November 2, 2017 • Volume 43-11

CCDR

CANADA COMMUNICABLE DISEASE REPORT

ANTIMICROBIAL RESISTANCE AND ONE HEALTH

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

CCDR
CANADA COMMUNICABLE DISEASE REPORT

The *Canada Communicable Disease Report* (CCDR) is a bilingual, peer-reviewed, open-access, online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public health professionals, and policy-makers to inform policy, program development and practice.

Editorial Office

CCDR Editorial Board

Photo Credit

The cover photo is a portrait of a farmer feeding cows on a farm, produced by Shutterstock (https://www.shutterstock.com/image-photo/portrait-farmer-feeding-cows-farm-571559599) and modified by Wendy Patterson, Ottawa ON.

Contact Us

ccdr-rmtc@phac-aspc.gc.ca
613.301.9930

 ISSN 1481-8531 / Cat. HP3-1E-PDF / Pub. 180145

CCDR
CANADA COMMUNICABLE DISEASE REPORT

ANTIMICROBIAL RESISTANCE AND ONE HEALTH

TABLE OF CONTENTS

FRAMEWORK

Pan-Canadian framework for action on antimicrobial resistance and antimicrobial use

Public Health Agency of Canada[1]*

Abstract

Antimicrobial-resistant infections are becoming more frequent and increasingly difficult to treat, and this situation is exacerbated by the widespread use of antimicrobials in both human and veterinary medicine and by the agriculture industry. As part of Canada's coordinated response to addressing antimicrobial resistance (AMR), *Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action*, was released in September 2017. The Framework is a high-level policy document that outlines the strategic objectives, outcomes and opportunities to guide collaborative action on AMR and antimicrobial use (AMU). It is grounded in a One Health approach, and was developed in collaboration with federal, provincial and territorial governments and external stakeholders in the human and animal health sectors. The Framework is based on four components: surveillance; infection prevention and control; stewardship; and research and innovation. It builds upon existing AMR activities already underway in the human and animal health sectors and strives to connect these activities together to strengthen Canada's approach to AMR.

Affiliation

[1] Centre for Communicable Disease and Infection Control, Public Health Agency of Canada, Ottawa, ON

***Correspondence:** ccdic-clmti@phac-aspc.gc.ca

Suggested citation: Public Health Agency of Canada. Pan-Canadian framework for action on antimicrobial resistance. Can Commun Dis Rep. 2017;43(11):217-9. https://doi.org/10.14745/ccdr.v43i11a01

Introduction

Antimicrobials are an essential tool against infections in both humans and animals. However, due to widespread use in human and veterinary medicine and in the agriculture industry, antimicrobials are losing their effectiveness more quickly than we are able to develop new ones. This has significant consequences for human and animal health and welfare, food safety, the environment and the economy. Canada must take coordinated action, both domestically and globally, to slow the rising trend of antimicrobial resistance (AMR) and minimize its impact while promoting appropriate antimicrobial use (AMU) to preserve the effectiveness of existing and future antimicrobials. The purpose of this article is to summarize the recently released document, *Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action* (1).

State of AMR and AMU in Canada

In Canada, rates of most AMR infections are stable and, in some cases, there has been a decline in the infection rates of select drug-resistant organisms; however, even these reduced rates exceed those of the early 2000s. Of concern, are the increased rates of some diseases; for example, *Neisseria gonorrhea* has increased by 43.1% over the past decade in Canada and now requires stronger and more complex antibiotic treatment (2).

In community settings, antibiotics are often prescribed without laboratory testing and confirmation and are often used inappropriately to treat viral infections, for which they are ineffective (e.g., colds, flu, acute sinusitis). In 2014, it was estimated that over 23 million antimicrobial prescriptions were written for human consumption in Canada and 93% were dispensed by community pharmacists (2). Of these, an estimated 30–50% were unnecessary (3).

Antimicrobials are also used in livestock for the treatment and control of disease and to improve production. The majority (73%) of antimicrobials distributed for use in animals belong to the same classes as those antimicrobials used in human medicine (2).

A Pan-Canadian approach to addressing AMR and AMU

Many AMR and AMU-related actions are underway in Canada; however, the endorsement of the Pan-Canadian Framework creates an opportunity to improve cross-sectoral coordination and collaboration through a coherent pan-Canadian response to AMR.

Federal, provincial and territorial (F/P/T) governments have employed a One Health approach in developing a Pan-Canadian Framework for Action, which recognizes the interconnectedness of humans, animals and the environment. The Framework was developed in collaboration with F/P/T governments and subject matter experts from academia, non-governmental organizations and industry representing human health, animal health and agriculture sectors. Its development was facilitated through a dedicated F/P/T governance structure, including senior governmental representatives and subject matter experts.

Pan-Canadian framework on antimicrobial resistance and antimicrobial use

The document *Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action* (1) was released in September 2017. Although all types of antimicrobials are critical for treating infections, the primary focus of the Framework is on bacterial resistance to antibiotics, as this is seen as the most significant threat to health.

The human and animal health aspects of the One Health approach are currently the focus of the Framework. As work advances in these areas, the environmental aspect will then be considered. The Framework focuses on four key components: surveillance; infection prevention and control; stewardship; and research and innovation. The overarching goal of the Framework is to strengthen Canada's ability to combat the risks of AMR in a coordinated, multi-sectoral and effective manner.

Surveillance

Strong, integrated surveillance systems are needed to provide a comprehensive picture of AMR and AMU in Canada. While pan-Canadian surveillance systems are producing useful and reliable data on AMR and AMU, there are still significant knowledge gaps in information for certain settings (e.g., community), the need for benchmarking to assess trends in AMR and AMU and an increased need for the standardization of laboratory and data collection methods, case definitions and improved timeliness of reporting.

Opportunities for action to address these gaps include coordination on robust and comprehensive surveillance systems, cross-sectoral data-sharing platforms and mechanisms and enhancement of coordinated technical guidance for data collection, collation and comparison.

Infection prevention and control (IPC)

To contain the spread of resistant organisms and reduce AMR and AMU, standardized infection prevention and control approaches, programs and policies must be in place. There are challenges to implementing IPC measures and practices in Canada within and across human and animal settings. These include few established IPC programs in long-term care facilities and other places where healthcare services are delivered, disparity in jurisdictional governance for IPC programs in the agriculture sector, and effective targeting and evaluation of IPC interventions.

Opportunities for action to address these challenges include multijurisdictional engagement of governments and stakeholders to take action within their realm of responsibility on delivering communication, education/training and tools on IPC practices and strategies and facilitating and promoting the application and oversight of IPC best practices.

Stewardship

Programs and policies that highlight education, awareness-raising and professional and regulatory oversight will be required to reduce inappropriate prescribing, dispensing and use of antimicrobials in humans and animals, and to conserve the effectiveness of new and existing antimicrobials.

