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From the horse's mouth: Calls to the British Columbia Drug and Poison Information Centre about ivermectin exposures during the COVID-19 pandemic

Concerns over unsafe use of ivermectin prompted a review and descriptive analysis of calls to the British Columbia Drug and Poison Information Centre from 1 January 2018 to 11 October 2021.

ABSTRACT

Background: As the COVID-19 pandemic continues to unfold, increasing numbers of Canadians have self-medicated with ivermectin, an antiparasitic drug used to treat infections and infestations in humans and livestock. This is despite a lack of good-quality evidence for its efficacy in preventing and treating infection with SARS CoV-2. Concerns over unsafe use of ivermectin prompted a review of calls to the British Columbia Drug and Poison Information Centre.

Methods: We performed a descriptive analysis of calls received from 1 January 2018 to 11 October 2021 about exposure to ivermectin and related compounds.

Results: The BC Drug and Poison Information Centre received 50 calls concerning exposure to ivermectin and related compounds during the period we studied. Prior to the COVID-19 pandemic, 23 calls were made, and all but one were unintentional exposures. The first ivermectin call referencing COVID-19 was received in March 2021, after which call frequency increased, leading to 27 more calls, of which 19 were intentional exposures to ivermectin referencing COVID-19. Of these calls, 11 concerned veterinary-grade ivermectin, and where doses were calculable, at 0.147–11.91 mg/kg, they were above the 0.15–0.2mg/kg therapeutic dose for most approved human uses. Three exposures were asymptomatic, 11 were considered to have minor effects, 1 was moderate, 4 were symptomatic but considered unrelated to ivermectin, and in 1 case symptoms were not recorded.

Conclusions: The use of ivermectin to prevent or treat COVID-19 is occurring in British Columbia, and both human and veterinary formulations are being ingested. Our case review suggests that these exposures occur most frequently in more agricultural regions, where the portion of adults vaccinated against COVID-19 has been lower and the portion infected higher than elsewhere in the province.

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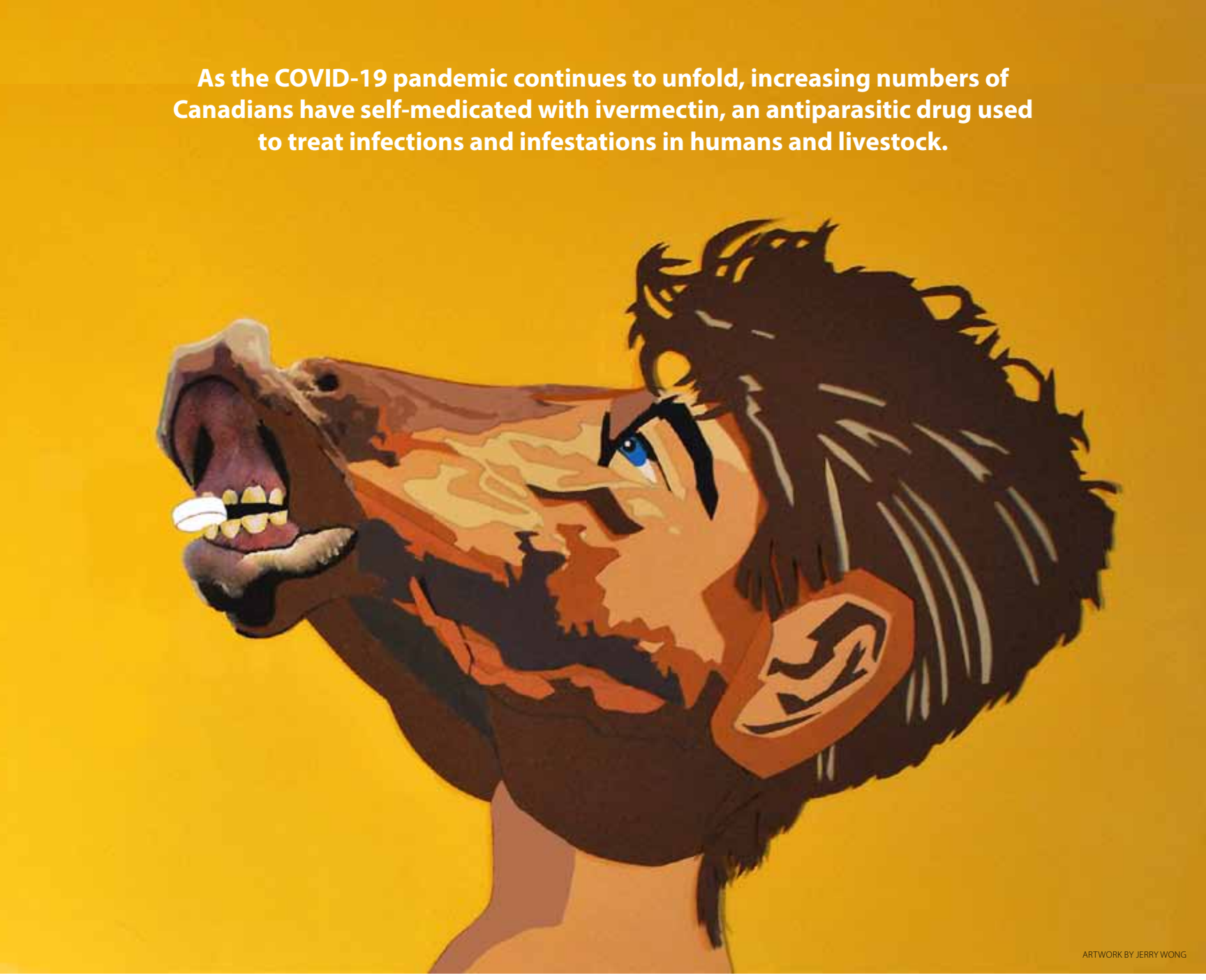
Background

