anti-nauseants and antidiarrheals) is a form of syndromic surveillance. The usefulness of this type of surveillance has been reviewed in a number of investigations in which OTC medication sales have been shown to provide an earlier signal of outbreaks of diarrheal (1) and respiratory (2) disease than do hospital diagnoses.

A recent Canadian study (3) of temporal distributions of GI-related OTC medication sales and emergency room (ER) visits for vomiting, diarrhea and bloody diarrhea found that seasonal patterns for ER visits and OTC medication sales were similar, but different than those of reportable GI cases based on laboratory isolates of bacteria and parasites. The study took place in a province where *Norovirus* and *Rotavirus* are not reportable.

Surveillance des cas d'infection à *Norovirus* par l'intermédiaire des ventes de médicaments sans ordonnance pour le traitement de maladies gastro-intestinales

BUT : L'étude de surveillance avait pour but de vérifier si les ventes de médicaments sans ordonnance pour le traitement de maladies gastro-intestinales étaient liées à des périodes d'infection virale, bactérienne ou parasitaire à déclaration obligatoire, dans la collectivité.

MÉTHODE : Les tendances observées dans les ventes hebdomadaires et saisonnières de produits sans ordonnance, liées au traitement de maladies gastro-intestinales ont été comparées avec celles liées aux infections virales, bactériennes ou parasitaires à déclaration obligatoire dans une province, au Canada.

RÉSULTATS : Les tendances observées dans la vente de produits sans ordonnance, dans le temps, coïncidaient avec les affections à *Norovirus*; en effet, les deux ont connu un pic d'activité pendant l'hiver. En revanche, les cas de maladies gastro-intestinales, attribuables à des bactéries ou à des parasites ont atteint un sommet entre la fin du printemps et le début de l'automne.

CONCLUSIONS : Les ventes d'antidiarrhéiques et d'anti-nauséux sans ordonnance sont un bon prédicteur d'infections à *Norovirus* dans la collectivité. La surveillance des cas d'infection par la vente de produit sans ordonnance pourrait être un indicateur précoce du début de la saison des maladies à *Norovirus*, ce qui permettrait de faire des interventions appropriées afin de réduire le nombre de cas d'infection.

As part of the Canadian National Enteric Surveillance Program (4), weekly aggregate counts of cases of infectious GI due to reportable bacteria, parasites and viruses are collected for each province. This laboratory-based surveillance system has shown that although the organism-specific infection patterns vary somewhat depending on regional climate, the incidence of bacterial and parasitic infections tends to be higher in summer and early fall, whereas that of viral infections (particularly *Norovirus* and *Rotavirus*) appears to peak in winter and spring (5). Under normal circumstances, this pattern is also seen in OTC medication sales (3), suggesting that the pattern reflects underlying community viral infections rather than bacterial or parasitic infections. If OTC medication sales are to be considered for use in syndromic surveillance of community GI, the nature of this relationship needs to be clarified.

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The objective of the present study was to compare temporal distributions of GI-related OTC medication sales with laboratory-isolate patterns of bacterial, parasitic and viral cases of human GI infections in a province where viral infections from *Norovirus* and *Rotavirus* are reportable. A specific objective was to determine the similarity between patterns in OTC medication sales and those linked with *Norovirus* and *Rotavirus* activity.

METHODS

Reportable disease data

National Enteric Surveillance Program (4) data were extracted for a province in which viruses are reportable. Organisms of interest included those that exceeded five cases per year. Counts of GI cases due to bacteria (*Salmonella*, *Campylobacter*, *Escherichia coli*, *Shigella* and *Yersinia*) were available from January 2001 to April 2004, and data from April 2001 to April 2004 were available for parasites (*Cryptosporidium*, *Entamoeba* and *Giardia*) and viruses (*Norovirus* [includes Norwalk-like virus (NLV), *Calicivirus* and small round enteric virus] and *Rotavirus*).

Pharmacy sales data

One major retailer was able to provide electronic data from their 19 pharmacies in the study area. These were dispersed in a region representing approximately 53% of the provincial population, and represented approximately 12% of all pharmacies in that region. The database provided included daily aggregate counts of in-store 'point of sale' purchases of antinauseant and anti-diarrheal products between January 2001 and April 2004.