Improved knowledge translation, awareness, communication, regulatory consistency, training and guidance about AMR and AMU by and for health and veterinary professionals, livestock producers and the public, in combination with better coordination of F/P/T governments' efforts, are needed to foster an effective and sustained culture of antimicrobial stewardship. Sufficient investments in surveillance, research and evaluation and audit and feedback mechanisms are also required.

Opportunities for action to enhance AMR stewardship include a cross-sectoral, multi-disciplinary antimicrobial stewardship network, the implementation of a robust system for collecting AMU data, the development of governance tools such as regulations, organizational accreditation requirements and consistent standards, and enhanced education and public awareness.

Research and innovation

Responses to AMR must be evidence-based and will require increased knowledge, innovative tools and collaborative approaches to better understand resistance and the development of new treatments and strategies.

Notwithstanding Canada's considerable research efforts, the global community continues to lack new antimicrobials, diagnostic tools and alternative treatments to antimicrobials. Gaps in research also include the economic costs of AMR, AMR transmission and risks, prescribing practices, behaviours towards antimicrobials and IPC practices in healthcare and community settings.

Opportunities for action to address these gaps include a cross-sectoral, multidisciplinary research network; capacity building and improved infrastructure to support the development of human and veterinary medicines and alternative tools; and a fast-tracked cost-effective process for licensing treatments and new diagnostic tools in Canada.

Conclusion and next steps

Canada is currently taking significant steps to address AMR and AMU. The Framework affirms the commitment of F/P/T governments to take coordinated and comprehensive action to mitigate the risks of AMR and to protect the health of Canadians. An associated action plan will be developed that identifies concrete deliverables, measurable outcomes and timeframes to support the implementation of the Framework. Implementation of the Framework will require continued engagement and committed actions by governments, industry and stakeholders in each of the four components to enable a sustainable and effective pan-Canadian response to AMR and AMU.

Acknowledgements

The Public Health Agency of Canada would like to thank all those who contributed their time and expertise during the development of Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action.

References

1. Public Health Agency of Canada. Tackling Antimicrobial Resistance and Antimicrobial Use. A Pan-Canadian Framework for Action. Ottawa ON: PHAC; Sept 2017. https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/tackling-antimicrobial-resistance-use-pan-canadian-framework-action.html
2. Public Health Agency of Canada. Canadian Antimicrobial Resistance Surveillance System – Report. Ottawa ON: PHAC; Sept 2016. https://www.canada.ca/en/public-health/services/publications/drugs-health-products/canadian-antimicrobial-resistance-surveillance-system-report-2016.html
3. National Collaborating Centre for Infectious Diseases. The Role of Human Health and Animal Health in Antimicrobial Resistance. Winnipeg MB: NCCID; 2016. https://cdn.centreinfection.ca/wp/sites/2/20170307163058/Katrime_Roles_Final_Eng.pdf

Enhancing antimicrobial stewardship by strengthening the veterinary drug regulatory framework

M Mehrotra[1]*, X-Z Li[1], MJ Ireland[1]

Abstract

Antimicrobial resistance is a major and growing public health threat. Recently, Health Canada introduced multiple regulatory changes to strengthen the oversight of antimicrobial drugs for veterinary use. These changes aim specifically at increasing control over importation of veterinary drugs and active pharmaceutical ingredients, mandatory reporting of antimicrobial sales data from manufacturers, importers and compounders and facilitating access to low risk veterinary health products. Additional policy changes under existing authorities are also being made to enhance veterinary supervision of antimicrobial use and to remove production claims for food animals from labels of medically important antimicrobial drugs. These important interlinked initiatives are aimed towards enhancing antimicrobial stewardship in Canada to preserve the effectiveness of existing antimicrobials and to protect the health of Canadians.

Affiliation

[1] Veterinary Drugs Directorate, Health Products and Food Branch, Health Canada, Ottawa, ON

***Correspondence:** manisha.mehrotra@hc-sc.gc.ca

ORCID number for XZL: 0000-0003-1722-3254

Suggested citation: Mehrotra M, Li X-Z, Ireland MJ. Enhancing antimicrobial stewardship by strengthening the veterinary drug regulatory framework. Can Commun Dis Rep. 2017;43(11): 220-3. https://doi.org/10.14745/ccdr.v43i11a02

Introduction

Antimicrobial resistance (AMR) continues to be a major public health risk that threatens the availability of effective antimicrobial therapy of infectious diseases worldwide. The development of AMR is associated with the use of antimicrobial agents in all sectors including human medicine, veterinary medicine, animal husbandry, aquaculture, plant agriculture and consumer products. As a federal authority for the regulation of antimicrobial drug products, Health Canada recognizes the human health risks associated with the emergence of AMR. Health Canada is committed to containing the development and spread of AMR while maintaining the efficacy of existing antimicrobials by promoting prudent and responsible use of these critical drugs. Health Canada's approach to evaluating and managing AMR risks associated with the use of antimicrobials in food animals is based on a complementary set of regulatory and policy initiatives. These initiatives are significant deliverables under the Government of Canada's "*Antimicrobial Resistance and Use in Canada: A Federal Framework for Action*" (1) and are essential elements of the stewardship component of the Pan-Canadian Framework on AMR (2). In this article, we provide an overview of the recent and ongoing initiatives being undertaken by Health Canada to strengthen the regulatory framework for veterinary antimicrobial drugs and to promote antimicrobial stewardship in veterinary medicine and the agri-food sector.

Background

Under the legal authority of the *Food and Drugs Act* and its Regulations, Health Canada evaluates information provided by sponsor companies concerning product quality, efficacy and animal and human safety before authorization to market a veterinary drug in Canada can be issued. The evaluation of human safety for an antimicrobial drug must include a microbiological safety assessment specific to AMR development risks. Since 2004, submission guidelines for new drug products have been made available by Health Canada to drug sponsors specifying the requirements for the human safety assessment of veterinary drugs relating to AMR (3). The safety assessment allows Health Canada to objectively analyze the AMR health risks and to determine whether current or future use of the antimicrobial drugs in animals warrants risk management actions. As a result, all new antimicrobials that are of importance to human medicine approved post-2004 have received the necessary scrutiny to limit potential unacceptable AMR risks (4). This has translated into AMR-specific warning statements on product labels, restrictions against certain uses and removal of claims that have shown to be of unacceptable risks to human health.

As Canada has a federated system of government, the provinces and territories (via the veterinarians and pharmacist professions they regulate) control the use of antimicrobial drugs, whereas the Federal Government approves the sale of these drugs. This division of responsibilities creates complexity and shared responsibility for oversight on what can be imported and sold and what can be imported and used. This has implications for proper stewardship of antimicrobial use.

