Truth and direct-to-consumer advertising in Canada of DUKORAL for traveler's diarrhea prevention

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The ability to practise as a primary care physician in a nonconflicted, evidence-based manner can be challenging within a practice environment full of questionable online information bombarding not only patients but also providers. Unfamiliar with specific interventions, physicians might rely too heavily on easily accessible messages created and tailored by the corporate world to put the private interests of shareholders ahead of the public interest. One understudied area of concern is the effect of direct-to-consumer advertising (DTCA) on physicians and other health providers,[1] both directly and through manufactured demand from patients for drugs and vaccines that might not be medically necessary.[2] While Canada has weakly prohibited the DTCA of prescription drugs,[3] it has not prohibited DTCA for immunizing agents.[4] While leakage of DTCA enters the Canadian market through American sources using cable television and the Internet, vaccines uniquely approved in our country but not in the United States provide a natural experiment on the outcome of domestic DTCA's effect on Canadian physicians, nurses, and pharmacists. The purpose of this article is to historically review a travel-related vaccine (ie, DUKORAL) that is currently being overprescribed by primary care physicians in Canada despite long-standing evidence-based guidelines demonstrating its lack of efficacy.

Background

After receiving an application from the manufacturer in July 2001, Health Canada expedited the approval of DUKORAL in February 2003 as an "oral, inactivated traveler's diarrhea and cholera vaccine" using the priority review process that has been soundly criticized.[5] There has never been another vaccine licensed in Canada simultaneously for 2 different conditions (ie, cholera and diarrhea caused by heat-labile toxin-producing enterotoxigenic *Escherichia coli* [LT-ETEC]) where the primary indication (ie, cholera) has been made subordinate to an unproven secondary indication (ie, LT-ETEC); or where the vaccine targets a clinical syndrome (eg, traveler's diarrhea [TD]) rather than a specific pathogen. Yet DUKORAL solely comprises cholera components (killed whole-cell *Vibrio cholerae* O1 bacteria and recombinant cholera toxin B subunit [rCTB]).[6] Although the cholera toxin might have some structural similarities to the LT-ETEC toxin, there is no direct evidence of DUKORAL's protective efficacy against LT-ETEC or TD in general among travelers. Looks can be deceiving.

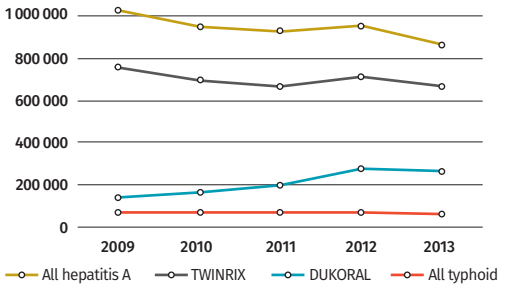
The only evidence, showing a 7% risk reduction of TD between travelers taking (ie, cases) and not taking (ie, controls) the vaccine, is based on one old study using a vaccine prototype of DUKORAL,[7] which is different from the currently marketed vaccine. DUKORAL itself has never been properly shown to reduce the incidence of TD using randomized controlled trials (RCTs),[8] especially in Canadians. While DUKORAL was used in the 1995 Scerpella et al RCT study,[9] subjects took the vaccine after arrival in Mexico, showing that it does not work if taken after departure to a developing country. In a preliminary RCT by Wiedermann et al in 2000,[10] there was no difference between the DUKORAL and placebo groups regarding incidence of diarrhea. A large non-RCT observational study among Spanish travelers found a 3% difference in the occurrence of TD between the group taking the vaccine and the group not taking it,[11] which was clinically insignificant. The manufacturer has not conducted any further RCTs on the licensed vaccine to address the lack of efficacy data following approval of its use in Canada in 2003.

When a vaccine is approved by Health Canada, it is automatically classified as not requiring a prescription in order to ensure that local public health agencies have access to appropriate vaccines for childhood and other publicly administered immunization programs. For use outside of these public health programs, the National Drug Scheduling Advisory Committee (NDSAC) is responsible for guidance to provincial pharmacy authorities on the scheduling of vaccines (and drugs) into 3 classifications pertaining to a particular product's access at the retail pharmacy.[12] At the request of the representatives of the manufacturer in December 2003, NDSAC created a unique dual status for DUKORAL, which included requiring a prescription (schedule I classification) for its use against cholera, as well as pharmacist dispensing behind the counter (schedule II classification) for its use against TD.[13] As only 1 component of the vaccine is being used for TD prevention (ie, rCTB), it was unusual to see NDSAC making public access much easier for an unproven secondary indication (ie, TD). However, NDSAC made it more difficult to access DUKORAL for the proven primary indication (ie, cholera) that the entire vaccine is being used to immunize. The result is that DUKORAL is mostly provided through retail pharmacies without prescription, including when patients are picking up more effective

pretravel interventions such as antibiotic (eg, azithromycin or ciprofloxacin) and nonantibiotic self-treatment (eg, loperamide).[14] While DUKORAL is generally considered safe in the context of being taken once every few years (ie, the cholera vaccine schedule), there are no formal safety studies on frequent use over a short period of time (eg, the LT-ETEC or TD vaccine schedule). This constitutes a long-term natural experiment among Canadian travelers since 2003.