Statistical analyses

SAS Version 9.1 (SAS Institute Inc, USA) was used for all statistical analyses. Temporal patterns were plotted for each organism, as were totals for bacteria, parasites and viruses. Using PROC ARIMA (SAS), weekly OTC medication sales were cross-correlated with the number of reported bacterial, parasitic, *Norovirus* and *Rotavirus* infections in the same week, and then with weekly counts lagged one to 24 weeks before and after. Twelve season-by-year indicators ('SEAS_YR') were created: 'Spring 2001' to 'Winter 2003/04'. 'Winter' was defined as December 1 to mid-April, 'Spring' was mid-April to the third week of June, 'Summer' was the last week of June to mid-September and 'Fall' was mid-September to the end of November. Descriptive statistics for weekly and seasonal infections and sales were done using PROC UNIVARIATE (SAS). Seasonal patterns of OTC medication sales and GI cases for combined bacteria and parasites, *Norovirus* and *Rotavirus* were presented as the difference between the weekly total and the overall mean, and were plotted together to highlight positive and negative changes from a common mean value of zero on the y-axis. Tukey's test (with Bonferroni adjustment) and LSMEANS within PROC GLM (SAS) were used to determine any significant differences between the SEAS_YR periods (ie, Winter 2001/02, Spring 2002 and Summer 2002) based on weekly mean counts of *Norovirus*, *Rotavirus* and OTC medication sales. All statistical tests were deemed significant if $P < 0.05$. OTC medication sales values presented were scaled by a constant for reasons of confidentiality.

RESULTS

Of all reported cases from April 2001 to April 2004, approximately 46% were due to bacteria, 18% to parasites and 36% to viruses (29% and 7% due to *Norovirus* and *Rotavirus*,

respectively). Figure 1 shows the temporal patterns in weekly counts of reportable cases of *Salmonella*, *Campylobacter* and *E coli* infections, which accounted for 96% of bacterial cases. *Giardia* was responsible for 60% of all parasitic infections in the study, followed by *Cryptosporidium* (26%) and *Entamoeba* (14%). Approximately 80% of viral infections were due to *Norovirus*. Similar seasonal patterns were seen for all reportable bacterial and parasitic infections, with the highest number of cases in summer and also in late spring and early fall; this pattern was not seen for *Norovirus* or *Rotavirus* cases (Figure 2). *Norovirus* infections peaked in late fall and winter, particularly during the winter of 2002 to 2003. *Rotavirus* infections occurred somewhat later than those of *Norovirus*, being highest in late winter and spring. Seasonal patterns, presented as differences from the mean (Figure 3), showed very little concordance between the combined bacteria and parasite patterns and OTC medication sales. Similarly, no temporal relationship between *Rotavirus* cases and OTC medication sales was evident. Temporal patterns within the OTC medication sales patterns were more closely synchronized with those of *Norovirus* infection, with peaks and troughs in the differenced values occurring during the same time periods.

Cross-correlation results showed that the highest correlation between weekly counts of OTC medication sales and *Norovirus* cases was in the same week ('lag 0') with an r^2 of 0.44. Correlation decreased with increasing weekly lags: $r^2=0.32$ and $r^2=0.2$ for ± 1 and ± 2 weeks, respectively. OTC medication sales were negatively correlated with counts of both bacteria and parasites for lags 0 to 10 weeks ($r^2=-0.32$ and less); the highest correlation with counts of *Rotavirus* ($r^2=0.21$) occurred at lags of ± 4 and ± 6 weeks.

Statistical comparisons of weekly averages by year and season for both OTC medication sales and cases of reported *Norovirus* and *Rotavirus* infections are shown in Table 1. Weekly case counts of *Norovirus* and *Rotavirus* infections ranged from 0 to 32 and from 0 to 13, respectively. Both OTC medication sales and cases of *Norovirus* infection were highest in winter. The average \pm SD weekly number of *Norovirus* cases in the winter of 2002 to 2003 ($n=11.5 \pm 9.17$) was significantly higher than in all other seasons over all years (range $n=1$ to 32). Winter 2003 to 2004 had significantly higher weekly averages for *Norovirus* than summer and fall of 2001, spring and summer of 2002 and spring of 2003; no other seasonal differences were significant for *Norovirus*. The highest mean weekly case counts of *Rotavirus* were found in the winter and spring periods, specifically in late winter and early spring (Figure 2). Average weekly OTC medication sales in the winters of 2002 to 2003 and 2003 to 2004 were not significantly different, but both were significantly higher than all other seasons; winter 2001 to 2002 sales were significantly higher than both the spring and fall of 2001.