Prior to the recently introduced amendments, the *Food and Drug Regulations* did not include appropriate oversight on importation of active pharmaceutical ingredients (APIs) of veterinary drugs. These APIs did not have to comply with the rules of Good Manufacturing Practices, and hence, did not have to meet conditions of who can import these drugs. Thus, APIs, in specific situations, could be imported and used directly in animals without further modifications. Furthermore, the

Food and Drug Regulations did not address drug importation for use in animals by animal owners for "personal use" (also known as "own use") purposes. The existing policy in this context was established to support human health by allowing individuals to import a maximum of a 90-day supply of a drug for their own use to continue and finish medication when travelling abroad; however, interpretation of this regulation for animal use as "personal use" by animal owners created a gap. Veterinary drugs imported for personal use under the existing rules included unauthorized products of unknown quality, efficacy or safety and thus have the potential to adversely impact food safety and human and animal health.

The existence of these gaps in regulatory oversight of veterinary drugs, including antimicrobial drugs, misaligned Canada with international partners (5). This limited Canada from effectively responding to World Health Organization and World Organisation for Animal Health international recommendations on AMR (i.e., effective national controls on licensing, manufacturing, sales, distribution, monitoring and use of antimicrobials in food producing animals and the resulting impacts) (6,7). This gap was also noted in a report on AMR from the Office of the Auditor General of Canada published in 2015 (8).

New regulatory changes for veterinary antimicrobials

To strengthen oversight and close the regulatory gaps in the *Food and Drug Regulations*, Health Canada introduced a set of amendments for consultation in July 2016 (9). As part of a multi-year effort and with effective collaboration and support from multiple stakeholders cutting across jurisdictional boundaries, Health Canada published the final regulatory changes to the *Food and Drug Regulations* in the Canada Gazette, Part II in May 2017 (10). These changes focused on four key measures detailed below.

Increasing oversight of unapproved veterinary drugs imported for food animals

Only drugs that Health Canada has determined not to be of risk to public health or food safety may be imported for personal use and only in limited quantities. The eligibility criteria do not allow for the importation of prescription drugs or medically important antimicrobials including active pharmaceutical ingredients. There is the *List of Certain Antimicrobial Active Pharmaceutical Ingredients* (List A) that specifies individual antimicrobial drugs considered important to human medicine (11).

Another provision will ensure that no person shall import a drug into Canada for the purpose of administering it to an animal that produces food or an animal that is intended for consumption as food, unless authorized by Health Canada. This will be set out in the *List of Certain Veterinary Drugs Which May be Imported But Not Sold* (List B). This list will contain specific unapproved veterinary drugs that may be imported but not sold (11) and that have met all the eligibility criteria as determined by Health Canada.

Increasing oversight on importation and quality of active pharmaceutical ingredients

Under the new rules, individuals who fabricate, package, label, import or test an API for veterinary use have to do so in accordance with an Establishment License, which is issued by Health Canada to a person in Canada allowing them to conduct licensable activities in a building that has been inspected and assessed as being in compliance with relevant requirements of the *Food and Drug Regulations*. More specifically, all importers of an ingredient for veterinary use on List A (11), including veterinarians and pharmacists, will have to apply for an Establishment License. In addition, the new regulations will prohibit the import or sale of veterinary APIs that are not manufactured according to the Good Manufacturing Practices. This provision creates requirements around the quality of veterinary drugs on the Canadian market and that only individuals with an Establishment License are importing APIs on List A and are doing so once registered with Health Canada.

Requirement to file annual sales reports for medically important antimicrobials

In contrast to the current situation, which relies upon voluntary reporting of veterinary antimicrobial sales data by drug manufacturers (via the Canadian Animal Health Institute) (12), this new mandatory data collection requirement will request manufacturers, importers and individuals who import, as well as individuals who compound medically important antimicrobials, to submit annual veterinary antimicrobial sales data to Health Canada. Data will be reported in the form of total quantity sold or compounded and an estimate of the quantity sold or compounded for each intended animal species. A data reporting template is being developed by Health Canada in collaboration with the Public Health Agency of Canada. This requirement will help measure the amount of antimicrobials available on the Canadian market for use in animals and support Canadian surveillance programs in the analysis of patterns and trends of AMR. Species-specific sales data could then be correlated with the species level AMR surveillance data, which is collected through the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) (12) and other programs. If hazards are identified from this surveillance and pursuant to a risk assessment, appropriate risk management actions would be considered in partnership with provincial regulatory bodies.

An alternative regulatory pathway for veterinary health products

Based on the premise that promoting the health and welfare of animals will help to reduce the severity and occurrence of infections and future antimicrobial usage, a flexible and risk appropriate regulatory framework for veterinary health products (VHPs) for animals has been developed to create a more streamlined approach for certain low risk health products. It provides admissible substances (such as vitamins, minerals, botanicals and traditional medicines with a history of safe use) and conditions for these products to be eligible for sale as VHPs, as identified on *List of Veterinary Health Products* (List C) (11).

A VHP can be sold with claims for maintaining general health and welfare of animals and cannot be marketed for the purposes of treating or preventing a disease or an infection. These low risk products are needed as an additional health management tool to reduce the need for conventional drugs (such as antimicrobials). These new rules require companies to notify Health Canada

at least 30 days before selling a VHP or making a change to a marketed VHP. Additional requirements include labels to state "Veterinary Health Product", the reporting of serious adverse drug reactions and the manufacturing of a VHP to follow the Good Manufacturing Practices for human natural health products.

These regulatory changes will be implemented starting in November 2017. Efforts are being made by Health Canada in collaboration with stakeholders to ensure a successful transition to the new rules.

Additional policy initiatives to promote antimicrobial stewardship

To complement this suite of new regulatory changes, Health Canada has worked over the years, in collaboration with provincial and territorial authorities and other stakeholders, to make additional changes within existing regulatory authorities to promote the responsible use of antimicrobials in animals. This initiative includes two key measures described below.

Making all medically important antimicrobials prescription drugs

It is anticipated that by December 1, 2018, a prescription will be required from a licensed veterinarian before an individual will be able to purchase a medically important antimicrobial drug for use in animals. Veterinarians, who prescribe for animals under their care, possess the scientific and clinical training to assess the health of animals, diagnose disease conditions, determine the need for antimicrobial drug treatment and choose the most appropriate course of treatment. Consequently, involving veterinarians in making antimicrobial therapeutic decisions is an indispensable component of enhancing antimicrobial stewardship. This is an internationally recognized best practice (7,13). Of note, since 2004, Health Canada has required that all new medically-important antimicrobials (4) for animals be sold pursuant to a prescription by a licensed practitioner. With this change, Health Canada aims to establish the same level of oversight for all medically important antimicrobials sold in Canada, including those approved prior to 2004.