Ivermectin is a broad-spectrum antiparasitic drug used to treat onchocerciasis (river blindness), strongyloidiasis, lice, and scabies among other parasitic infections and infestations, as well as rosacea.[1] In Canada, besides for treatment of such conditions in humans, ivermectin is used in veterinary medicine to treat livestock, including horses and cattle, as well as household pets, most commonly for heartworm and mites.[2]

As the COVID-19 pandemic drags on, a variety of existing medicines, notably ivermectin, has been studied to assess their potential in preventing and treating infection with SARS-CoV-2. When it was demonstrated early in the pandemic that, in vitro, high doses of ivermectin suppressed SARS-CoV-2 replication in a primate cell line,[3] numerous clinical trials were conducted to study whether ivermectin is effective in preventing or treating COVID-19. A scientific basis for this hypothesis exists; ivermectin has been studied for antiviral and anti-inflammatory activity for many years, and a recent computational simulation showed that ivermectin might block the

As the COVID-19 pandemic continues to unfold, increasing numbers of Canadians have self-medicated with ivermectin, an antiparasitic drug used to treat infections and infestations in humans and livestock.



ARTWORK BY JERRY WONG

SARS-CoV-2 spike protein from binding to the angiotensin-converting enzyme 2 receptor,[4] the receptor required for SARS-CoV-2 to attach and enter human cells. However, randomized controlled trials have produced very low to low certainty evidence of the efficacy of ivermectin for this use,[5] with some studies raising serious concerns about flaws in methodology and data interpretation.[6] In the absence of clear evidence for using ivermectin to prevent or treat COVID-19, health authorities worldwide, including Health Canada, have not authorized such use. Nevertheless, commentators (particularly in the US) have promoted its benefits, and it became apparent in spring and summer 2021 to the Health Products and Food Branch of Health Canada that increasing numbers of Canadians were seeking and using ivermectin, including veterinary formulations.[7] In parallel, a shortage of prescription ivermectin formulated for human use began in January 2021 and is ongoing.[8]

Concerns over ivermectin misuse include toxicity, which can result in abdominal pain, nausea, vomiting, diarrhea, headache, visual disturbances including hallucinations, dizziness, tachycardia, hypotension, metabolic acidosis, respiratory failure, ataxia, seizures, central nervous system depression, and death.[9] Given this concern, we reviewed calls to the BC Drug and Poison Information Centre (BC DPIC) about exposure to ivermectin and two related compounds, avermectin (used in pesticides) and selamectin (used in veterinary medicine). The BC DPIC is the provincial telephone poison control service available to the public and to health care providers; it is staffed by pharmacists, nurses, and physicians who provide consultation on management.