DISCUSSION

Previous retrospective studies of large-scale waterborne outbreaks of GI (involving *Cryptosporidium*, *E coli* and *Campylobacter*) have shown that OTC medication sales increased dramatically in synchrony with the underlying epidemic curve (6-8). This suggests that automated access to electronic OTC medication sales data for use in a syndromic surveillance system may be useful as a public health tool for providing near real-time (within 24 h to 48 h) indicators of community GI activity. Our results show, however, that GI

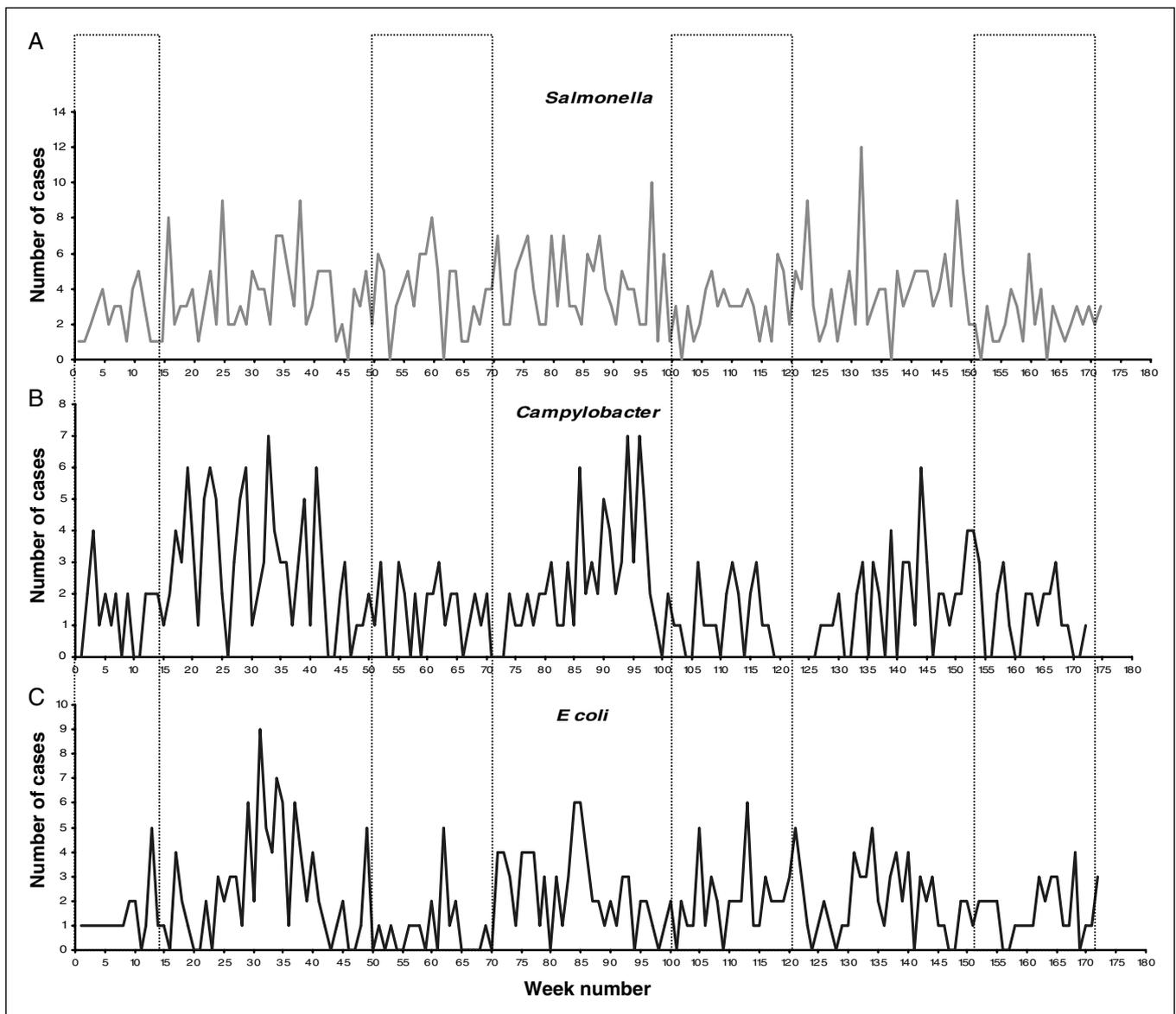


Figure 1) Comparison of total weekly cases of reportable bacteria: *Salmonella* (A), *Campylobacter* (B) and *Escherichia coli* (C) in a Canadian province (January 2001 to April 2004). Dotted areas represent approximate winter periods

trends under nonoutbreak conditions are predominantly driven by *Norovirus* infections.

This finding has important ramifications when deciding on the usefulness of an OTC medication sales-based syndromic surveillance tool for routine surveillance or as an early warning system. If this tool is biased toward *Norovirus* infections and the early detection of extremely large outbreaks, it is yet to be determined whether it can make a significant contribution to surveillance above and beyond current laboratory-based methods. However, our findings do suggest that OTC medication sales data could contribute a unique aspect to surveillance with established laboratory approaches.

Under-reporting of GI and associated etiology is a recognized problem worldwide (9-12). In England, an estimated 1500 more cases of NLV occur in the community for each case recorded (13). A study based in Ontario (14), where *Norovirus* is not reportable, indicated that approximately one in 300 community GI cases are actually reported. Knowledge of

the proportion of GI cases due to viruses, bacteria and parasites is still formative and incomplete in Canada, and would be particularly difficult to determine in provinces where *Norovirus* is not reportable. However, the etiologies of reported outbreaks alone indicate a preponderance of viral infections. In Ontario, as much as 62% of all GI outbreaks (2000 to 2002) of known etiology were reported to be viral (15). Internationally, the same picture is emerging. In the United States, a study by Fankhauser et al (16) indicates that 93% of nonbacteriological outbreaks are of NLV origin; research by Miller and Mikol (17) indicates that viral agents (NLV and *Rotavirus*) may account for most GI cases from January to April.

A national laboratory survey (18) in Canada shows that a relatively small percentage of laboratories tested for viruses, 67% of which conducted on-site (stool) enteric testing for bacteria, 31% for parasites and 10% for viruses. Of those laboratories that tested for viruses, 95% tested for *Rotavirus* and 31% tested for *Norovirus*. Additionally, the motivation for physicians