The prescription drug status of in-feed formulations means that a veterinary prescription will be required prior to the sale of medicated feed containing a prescription drug. As per the anticipated policy changes, it is intended that the medicated feed containing a prescription drug can be prepared by a feed mill in advance of receiving a prescription, as long as the feed is made as per the Compendium of Medicating Ingredients Brochure (CMIB). The CMIB is maintained by the Canada Food Inspection Agency (CFIA) (14) and is an important resource for feed mills, veterinarians and producers. It provides instructions on how to manufacture medicated feeds and directions for its use. The CMIB currently includes only non-prescription (over-the-counter) in-feed medications and no drugs with a prescription status are listed. Moving forward, Health Canada and the CFIA intend to include all the approved in-feed drug products, including prescription drugs, in the new version of the CMIB. The prescription will be required prior to the sale of the medicated feed. A prescription will continue to be required prior to the manufacturing of a medicated feed if it is made in a manner not consistent with the CMIB (i.e., in an extra-label manner). The new version of CMIB is anticipated to be launched in spring 2018.

Removing growth promotion claims from medically important antimicrobials

Specific veterinary antimicrobials were historically authorized for production claims in food animals to promote growth and to improve feed efficiency. This is no longer considered to be a prudent use of such antimicrobials. The decision to remove growth promotion claims from the product labels of medically important antimicrobials is in line with international best practices and principles (6,13). These important drugs should be reserved for treating or preventing diseases and not for enhancing weight gain in animals.

Changes to the drug prescription status and removal of production claims are being implemented concurrently; both require changes to drug labelling. Companies that need to modify labels to identify them as prescription drugs and to remove growth promotion claims will be able to do so simultaneously. Health Canada aims to implement these changes in collaboration with relevant partners including provinces and territories, which have oversight on the distribution and dispensing of these drugs. Implementation is anticipated between February and December 2018 so that there is adequate time to adapt to these changes. Additionally, end users, such as food animal producers, feed mill owners and veterinarians, are being informed of and prepared for these modifications. These changes have required extensive consultation and collaboration among multiple stakeholders over the last several years.

Implications of the new measures

All regulatory changes and policy measures described above are important and concrete elements of the Government of Canada's *Federal Framework and Action Plan on Antimicrobial Resistance and Use* (1,15). By the end of the implementation period (expected in late 2018), Canada will have a sound regulatory infrastructure in place at the federal level to further enhance and support antimicrobial stewardship in Canada as summarized in **Table 1.**

Table 1: Summary of the federal veterinary drug regulatory infrastructure to advance antimicrobial stewardship

Type of infrastructure	How it will advance antimicrobial stewardship
New regulatory provisions	Increased controls over the importation of medically important antimicrobials for veterinary use
	Increased controls over the quality of active pharmaceutical ingredients for veterinary use coming into Canada (aligned with human drugs)
	Increased surveillance of the amount of medically important antimicrobials for veterinary use available for sale in Canada
	Improved access to veterinary health products, which are drugs in dosage form that are used to maintain or promote the health and welfare of animals and are not for use to treat or cure disease
New policies under existing regulatory provisions	Making all medically important antimicrobials prescription drugs
	Removing growth promotion claims from labels of medically important antimicrobials

Conclusion

The prudent use of antimicrobial drugs in animals is a shared responsibility across governments, industry and veterinary and agriculture sectors. Health Canada's contributions via the regulatory amendments to the *Food and Drug Regulations*, as well as other complementary policy initiatives, are essential to ensure safe and effective drug products are on the market and to enhance antimicrobial stewardship in Canada. These efforts will support enhanced understanding of the linkages between antimicrobial use in animals and AMR in animals and humans. It is important that these changes are supplemented and supported by ongoing activities from other partners and stakeholders, including provincial and territorial authorities, veterinarians, pharmaceutical industries and food animal producers, to successfully promote the health and wellbeing of animals and Canadians.

Authors' statement

MM, X-ZL–writing of original draft, review and editing; MJI–writing, review and editing

Conflict of interest

None.

Acknowledgements

The authors would like to thank all those who have been part of this journey and have contributed significantly to these important initiatives to strengthen antimicrobial stewardship in Canada.

References

1. Government of Canada. Antimicrobial Resistance and Use in Canada: A Federal Framework for Action. Public Health Agency of Canada, Ottawa ON: 2014. https://www.canada.ca/content/dam/canada/health-canada/migration/healthy-canadians/alt/pdf/drugs-products-medicaments-produits/buying-using-achat-utilisation/antibiotic-resistance-antibiotique/antimicrobial-framework-cadre-antimicrobiens-eng.pdf
2. Government of Canada. Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action. https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/tackling-antimicrobial-resistance-use-pan-canadian-framework-action.html
3. Health Canada. Guidance for Industry Preparation of Veterinary New Drug Submissions. Ottawa ON: 2007. https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/legislation-guidelines/guidance-documents/guidance-industry-preparation-veterinary-new-drug-submissions-health-canada-2007.html
4. Health Canada. Categorization of Antimicrobial Drugs Based on Importance in Human Medicine. Ottawa ON: 2009. https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/antimicrobial-resistance/categorization-antimicrobial-drugs-based-importance-human-medicine.html
5. Health Canada. Uses of Antimicrobials in Food Animals in Canada: Impact on Resistance and Human Health. Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health. Report Prepared for Veterinary Drugs Directorate, Health Canada. Ottawa ON: 2002. https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/veterinary-drugs/uses-antimicrobials-food-animals-canada-impact-resistance-human-health-health-canada-2002.html
6. World Health Organization. WHO Global Strategy for Containment of Antimicrobial Resistance. WHO, Switzerland: 2001. http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf
7. World Organisation for Animal Health. OIE International Standards on Antimicrobial Resistance. OIE, Paris, France: 2003. http://www.oie.int/doc/ged/D9769.pdf
8. Office of the Auditor General of Canada. Report 1 – Antimicrobial Resistance. Ottawa ON: 2015. http://www.oag-bvg.gc.ca/internet/English/parl_oag_201504_01_e_40347.html
9. Government of Canada. Regulations Amending the Food and Drug Regulations (Veterinary Drugs – Antimicrobial Resistance). Canada Gazette Part I 2016;150(27):2357-2405. http://www.gazette.gc.ca/rp-pr/p1/2016/2016-07-02/pdf/g1-15027.pdf
10. Government of Canada. Regulations Amending the Food and Drug Regulations (Veterinary Drugs – Antimicrobial Resistance). Canada Gazette Part II 2017;151(10):942-999. http://www.gazette.gc.ca/rp-pr/p2/2017/2017-05-17/pdf/g2-15110.pdf
11. Government of Canada. Antibiotic Resistance and Animals. Ottawa ON: 2017. https://www.canada.ca/en/public-health/services/antibiotic-antimicrobial-resistance/animals.html
12. Government of Canada. Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) 2014 Annual Report. Public Health Agency of Canada, Guelph ON: 2016. http://www.phac-aspc.gc.ca/cipars-picra/pubs-eng.php
13. Codex Alimentarius Commission. Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC/RCP 61-2005). 2005. www.fao.org/input/download/standards/10213/CXP_061e.pdf
14. Canadian Food Inspection Agency. Compendium of Medicating Ingredient Brochures. Ottawa ON: 2017. http://www.inspection.gc.ca/animals/feeds/medicating-ingredients/eng/1300212600464/1320602461227
15. Government of Canada. Federal Action Plan on Antimicrobial Resistance and Use in Canada: Building on the Federal Framework for Action. Public Health Agency of Canada, Ottawa ON: 2015. https://www.canada.ca/content/dam/canada/health-canada/migration/healthy-canadians/alt/pdf/publications/drugs-products-medicaments-produits/antibiotic-resistance-antibiotique/action-plan-daction-eng.pdf