Methods

We performed a descriptive analysis of ivermectin exposure calls received by BC DPIC from 1 January 2018 to 11 October 2021. We included calls regarding exposure to related substances, specifically avermectin (commonly used in insecticides) and selamectin (a veterinary product). Calls were extracted from BC DPIC's electronic record using Poisindex (a poison information/classification system for quickly identifying and managing toxic exposures)[10] substance code "077715 Non-ANTHELMINTIC: OTHER" and searching for "ivermectin," "avermectin," and "selamectin" in the noncoded specific substance field. Using a purpose-designed extraction form, we manually extracted data from standard record fields as well as verbatim case notes. Information captured included demographics of the exposed individual, substance type (avermectin, selamectin, ivermectin), formulation (veterinary, human, insecticide), dose in mg/kg when known, reason for exposure (accidental or intentional, unrelated or related to COVID-19, for COVID-19 prevention or treatment), intended application (e.g., topical, oral), route of exposure (e.g., topical, oral), caller type (self, friend or relation, health care provider), health authority of exposed person's residence, symptoms, and BC DPIC recommendation. Medical outcomes at time of call were classified as minor, moderate, or major as determined by National Poison Data System classification based on clinical effects.[11] Extraction data were validated and entered into a Microsoft Excel spreadsheet for analysis.

Results

Fifty calls concerning exposure to avermectin, selamectin, and ivermectin were received at BC DPIC from 1 January 2018 to 12 October 2021. Of these, 15 calls were made by the exposed person, 24 by a friend or relation, and 11 from a health care provider. All 11 calls from providers occurred after the start of the COVID-19 pandemic. Of the 50 calls, 23 occurred from 2018 to 2020 (0.64 calls per month), and 27 occurred from January to 11 October 2021 (2.57 calls per month). The first call referencing COVID-19 was received in March 2021, after which BC DPIC took increasing numbers of ivermectin calls **[Figure 1]**. Over the almost 4-year study period, 20 calls concerned exposures to avermectin or selamectin, 11 were about exposures to ivermectin unrelated to COVID-19, and 19 concerned exposures to ivermectin for reasons related to COVID-19. As summarized in **Table 1**, 29 of 31 calls for avermectin, selamectin, and ivermectin unrelated to COVID-19 were in accidental exposures, whereas all 19 calls for ivermectin related to COVID-19 were intentional ingestions: 5 ingestions were for COVID-19 prevention, 12 for treatment, and 2 for an unspecified reason related to COVID-19.

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Calls about ivermectin related to COVID-19

Of the 19 calls about ivermectin exposure referencing COVID-19, 13 exposures (65%) were in males. The mean age was 53.2 (range 19–97). There were no calls about persons aged 18 or younger where COVID-19 was referenced, whereas there were four calls concerning children exposed to ivermectin unrelated to COVID-19, all of which were accidental exposures, three received before March 2021 and one received after. Seven COVID-19 related calls were from the exposed individual, 4 from a friend or relation, and 8 from a health care provider.