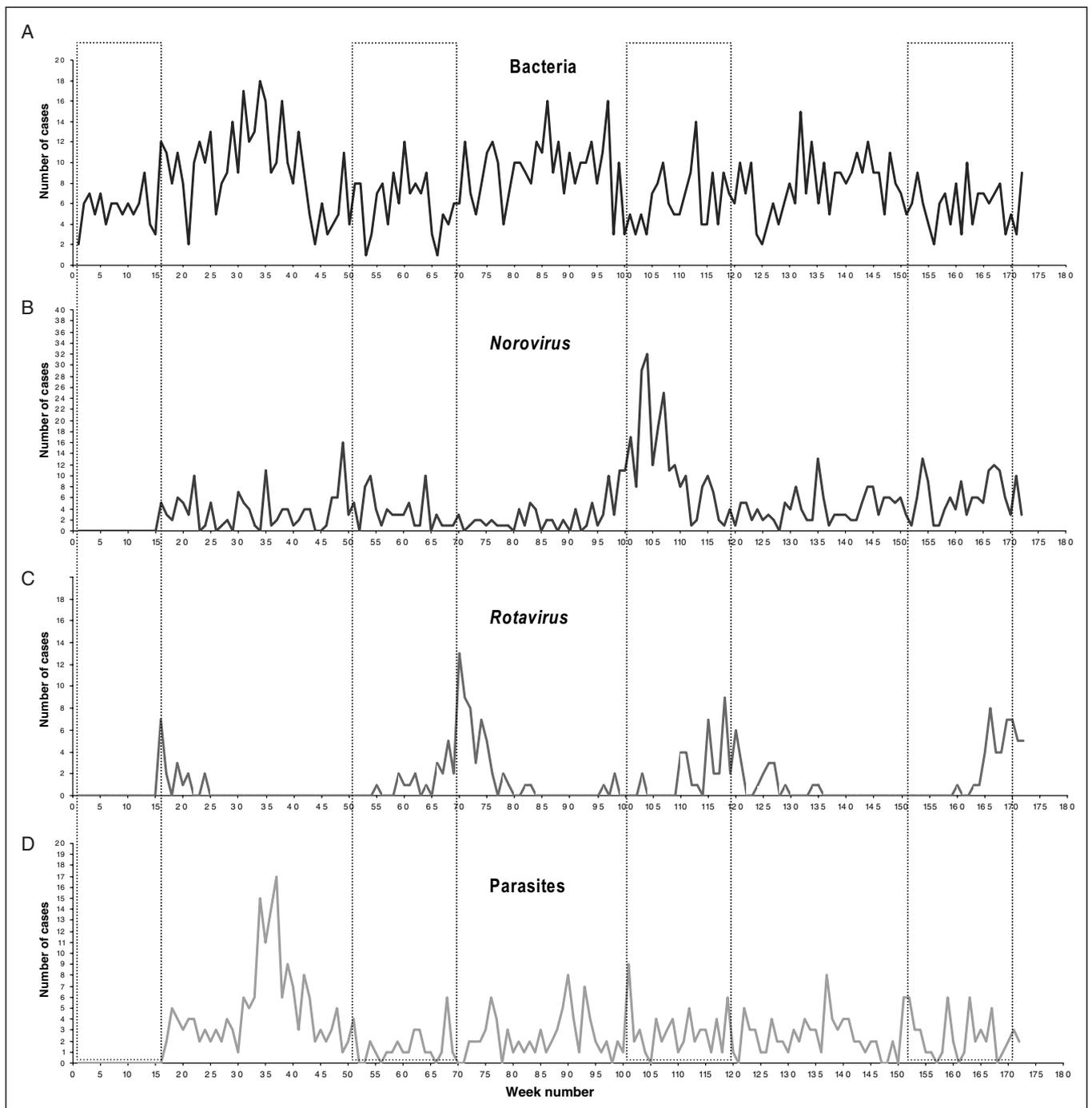


Figure 2 Comparison of weekly counts of reportable cases for (A) all bacteria (*Salmonella*, *Campylobacter*, *Escherichia coli*, *Yersinia*, *Shigella*) (January 2001 to April 2004), (B) *Norovirus*, (C) *Rotavirus* and (D) all parasites (*Giardia*, *Cryptosporidium*, *Entamoeba*) (April 2001 to April 2004) in a Canadian province. Dotted areas represent approximate winter periods

to request tests for viruses is low (19). This relates in part to the cost and availability of suitable tests and to symptom expression of the various agents. Test results for viral identification using polymerase chain reaction assay would generally only be available after the illness episode, because in reasonably healthy individuals, *Norovirus* infections are characterized by the rapid onset of severe and relatively short-lived (24 h to 60 h) symptoms of nausea, vomiting and diarrhea. Self-medication may provide adequate symptom relief for the one or two days of illness, likely precluding a physician visit. In

comparison, symptoms from infections due to *Salmonella*, *Campylobacter* and *E coli* can develop more slowly and last longer, possibly increasing the likelihood of an individual seeking professional medical care, which, in turn, may also discourage the use of antidiarrheals in particular. Consequently, proportionally more people with *Norovirus* may be purchasing OTC products than those who have sporadic bacterial or parasitic infections, or those who are involved in outbreaks, increasing the probability of detecting *Norovirus* cases through sales of medications. The observed lack of correlation between