In 2005, the federal Committee to Advise on Tropical Medicine and Travel (CATMAT) published specific guidelines for the evidence-based use of DUKORAL, recommending that it be used in very limited circumstances in the context of TD or LT-ETEC prevention.[15] This guideline and subsequent CATMAT statements on the prevention and treatment of TD appear to have had little effect on the sale of DUKORAL in Canada, which is being provided in greater quantities than typhoid fever immunization that prevents a condition considered clinically more concerning for practice experts (**Figure 1**).[16] From an international perspective, the manufacturer states that "Canada represents the single largest market for DUKORAL, accounting for more than 50% of global product sales in 2016."[17] In 2007, the first revision of the product monograph did not reference the 2005 CATMAT statement on the vaccine; however, it did incorporate an irrelevant 2006 CATMAT statement on treating persistent or chronic diarrhea in return travelers.[18] Similarly, a revision in 2011 did not correct this glaring omission. In 2015, after reassessing the original application, Health Canada directed the manufacturer to change the indication for DUKORAL to an "oral, inactivated cholera and ETEC diarrhea vaccine." Indications for the vaccine were not further restricted to a "cholera only" vaccine, in a manner similar to that of the European Union,[19] where the vaccine is manufactured. Again, no considerable revisions of references in the 2015 monograph were made to include the 2005 CATMAT statement,[15] the 2013 systematic review of the lack of efficacy of DUKORAL against TD,[6] or the updated CATMAT statement on TD in 2015.[14]

Figure 1. Estimated total number of units of selected travel vaccines purchased by Canadian drugstores and hospitals from manufacturers and wholesalers from 2009 to 2013*



TRAVEL VACCINES	2009	2010	2011	2012	2013
All hepatitis A	1 019 911	943 840	923 161	948 850	856 937
TWINRIX	752 201	692 911	665 845	704 326	667 253
DUKORAL	144 148	169 441	199 833	279 745	273 137
All typhoid	72 477	77 694	81 068	80 874	70 028

*Data from IQVIA Solutions Canada Inc.[16] The information contained in this figure is derived in whole or in part from data obtained under licence from IQVIA Solutions Inc. Source: Canadian Drug Store and Hospital Purchases Audit, 2009-2013. All rights reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IQVIA Solutions Canada Inc, or any of its affiliated or subsidiary entities.

Truth in advertising?

The DTCA of DUKORAL currently remains focused on promoting this cholera vaccine primarily as prevention against ETEC causing diarrhea.[20] The interim Health Canada guidance published in 2009 gave formal permission for DTCA of DUKORAL, which became noticeable through increasing patient demand within travel and tropical medicine practice by 2010 (personal observation). Health Canada has indicated that the reference document to validate "truth" in DTCA is the approved product monograph and its companion consumer information pamphlet.[4] The latter continues to describe ETEC prevention first and in greater detail than cholera prevention, subordinating the vaccine's primary and proven indication. What then is the problem with overusing this relatively safe but ineffectual vaccine for TD prevention? DUKORAL does contain a buffering solution to protect the rCTB portion from destruction by gastric acid.[21] All commonly encountered adverse effects including nausea, vomiting, abdominal cramps, and diarrhea are attributed to this buffering solution. Thus, it is medically unethical to expose a patient to regular harms where there is little evidence of benefit (ie, TD prevention).

Cholera is also considered an uncommon disease among Canadian and other Western travelers.[22] Unlike malnourished populations in refugee camps, few if any healthy Canadian travelers will die of cholera, which can also be effectively addressed using antibiotic self-treatment, as well as oral rehydration.[23] In the context of travel and tropical medicine practice, the evidence-based use of DUKORAL would be infrequent and not considered a priority except for those working within a cholera outbreak region (eg, humanitarian workers). Because Canada has delisted and defunded pretravel clinical prevention, there will also be opportunity costs for high-risk patients such as working-class immigrants and their children visiting friends and relatives in developing countries.[24] Many of these vulnerable Canadian travelers must set priorities on what they can and cannot afford to pay to protect themselves and their families. Clinical prevention of life-threatening conditions such as malaria, typhoid fever, and high-altitude illnesses should be the priority, along with proven antibiotic

self-treatment of diarrhea to avoid unnecessarily engaging with the local medical system overseas (ie, iatrogenic prevention). If these vulnerable travelers waste limited financial resources on an overmarketed ineffectual vaccine for a common but rarely serious medical condition, then they might not have the money to pay for prevention against more important health risks. The overuse of DUKORAL might lead to the underuse of proven prevention priorities. This is a serious opportunity cost.

Conclusion

While there currently is no formal research into the direct effects of DTCA on health providers,[1] physicians and pharmacists are prescribing and dispensing this vaccine in a manner at odds with well established clinical guidelines and systematic reviews. This suggests that DTCA of vaccines in Canada is having an effect on physicians, nurses, and pharmacists, as well as the general public, that is not necessarily in the interest of patient care. If any Canadian health provider does not know that DUKORAL is a cholera vaccine and is not marketed in most industrialized countries for TD or LT-ETEC prevention, then that health provider might be influenced by DTCA directly, as well as through demand from his or her patients. It is unlikely that Health Canada is going to improve the validation of DTCA for vaccines in the near future.[3] Therefore, it behooves all primary care physicians to take time to review nonconflicted medical information on vaccine and drug products before making recommendations to their patients. In an era of online information cacophony, medical doctors might be one group of health providers who can speak truth to corporate power for the sake of safe and appropriate health care.

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Competing interests
None declared

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