All exposures to ivermectin for reasons related to COVID-19 were intentional ingestions. Eleven were veterinary products, one was a product for humans, and in seven cases the formulation was unknown. Of the 11 exposures to a veterinary product, 8 were oral products, 1 was a product meant for topical application that was taken orally, and in 2 cases the intended application was not recorded. In terms of health authorities, 8 calls came from Interior (IHA), 3 from Northern (NHA), 5 from Fraser (FHA), 2 from Vancouver Island (VIHA), and 1 from Vancouver Coastal (VCH). Dose ingested was recorded in 13 calls, for which the mean was 2.18 mg/kg and range 0.147–11.905 mg/kg. Twelve of 13 known doses were above the 0.15–0.2mg/kg typical therapeutic dose for treatment of parasitic infections in humans,[12] of which 6 were above 2 mg/kg, a dose below which no CNS toxicity has been shown.[13] Six of the exposed individuals stated that they took a dose higher than intended due to calculation errors, of which 4 were of veterinary products and 2 were unrecorded formulations.

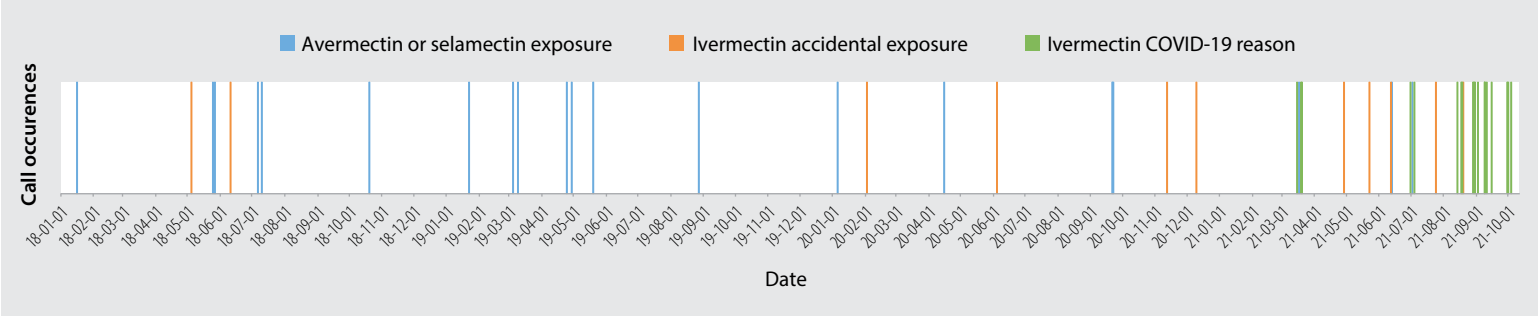

FIGURE 1. Occurrence of calls to BC DPIC about exposures to ivermectin or an ivermectin-like substance, 1 January 2018 to 11 October 2021.

TABLE 1. Calls to BC DPIC from 1 January 2018 to 11 October 2021 related to an exposure to ivermectin or an ivermectin-like substance.

	Accidental	Intentional
January 2018–December 2020		
Avermectin or selamectin	16	1
Ivermectin unrelated to COVID-19	6	—
Ivermectin related to COVID-19	—	—
January 2021–11 October 2021		
Avermectin or selamectin	3	—
Ivermectin unrelated to COVID-19	4	1*
Ivermectin related to COVID-19	—	19
COVID-19 prevention	—	5
COVID-19 treatment	—	12
Reason for use not specified	—	2

*Reason for use of ivermectin unclear and without reference to COVID-19.

Three individuals were asymptomatic at the time of call (reasons for these calls were concerns from a friend or relation and a query after a regretted ingestion). Eleven had symptoms attributable to their ivermectin exposure: 9 were coded as having minor effects (2 dizziness, 1 headache, 1 tingling lips, and 1 nonspecific sensations), 1 moderate effect (visual disturbances), and 1 unclear. Four were symptomatic but it was considered by the BC DPIC poison specialist that the symptoms were not attributable to the ivermectin exposure. These four included one individual who had severe central nervous system and respiratory depression resulting in death, but whose timing of ivermectin ingestion was not known and the potential effect of ivermectin could not be distinguished from that of their known COVID-19 illness; one person whose dose was too small to have any expected toxicity and whose respiratory symptoms were consistent with their known COVID-19 illness; one whose symptoms of diarrhea and headache started prior to ivermectin ingestion, along with respiratory symptoms consistent with their known COVID-19 illness; and one whose fever, anorexia, and fatigue started prior to their ivermectin ingestion. Symptoms were not recorded for one call. For four calls, BC DPIC referred the individual to hospital, 8 were already en route to or in hospital, 6 were given management advice or reassurance but were not recommended to present to hospital, and 1 was lost to follow up.