Agriculture and Agri-Food Canada's research program on antimicrobial resistance

E Topp[1]*

Abstract

A key strategy for attenuating the development of antimicrobial resistance (AMR) is ensuring judicious use of antimicrobials in human and veterinary medicine and in agriculture. Research on AMR in agriculture includes risk assessment, risk management, and identifying the role of agricultural practices in development of AMR. Risk assessment includes an impact assessment of antimicrobial use in livestock and on the environment; for example, many antimicrobials are excreted unchanged and thus reach the environment through manure application. This creates the potential for AMR transmission through the food processing chain and into agro-ecosystems receiving the agricultural waste. Risk management includes the assessment of cost-effective methods to keep animals healthy without the need for antimicrobial use, such as the use of vaccines, nutritional supplements and pre-, pro- or synbiotics and of waste management strategies to avoid AMR transmission. Currently, there is an important gap in understanding the degree of human exposure to AMR that is generated through agriculture, the burden of illness of AMR pathogens in human populations and the relationship between exposure and burden of illness. It is important that research on the agricultural, environmental and human medicine dimensions of AMR not be undertaken in silos, which is why the United Nations and countries around the world are working together within the One Health Framework that considers the inter-relatedness of humans, animals and the environment.

Affiliation

[1] London Research and Development Centre, Agriculture and Agri-Food Canada, London, ON

***Correspondence:** ed.topp@agr.gc.ca

Suggested citation: Topp E, Agriculture and Agri-Food Canada's research program on antimicrobial resistance. Can Commun Dis Rep. 2017;43(11):224-7. https://doi.org/10.14745/ccdr.v43i11a03

Introduction

Antimicrobial resistance (AMR) is a seminally important global public health concern and will evolve into a global public health catastrophe should predictions of pandrug resistance come to pass (1). In response to this threat, national governments, including Canada's, are developing and implementing AMR national action plans. These plans generally have four pillars: surveillance; infection control; stewardship; and innovation. Activities on these four pillars are best undertaken within the One Health Framework, recognizing the continuum between humans, animals and the environment.

Context

A key strategy for attenuating the development of AMR is ensuring judicious antimicrobial use in human medicine, veterinary medicine and agriculture. With respect to agriculture, the level of use of specific antimicrobials is highly correlated with resistance to those antimicrobials observed in generic *Escherichia coli* isolated from cattle, swine or poultry (2). This type of evidence clearly indicates the importance of reducing the agricultural use of antimicrobial agents, with the anticipated outcome being a reduction in the burden of bacteria that carry genes conferring AMR into the food animal production systems (3). This should reduce human exposure to pathogens (e.g., salmonella), which have acquired AMR in the food production system and to commensal bacteria, which carry AMR genes and have the potential to be mobilized into pathogens in the digestive tracts of humans.

A number of developments are underway that will result in a reduction in the use of antimicrobials in food animal production. Market pressure is driving reduced antimicrobial use; for example, consumer demand for "antibiotic-free" chicken and beef. Regulations on drug sale and use are becoming more stringent; for example, enhancement of veterinary supervision of antimicrobial use and removing the claims of the use of medically important antimicrobials for the purposes of growth promotion in food animals. Reducing antimicrobial use in food animal production represents a challenge for producers who rely on these agents to help keep their animals healthy. The specific health problems that may accompany a reduction in antimicrobial use and the desirable and effective alternative solutions to the use of antimicrobials will vary according to the commodity (i.e., poultry, swine, dairy or beef). Overall, changes in agricultural practices and the effective deployment of technologies that ensure continued animal health and wellness, quality and safety of the food products, food security and the economic prosperity of producers are foundational for a reduction in antimicrobial use in agriculture.

Agriculture and Agri-Food Canada (AAFC) is unique amongst the Canadian federal science-based departments and agencies as it has the mandate, expertise and infrastructure required

to undertake research on all the major food animal and crop production systems. Research is undertaken in support of the overall Canadian agriculture and agri-food system, which accounts for 6.6% of the national gross domestic product and employs one in eight Canadians. For many years, AAFC's Science and Technology Branch has undertaken research on AMR in agriculture. AAFC research centres in Sherbrooke, Guelph, London, Lethbridge, Lacombe and Summerland, in particular, have active programs on dairy, swine, poultry, beef and environmental aspects of AMR.

This article provides an overview of the research being done by AAFC within three broad areas; risk assessment; risk management; and the elucidation of animal agriculture's role in AMR development and transmission and the need for international collaboration within the One Health Framework. Within the scope of this article, an antimicrobial agent is defined as a medicine that is specifically used to treat or prevent a bacterial infection, and not viral, fungal or protozoal infection.

Research on AMR and agriculture

Risk assessment

Risk assessment of AMR within the agricultural context examines the relationship between antimicrobial use and the likelihood of development of AMR in the agricultural production system. The experimental approach often compares the impact of varying antimicrobial use on the AMR burden in the gut microbiome of animals (4,5). The fate of antimicrobial-resistant bacteria through the food processing chain is a key component of human exposure to these bacteria through food consumption (6). Many antimicrobial agents are excreted unchanged and thus reach the environment through manure application. Crops, including fresh produce grown in manure-fertilized ground, represent a potential route of exposure to humans or foraging animals. The ecology of antimicrobial-resistant enteric bacteria in crop production systems fertilized with manure is being investigated to assess the potential increase in AMR burden on crops at harvest (7,8). The fate of antimicrobials in soil and their potential impacts on soil microorganisms is of interest (9,10). Overall, the objective is to understand the dynamics of AMR development in animal and crop production systems and the potential transmission through the food processing chain into agroecosystems receiving the agricultural waste. This information can then be used to inform quantitative models that explore associations between use and resistance, quantitative human AMR microbial risk assessments and better management practices (BMPs) that reduce human exposure to antimicrobial-resistant bacteria.