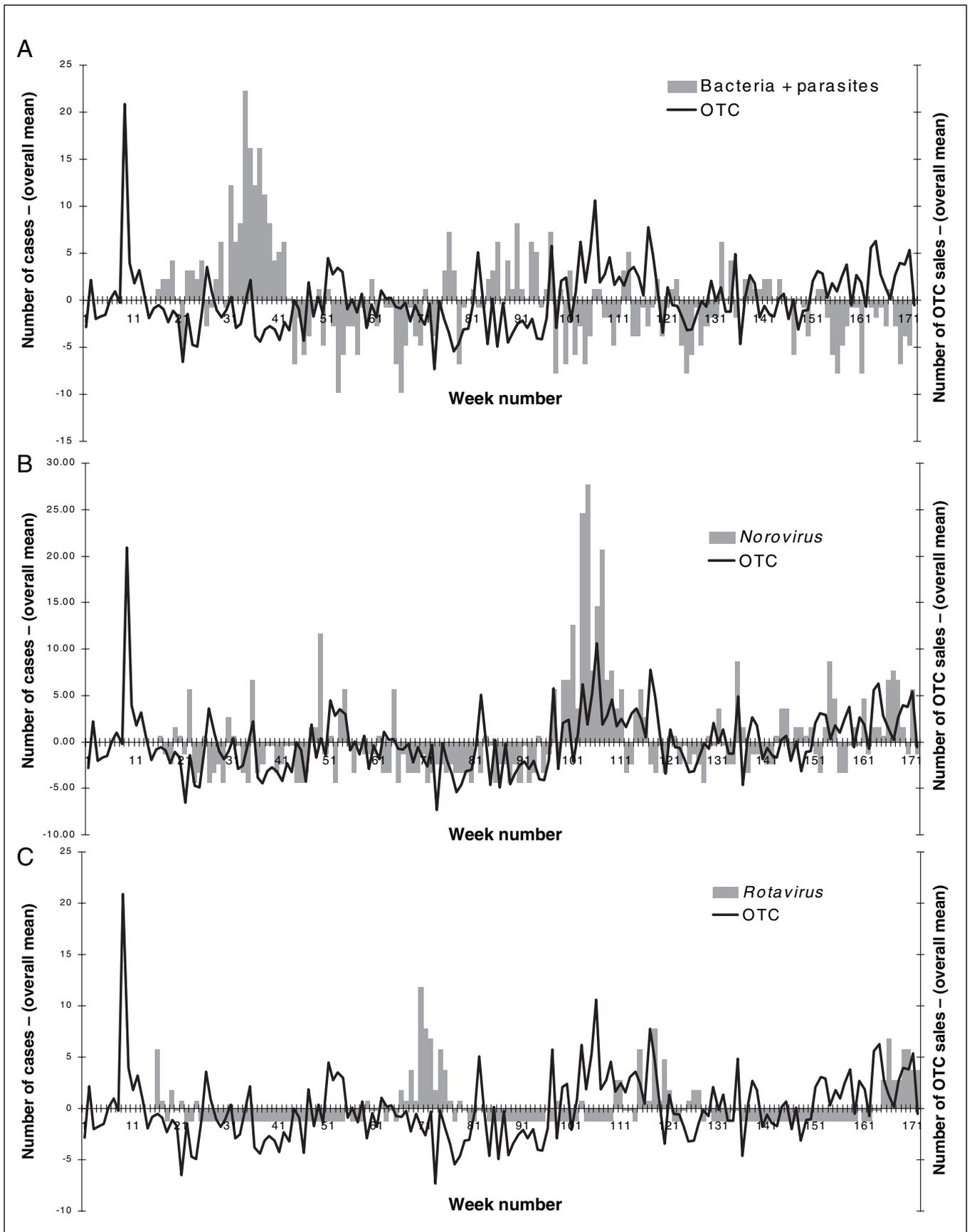


Figure 3) Case counts of reportable gastrointestinal illness (April 2001 to April 2004) compared with over-the-counter (OTC) medication unit sales (January 2001 to April 2004), both represented as a difference between the weekly total and the overall mean, showing bacterial and parasitic infections (A), Norovirus (B) and Rotavirus (C) in a Canadian province

TABLE 1
Season and year comparisons* of mean weekly over-the-counter (OTC) medication sales (transformed for confidentiality) and average weekly cases of *Norovirus* and *Rotavirus* in a Canadian province (April 2001 to April 2004)