Table 2 compares some of the above characteristics between calls about ivermectin related and unrelated to COVID-19. There were notable differences: (1) there were four accidental pediatric exposures in the unrelated group and none in the related group, and (2) the exposures unrelated to COVID-19 included dermal, ocular (accidental splashes to the eyes), and parenteral (a needlestick injury) routes, whereas all COVID-19 related exposures were by ingestion.

Conclusions

Clearly, use of ivermectin to prevent or treat COVID-19 is occurring in BC, and both human and veterinary products are being used. These findings are consistent with reviews from the United States, where the American Association of Poison Control Centers compiled more than triple the number of ivermectin calls in 2021 compared to 2019 and 2020, and recorded serious adverse events including deaths attributed to ivermectin used to prevent or treat COVID-19.[14] This review of BC poison control call records revealed no severe effects clearly attributable to ivermectin, with asymptomatic exposures and minor effects predominating, and one severe outcome that could not be distinguished from the individual's known COVID-19 disease. In contrast, a recent review of calls to the Oregon Poison Center regarding ivermectin included a number of individuals who had more severe effects, with some requiring care in an intensive care unit, although it is less clear if the dose and ivermectin formulation (i.e., human or veterinary) taken by these individuals was known.[15]

Notably, 11 of the 12 exposures to ivermectin related to COVID-19 where formulation was known were exposures to a veterinary product, of which four involved an error in dosing. Veterinary ivermectin is most commonly used for farm animals. Total agricultural land area ranked from most to least by health authority is NHA, IHA, and FHA.[16] This ranking is the same for the portion of individuals by health authority not vaccinated against COVID-19 as of 11 October 2021.[17] This is also the order from highest to lowest for rate of cases of COVID-19 over the 7-day period between 5 and 11 October 2021.[17] Similarly, the rate by population of calls to BC DPIC for ivermectin referencing COVID-19 was highest from IHA, followed by NHA, FHA, VIHA, and VCH. These patterns suggest an association between access to and familiarity with ivermectin, and attitudes and beliefs about COVID-19. As for caller type, the four calls from a friend or relation emphasize one of the social science lessons of the pandemic: the importance of health literacy not just in individuals but in their social networks.[18]

Calls to BC DPIC regarding exposures to ivermectin and related compounds are not a new occurrence, but the most noticeable changes since the beginning of the COVID-19 pandemic are the quadrupling of calls per month that occurred in 2021, the increased frequency of intentional exposures in general and to veterinary formulations, and the increased frequency of calls from health care providers who, prior to the pandemic, would not have encountered such frequent misuse of ivermectin and thus presentations of toxicity from either human or veterinary formulations. Of note, Google searches for "ivermectin" spiked when the pandemic reached BC in spring 2020 **[Figure 2]**,[19] but no calls to BC DPIC about exposure to ivermectin were made until spring 2021, around

TABLE 2. Calls to BC DPIC about ivermectin related and unrelated to COVID-19.

	Ivermectin calls related to COVID-19	Ivermectin calls unrelated to COVID-19
Sex		
F	6	4
M	13	7
Age		
≤ 18	—	4
Age unknown	—	4
Mean	53.2	19.9
Range	19–97	3–63
Caller type		
Self	7	3
Friend or relation	4	6
Health care provider	8	2
Health authority of exposed individual		
IHA	8	5
NHA	3	2
FHA	5	2
VIHA	2	1
VCH	1	—
Not recorded	—	1
Intended use		
Veterinary	11	11
Human	1	—
Not recorded	7	—
Dose		
Dose recorded	13	2
Mean (mg/kg)	2.18	3.6
Range (mg/kg)	0.147–11.905	0.3–6.9
Route of exposure		
Oral	19	6
Dermal	—	2
Ocular	—	2
Parenteral	—	1
Clinical severity[11]		
Asymptomatic	3	6
Symptomatic	11	5
Minor	10	5
Moderate	1	—
Major	—	—
Symptoms unrelated to exposure	4*	—
Unknown	1	—