Risk management

Risk management is defined here as the implementation of production practices that reduce the need for antimicrobial use, while maintaining or improving the production system's performance. The objective is to implement cost-effective methods to keep animals healthy and reduce the need for prophylactic or therapeutic use of antimicrobials (11). Options available could include vaccines, nutritional supplements, pre-, pro- or synbiotics, breeding more robust animals and improved barn design in confined production systems. Potentially the microbiomes of young animals could be optimized through inoculation (similar to fecal transplantation in humans) or through nutritional interventions that mimic the impact of growth-promoting antimicrobials on the animals. Innovations in technology and husbandry that are efficacious and cost-effective will vary according to the commodity.

An additional risk management strategy is to reduce environmental exposure to antimicrobial-resistant bacteria and antimicrobial residues that are excreted by farm animals. In some confined production practices, manure can be managed to reduce the burden of AMR prior to land application through digestion or composting (12). Fundamental and translational research in this domain has rich potential to develop and validate means of reducing agricultural antimicrobial use and thus human exposure to AMR throughout the food chain or the various environments impacted by agricultural waste.

Relative significance of agriculture in development of AMR

Determining the significance of agricultural antimicrobial use relative to other potential areas for the development and transmission of AMR to humans within the One Health Framework is a daunting task. With respect to waterborne transmission, ascribing enteric pollution from livestock vs. people in a landscape with significant populations of both human and livestock is a challenge (13,14). Surveillance programs (e.g., Canadian Integrated Program for Antimicrobial Resistance or CIPARS) and various research initiatives have now generated a wealth of information on the burden of AMR in foods and in environments impacted by food animal production; however, surveillance data does not generally capture information pertaining to what happens to people once they have been exposed to antimicrobial-resistant bacteria. Hence, there is a critical gap in understanding the relationship between human exposure to AMR generated through agriculture and the overall burden of AMR pathogens in human populations. The development of methods to produce such evidence (e.g., a robust human health risk assessment) (15) would be critical to understanding the relative potential benefits of a reduction in antimicrobial use in agricultural vs. a reduction of antimicrobial use in human medicine for mitigating AMR in human pathogens.

One Health Framework

Bacteria readily circulate between people, animals and the environment. It is, therefore, important that research concerning the agricultural, environmental and human medicine dimensions of AMR not be undertaken in silos (3). As such, AAFC's research program on AMR is highly collaborative. AAFC's Science and Technology Branch overtly solicits advice from the agricultural industry and regulatory stakeholders (e.g., Veterinary Drugs Directorate of Health Canada) with respect to establishing responsible and impactful priorities for AMR research. In addition, AAFC collaborates extensively with national and international academic colleagues and with the other federal science-based departments and agencies with a stake in AMR. The Genomics Research and Development Initiative interdepartmental project on AMR (GRDI-AMR) is an excellent example of how the expertise and resources of all relevant science-based departments and agencies (AAFC, Public Health

Agency of Canada, Canadian Food Inspection Agency, Health Canada and the National Research Council) can be leveraged for a common cause (16). The GRDI-AMR project has two overriding goals. The first goal is to gain understanding of the key activities that contribute to development of AMR in food production systems and of important exposure pathways by which AMR bacteria reach humans. This information will identify critical intervention points for mitigation. The second goal is to validate economically-sustainable technologies, practices and policies to mitigate AMR development in food production systems. This information will inform how best to manage the critical intervention points. Finally, recent position statements from the World Health Organization, the World Organisation for Animal Health and the United Nations have endorsed the One Health Framework, and these statements were recently articulated in the Pan-Canadian Framework for Action on AMR (17).

Conclusion

Antimicrobial resistance is a seminally important contemporary public health challenge. We need to use antimicrobials more judiciously and responsibly in food animal production to minimize selection for resistance and the subsequent risk of resistance transmission to humans via the food chain or the environment. The role of AAFC within the Pan-Canadian Framework for Action on AMR and antimicrobial use is to contribute to the development of innovative animal production and waste management strategies to reduce AMR in the food production system, while maintaining productivity and profitability, animal welfare, food safety and security and environmental quality. In partnership with external collaborators and stakeholders, research undertaken by AAFC will help provide Canadian farmers the tools they need to meet this challenge.

Conflict of Interest

None.

Acknowledgements

The author thanks the numerous Agriculture and Agri-Food Canada colleagues who are working towards mitigating antimicrobial resistance for the benefit of the agricultural community and all Canadians. Many thanks to C. Carson, J. Gracia-Garza, A. Lamoureux, X.-Z. Li, and R. Menassa for critically reviewing the manuscript.

References

1. O'Neill J. Tackling drug-resistant infections globally: Final report and recommendations. 2016. http://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf
2. Chantziaras I, Boyen F, Callens B, Dewulf J. Correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing animals: a report on seven countries. J Antimicrob Chemother. 2014;69:827-34. DOI (http://dx.doi.org/10.1093/jac/dkt443). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=24216767&dopt=Abstract).
3. O'Brien TF. Emergence, spread, and environmental effect of antimicrobial resistance: how use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else. Clin Infect Dis. 2002;34:S78-S84. DOI (https://doi.org/10.1086/340244). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11988877&dopt=Abstract).
4. Diarra MS, Silversides FG, Diarrassouba F, Pritchard J, Masson L, Brousseau R, Bonnet C, Delaquis P, Bach S, Skura BJ, Topp E. Impact of feed supplementation with antimicrobial agents on growth performance of broiler chickens, Clostridium perfringens and Enterococcus counts, and antibiotic resistance phenotypes and distribution of antimicrobial resistance determinants in Escherichia coli isolates. Appl Environ Microbiol. 2007;73:6566-76. DOI (http://dx.doi.org/10.1128/AEM.01086-07). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=17827305&dopt=Abstract).
5. Zaheer R, Cook SR, Klima CL, Stanford K, Alexander T, Topp E, Read RR, Mcallister TA. Effect of subtherapeutic vs. therapeutic administration of macrolides on antimicrobial resistance in Mannheimia haemolytica and enterococci isolated from beef cattle. Frontiers in Microbiology 2013;4:133. DOI (http://dx.doi.org/10.3389/fmicb.2013.00133). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=23750157&dopt=Abstract).
6. Noyes NR, Yang X, Linke LM, Magnuson RJ, Dettenwanger A, Cook S, Geornaras I, Woerner DE, Gow SP, McAllister TA, Yang H, Ruiz J, Jones KL, Boucher CA, Morley PS, Belk KE. Resistome diversity in cattle and the environment decreases during beef production. eLife 2016;5:e13195. DOI (http://dx.doi.org/10.7554/eLife.13195). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=26952213&dopt=Abstract).
7. Marti R, Scott A, Tien Y-C, Murray R, Sabourin L, Zhang Y, Topp E. The impact of manure fertilization on the abundance of antibiotic-resistant bacteria and frequency of detection of antibiotic resistance genes in soil, and on vegetables at harvest. Appl Environ Microbiol. 2013;79(18):5701-5709. DOI (http://dx.doi.org/10.1128/AEM.01682-13). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=23851089&dopt=Abstract).
8. Marti R, Tien Y-C, Murray R, Scott A, Sabourin L, Topp E. Safely coupling livestock and crop production systems: how rapidly do antibiotic resistance genes dissipate in soil following a commercial application of swine or dairy manure? Appl Environ Microbiol. 2014;80:3258-65. DOI (http://dx.doi.org/10.1128/AEM.00231-14). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=24632259&dopt=Abstract).
9. Topp E, Chapman R, Devers-Lamrani M, Hartmann A, Marti R, Martin-Laurent F, Sabourin L, Scott A, Sumarah M. Accelerated biodegradation of veterinary antibiotics in