Season and year label	Season and year	Average weekly OTC sales, n ± SD	Average weekly cases of <i>Norovirus</i> , n ± SD (range)	Average weekly cases of <i>Rotavirus</i> , n ± SD (range)
A	Spring 2001	60±8.08 ^{D,H,J,L}	3.6±2.98 (0–10) ^H	1.55±2.11 (0–7) ^E
B	Summer 2001	63±5.56 ^{H,L}	3.2±3.58 (0–11) ^{H,L}	0±0 (0–0) ^{E,L}
C	Fall 2001	59±5.66 ^{D,H,J,K,L}	2.8±2.12 (0–6) ^{H,L}	0±0 (0–0) ^{E,L}
D	Winter 2001/02	67±5.76 ^{H,L}	4.3±4.12 (0–16) ^H	0.68±0.95 (0–3) ^{E,L}
E	Spring 2002	58±6.79 ^{D,H,J,L}	1.4±0.81 (0–3) ^{H,L}	5.09±3.86 (0–13) [§]
F	Summer 2002	62±9.32 ^{D,H,L}	1.9±1.85 (0–5) ^{H,L}	0.3±0.48 (0–1) ^{E,L}
G	Fall 2002	62±9.16 ^{H,L}	4.3±4.16 (0–11) ^H	0.25±0.62 (0–2) ^{E,L}
H	Winter 2002/03	76±8.62 [†]	11.5±9.17 (1–32) [†]	1.79±2.57 (0–9) ^E
I	Spring 2003	63±5.39 ^{H,L}	3.0±1.73 (0–5) ^{H,L}	1.73±2.57 (0–6) ^E
J	Summer 2003	67±7.93 ^{H,L}	4.5±3.63 (1–13) ^H	0.2±0.42 (0–1) ^{E,L}
K	Fall 2003	65±5.24 ^{E,H,L}	4.6±2.35 (1–8) ^H	0±0 (0–0) ^{E,L}
L	Winter 2003/04	73±6.16 [‡]	6.5±3.63 (1–13) ^{B,C,E,F,I}	2.35±2.83 (0–8) ^{B,D,E,F,H}

*Significant differences ($P<0.05$) between the periods spring 2001 to winter 2003–2004 are indicated by superscripts A to L, where A=significantly different than spring 2001, B=significantly different than summer 2001, etc. †Significantly different from all periods except winter 2003–2004; ‡Significantly different from all periods except winter 2002–2003; §Significantly different from all other periods

OTC medication sales trends and *Rotavirus* cases may reflect that most of these cases are pediatric and that parents may tend to take their children to a physician rather than medicate with OTC products. Because we were unable to differentiate between adult and pediatric OTC products, we could not investigate this issue further.

The use of OTC medication sale trends as a supplemental surveillance tool for monitoring *Norovirus* levels could, theoretically, be very useful for public health officials. Indications are that viral GI likely has, through sheer volume, a very large impact on community burden of illness, particularly on the more frail or susceptible members of the community. This is especially evident where person-to-person contact is high (nursing homes, day care facilities and hospitals) and where spread is exacerbated by increased confinement in cold weather. An early warning of a rise in community infections (based on OTC medication sales) would allow for extra vigilance and preventive actions (as simple as handwashing) in these facilities.

A limitation of our study was that we did not know whether people were buying products in response to illness (which could be chronic, infectious or noninfectious), for prevention (holidays or travel) or because of a store promotion. Thus, a pharmacy-level consumer study would be valuable for ascertaining more specifically the type of medications being purchased and the reason for the purchase. As well, associated demographic, economic, social and cultural information would further enhance our understanding of OTC medication practices.

Targeted investigations to determine the percentage of GI cases due to bacterial, parasitic or viral infections would address our current lack of information on the relative magnitude of viral illnesses. Key locations for such studies would be hospital emergency rooms, because they would provide community representation and because sample-taking would be easier. An important complement to this would be a population-based study on GI-related behaviours, including the investigation of factors that prompt self-medication, media and

marketing influences, and changes in the availability of health care in Canada.

Improved monitoring and understanding of population GI due to *Norovirus*, either through syndromic surveillance using OTC medication sales or changes in laboratory testing techniques and protocols, would be expected to have a direct and significant impact on reducing the burden of illness due to this virus.

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