*This includes the one individual who had severe central nervous system and respiratory depression resulting in death, but whose timing of ivermectin ingestion was not known and the potential effect of ivermectin could not be distinguished from that of their known COVID-19 illness.

the time of a relative rise in COVID-19 cases in the province. Calls were received most frequently in August 2021, paralleling another rise in cases, and also when Google searches for "ivermectin" were at their highest. Just as Google searches can act as surrogate markers for public awareness, calls received by poison control centres have been used as a source of information to identify and monitor emerging public health issues, including trends in adverse drug reactions[20,21] and in injuries and adverse effects of consumer products.[22]

Limitations

While all poison centre calls by and about BC residents were captured, individuals who took ivermectin without consequence, who had minimal symptoms, or whose symptoms were so severe that the poison centre was not consulted prior to or in association with a hospital visit would not have been recorded. The information retrieved from poison centre records may have had gaps or inaccuracies based on what the caller told BC DPIC, or what the BC DPIC poison specialist recorded. While poison centre calls can and did signal that ivermectin is being used, they cannot approximate its total use in the province. Determining total use in British Columbia, which was beyond the scope of this study, would require review of PharmaNet data to determine prescription rates for human ivermectin, as well as a review of retail veterinary ivermectin sales, for which there is no readily accessible centralized database.

Tips for health care providers

BC DPIC is available 24/7, 365 days a year to provide consultation on management or to answer questions on any type of suspected or confirmed poisonings by medication, chemicals, and other substances. The service is available to the BC public and health care providers, and is staffed by pharmacists, nurses, toxicologists, and environmental health specialist physicians. When required, callers and patients can be followed by BC DPIC for the duration of symptoms, whether the individual is at home, in the emergency department, or an inpatient. BC DPIC can be reached at 604 682-5050 or toll free at 1 800 567-8911. For more information, go to www.dpic.org.

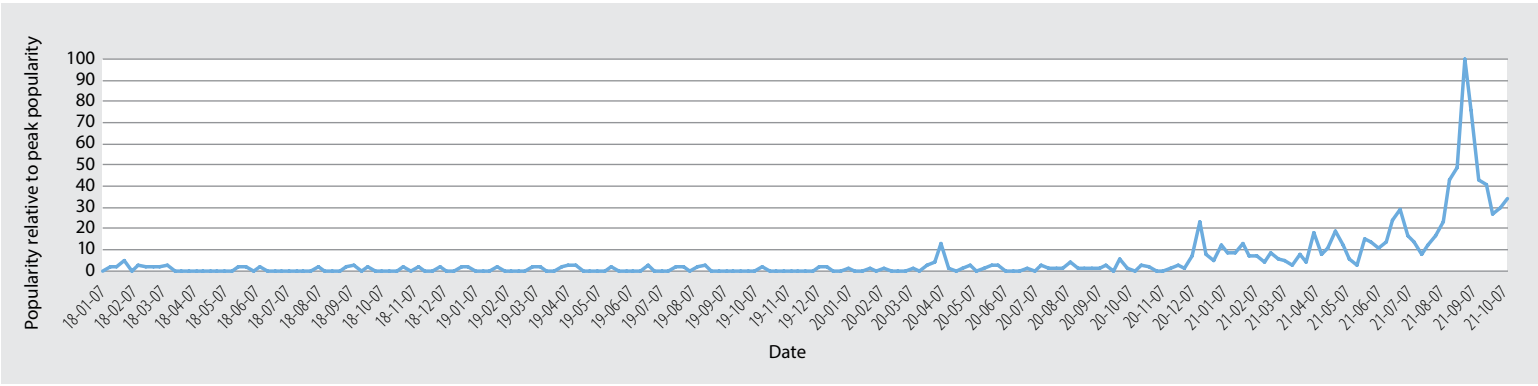

FIGURE 2. Google searches for "ivermectin" in BC 1 January 2018 to 11 October 2021, relative to the highest number of searches in the given time frame, where a value of 100 is the peak popularity for the term and a value of 50 means that the term is half as popular. Data source: Google Trends (www.google.com/trends).