agricultural soil following long-term exposure, and isolation of a sulfamethazine-degrading Microbacterium sp. J Environ Qual. 2013;42(1):173-8. PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=23673752&dopt=Abstract).

10. Lau CH-F, van Engelen K, Gordon S, Renaud J, Topp E. Novel antibiotic resistance determinants from agricultural soil exposed to antibiotics widely used in human medicine and animal farming. Appl Environ Microbiol. 2017;pii:AEM.00989-17. DOI (http://dx.doi.org/10.1128/AEM.00989-17). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=28625995&dopt=Abstract).
11. Diarra MS, Malouin F. Antibiotics in Canadian poultry productions and anticipated alternatives. Front Microbiol. 2014;5:282. DOI (http://dx.doi.org/10.3389/fmicb.2014.00282). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=24987390&dopt=Abstract).
12. Tien Y-C, Li B, Zhang T, Scott A, Murray R, Sabourin L, Marti R, Topp E. Impact of dairy manure pre-application treatment on manure composition, soil dynamics of antibiotic resistance genes, and abundance of antibiotic-resistance genes on vegetables at harvest. Sci Total Environ. 2017;581–582:32-9. DOI (https://doi.org/10.1016/j.scitotenv.2016.12.138). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=28076772&dopt=Abstract).
13. McAllister TA, Topp E. Role of livestock in microbiological contamination of water: Commonly the blame, but not always the source. Animal Front. 2012;2(2):17-27. DOI (http://dx.doi.org/10.2527/af.2012-0039).
14. Marti R, Gannon VPJ, Jokinen C, Lanthier M, Lapen DR, Neumann NF, Ruecker NJ, Scott A, Wilkes G, Zhang Y, Topp E. Quantitative multi-year elucidation of fecal sources of waterborne pathogen contamination in the South Nation River basin using Bacteroidales microbial source tracking markers. Water Res. 2013;47:2315-24. DOI (https://doi.org/10.1016/j.watres.2013.02.009). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=23497974&dopt=Abstract).
15. Ashbolt NJ, Amézquita A, Backhaus T, Borriello SP, Brandt KK, Collignon P, Coors A, Finley R, Gaze WH, Heberer T, Lawrence JR, Larsson DGJ, McEwen SA, Ryan JJ, Schönfeld J, Silley P, Snape JR, Van den Eede C, Topp E. Human health risk assessment (HHRA) for environmental development and transfer of antibiotic resistance. Environ Health Perspect 2013;121(9):993-1001. DOI (http://dx.doi.org/10.1289/ehp.1206316). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=23838256&dopt=Abstract).
16. Genomics Research and Development Initiative (GRDI). Shared priority projects. Ottawa (ON): Government of Canada. http://grdi-irdg.collaboration.gc.ca/eng/projects/priority.html
17. Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action. https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/tackling-antimicrobial-resistance-use-pan-canadian-framework-action.html

Surveillance of laboratory exposures to human pathogens and toxins: Canada 2016

A Bienek[1], M Heisz[1], M Su[1]*

Affiliation

[1] Centre for Biosecurity, Public Health Agency of Canada, Ottawa, ON

***Correspondence:** ming.su@canada.ca

Abstract

Background: Canada recently enacted legislation to authorize the collection of data on laboratory incidents involving a biological agent. This is done by the Public Health Agency of Canada (PHAC) as part of a comprehensive national program that protects Canadians from the health and safety risks posed by human and terrestrial animal pathogens and toxins.

Objective: To describe the first year of data on laboratory exposure incidents and/or laboratory-acquired infections in Canada since the *Human Pathogens and Toxins Regulations* came into effect.

Methods: Incidents that occurred between January 1 and December 31, 2016 were self-reported by federally-regulated parties across Canada using a standardized form from the Laboratory Incident Notification Canada (LINC) surveillance system. Exposure incidents were described by sector, frequency of occurrence, timeliness of reporting, number of affected persons, human pathogens and toxins involved, causes and corrective actions taken. Microsoft Excel 2010 was used for basic descriptive analyses.

Results: In 2016, 46 exposure incidents were reported by holders of 835 active licences in Canada representing 1,352 physical areas approved for work involving a biological agent, for an overall incidence of 3.4%. The number of incidents was highest in the academic (n=16; 34.8%) and hospital (n=12; 26.1%) sectors, while the number of reported incidents was relatively low in the private industry sector. An average of four to five incidents occurred each month; the month of September presented as an outlier with 10 incidents. A total of 100 people were exposed, with no reports of secondary exposure. Four incidents led to suspected (n=3) or confirmed (n=1) cases of laboratory-acquired infection. Most incidents involved pathogens classified at a risk group 2 level that were manipulated in a containment level 2 laboratory (91.3%). Over 22 different species of human pathogens and toxins were implicated, with bacteria the most frequent (34.8%), followed by viruses (26.1%). Eleven (23.9%) incidents involved a security sensitive biologic agent. Procedure breaches (n=15) and sharps-related incidents (n=14) were the most common antecedents to an exposure. In 10 (21.7%) cases, inadvertent possession (i.e., isolation of an unexpected biological agent during routine work) played a role. Possible improvements to standard operating procedures were cited in 71.7% of incidents. Improvements were also indicated for communication (26.1%) and management (23.9%).

Conclusions: The Laboratory Incident Notification Canada is one of the first surveillance systems in the world to gather comprehensive data on laboratory incidents involving human pathogens and toxins. Exposure incidents reported in the first year were relatively rare, occurring in less than 4% of containment zones within laboratory settings.