How should physicians assess a patient who has taken ivermectin?

Patients taking ivermectin intended for humans typically will not present with symptoms, unless an excessive dose was ingested. If you are concerned about the potential for toxicity, you can call BC DPIC for guidance. Ask the patient how much they have taken, if the formulation is a human or a veterinary product, and when it was taken. Mild and moderate toxicity can present as abdominal pain, nausea, vomiting, diarrhea, headache, visual disturbances including hallucinations, dizziness, tachycardia, and hypotension; severe toxicity can result in metabolic acidosis, respiratory failure, ataxia, seizures, CNS depression, and death.

The therapeutic dose for treatment of parasitic infections in humans is typically in the range of 0.15–0.2 mg/kg orally for adults and children ≥ 15 kg, with 2 mg/kg being a dose documented in a human safety study to result in no CNS toxicity. Lower doses are less likely to result in toxicity, although it is still possible based on patient factors. Ivermectin achieves peak plasma concentrations 4 hours after oral ingestion, so if medical observation is required, a typical period of observation of 4 to 8 hours in an asymptomatic or mildly symptomatic patient may be reasonable. As there is no antidote for ivermectin, management is typically supportive. If the patient has taken a veterinary product, calculations for dose would be based on the concentration of active ingredient, if known, but since veterinary products often contain drug-delivery vehicles and other filler ingredients that may not have been studied in humans or approved for human use, symptoms of toxicity may not appear as expected and the patient may require closer observation.

What should physicians do if patients ask about ivermectin?

Inform the patient, at this time, that Health Canada has not authorized its use for COVID-19 prevention or treatment because there is insufficient evidence to support this use. Patients may have heard or read about a number of clinical trials for ivermectin and COVID-19, but explain that the large trials and the studies that summarize findings from these trials have not provided strong enough evidence to show that it is effective. You can refer patients to resources and health advisories from Health Canada, the US CDC, and the WHO.

You can also advise patients that veterinary formulations have not been tested in humans, that they often contain filler ingredients with unknown effects on humans, and that taking veterinary products may deliver excessive doses leading to harm. You can inform them about the potential for ivermectin toxicity as described above, and share that there are instances of serious adverse events from ivermectin, including deaths, documented in the US.

If the patient still requests a prescription, inform them that the College of Physicians and Surgeons of BC, the College of Pharmacists of BC, and the BC College of Nurses and Midwives do not approve of the use of ivermectin for either treatment or prevention of COVID-19 and providers must not prescribe it for this purpose. ■

Competing interests

None declared.

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Mountain ski patrol. My advice was, take it! He quickly learned that mountain medicine was much different than that in the confines of a hospital, and he thrived. He spent time with the orthopod Dr Pat McConkey and honed his physical diagnostic skills in sports medicine. Rob often complained that he felt bad having his patients pay for an MRI of their knee when he had already given them their diagnosis.

In the early 1980s, Rob, along with Dr Christine Rodgers, offered full family practice services out of an ATCO trailer. The medicine was never boring and was often carried out in challenging outdoor settings. Rob joined an energetic community and worked to expand Whistler's health care facilities to the high standard that is provided today.

Rob gave a lot to the mountain community and the mountain community gave a lot to Rob. He relished the opportunities offered to him. Whether it was as physician to the National Alpine Ski Team or physician guide to various heli-ski companies, all parties benefited.

A few years ago, Rob gave up his family practice but was unable to give up on his community. He continued to be busier than ever with locums and his aviation physicals. He regretted having to give up a COVID vaccine clinic following his diagnosis. His friends and community have been widely supportive following his passing.

To a man well loved and a life well lived. We will all miss you, Rob.

—William Akeroyd, MD
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