Suggested citation: Bienek A, Heisz M, Su M. Surveillance of laboratory exposures to human pathogens and toxins: Canada 2016. Can Commun Dis Rep. 2017;43(11):228-35. https://doi.org/10.14745/ccdr.v43i11a04

Introduction

The study of biological agents in academic, veterinary, industry, and government laboratory settings has many benefits; it also poses an inherent risk of exposure due to the nature of the work and the pathogens and toxins involved. Internationally, this risk to human biosafety and biosecurity has led to injury, with accidents reported in the literature and by governments (1-4). Albeit rare, deaths have also occurred (5,6).

Currently, there are limited and variable international requirements governing the reporting of laboratory incidents involving biological agents. In Great Britain, as part of a larger reporting system, the Health and Safety Executive enforces the mandatory reporting of incidents that involve disease caused by biological agents in a wide range of workplaces (including academic, hospital and central and local government facilities) (7). In England, Wales and Northern Ireland, an active surveillance system was developed to capture occupational exposures, but only to specific blood-borne viruses (8). Otherwise, most reporting of laboratory-acquired infection incidents is voluntary in nature or captured through surveys (9-11).

Canada has one of the first comprehensive national surveillance systems, which gathers data from reports submitted in close to real time on incidents pertaining to a wide range of human and terrestrial animal pathogens and toxins used in laboratory-specific settings. The Laboratory Incident Notification Canada (LINC) surveillance system was officially

launched in December 2015 in response to the assent of the *Human Pathogens and Toxins Act (HPT Act)* in 2009 and the enactment of the *HPT Regulations* in 2015, and as part of a larger comprehensive national biosafety and biosecurity program that protects the Canadian public from the health and safety risks posed by human pathogens and toxins (HPTs) (12,13). An overview of the scope, licensing requirements for laboratories and mandate of the Public Health Agency of Canada (PHAC) in the regulation and monitoring of HPT use can be found elsewhere (14). See the **Appendix** for the definition of some commonly used terms.

Under Canada's *HPT Act*, pathogens (including bacteria, viruses, fungi, protozoa and prions) and toxins are classified into four risk groups based on the risk level presented to an individual (e.g., laboratory staff) and the community (i.e., the Canadian public) (15). Factors considered include the pathogenicity of the HPT, route of infection, mode of transmission, availability of treatment and/or preventive measures, host range, natural distribution and impact of release into the environment (16). Work with risk group 1 pathogens is of lowest risk and is unregulated in Canada. Of the work under federal regulation, the majority is performed with risk group 2 pathogens (92.8%). These pathogens pose a moderate risk to individuals but low risk to public health, because they can cause serious disease in humans but are unlikely to do so. Work with risk group 3 pathogens currently represents 6.6% of all regulated work. These pathogens pose a high risk to individuals but a low risk to public health, because they are likely to cause serious disease but unlikely to spread. The remaining category (risk group 4, 0.2%), as well as a specialized category of security sensitive biological agents above a trigger quantity (0.5%), constitutes only a small proportion of the work in Canada using HPTs, but are of highest risk to health at both the individual- and population-level.

The Centre for Biosecurity at PHAC is mandated to oversee the ongoing surveillance of laboratory incidents involving HPTs. The data in the LINC surveillance system are provided by regulated parties across Canada who recognize that an incident has occurred and is reportable as per the *HPT Regulations* (12-15). Currently, four types of incidents are reportable:

- exposures and laboratory-acquired infections;
- inadvertent possession, production and/or release of an HPT;
- missing, lost, or stolen HPT, including a security sensitive biological agent not being received within 24 hours of expected arrival; and
- changes affecting biocontainment.

When an incident occurs, the licence holder must inform PHAC in a timely manner to ensure that the situation is managed appropriately (12-15). For incidents involving an exposure and/or laboratory-acquired infection, the initial notification report is submitted 'without delay' to observe requirements for notification identified in the *HPT Act*.

The initial report provides only the immediate, essential elements related to the incident, including key dates, cause of exposure, affected persons and HPT(s) involved. A follow-up report is then expected within 15 days after the first notification for incidents involving security sensitive biological agents, or within 30 days after the first notification for all other exposures and/or laboratory-acquired infections. The aim of the follow-up report is to provide information on the investigation outcomes, including the treatment and monitoring of the affected person(s), root causes and corrective actions that aim to reduce the risk of future incidents. The licence holder or local Biological Safety Officer leads the response to the incident, with support from PHAC when required, until a satisfactory resolution is reached and the file is closed.

Standardized and systematic reporting documents exposures in a way that permits comparison between incidents and over time. Collective and active analysis of reported incidents allow for the identification of patterns or trends that highlight common or emerging issues at the national level. Using the data collected and housed in the LINC surveillance system, this study provides a descriptive summary and interpretation of the first full year of data collected relating to exposures and/or laboratory-acquired infections in Canada between January 1 and December 31, 2016.

Methods

The LINC surveillance system is the single window for electronic incident reporting. The system is housed within a customized Microsoft Dynamics Customer Relations Management system maintained and secured by in-house information technology support at PHAC. Most data fields are mandatory, and high specificity is obtained through the use of a standardized form. Data inputs in this surveillance system are self-reported; accuracy is validated through the ongoing investigatory process involving both PHAC and the reporter. If, during the course of the investigatory process, an incident is deemed to be outside the scope of requirements defined within the *HPT Act*, the incident is ruled out and is excluded from analysis.

Data on laboratory incidents involving exposure and/or laboratory-acquired infection (classified as 'exposures', 'suspected laboratory-acquired infection' or 'confirmed laboratory-acquired infection') that occurred in 2016 were extracted from the system. Data elements include licence information (number of licences, number of containment zones), sector (academic, hospital, private industry/business, public health, veterinary/animal health, environmental), key dates (incident date, initial notification date, follow-up report date), affected persons (number of primary affected, number of secondary affected), implicated HPTs (type, risk group level), cause of incident (procedure, sharps, personal protective equipment, animal, spill, insect, equipment, loss of containment) and areas for improvement (standard operating procedures, training, communications, management and oversight, equipment, human interaction). Microsoft Excel 2010 was used for basic descriptive analyses on categorical variables (counts, proportions) and continuous variables (mean, range). Because the breadth of information collected allows for the identification of the licenced facility, identifiable characteristics were suppressed when necessary. All data were reported, except in instances where there was a risk of identifying a specific incident and/or laboratory.

Results

In the 2016 calendar year, there were 835 active licences permitting the use of HPTs across Canada, representing 1,352 containment zones. A containment zone is a physical area that meets requirements for a specific containment level required for work with particular HPTs. One laboratory can contain several containment zones (see Appendix for full definition).

A total of 50 incidents involving a potential exposure were extracted from the database, including four incidents that were reported in 2017 but that occurred in 2016. During the investigation process, it was determined that an exposure did not occur in four incidents; these were ruled out and removed from analysis, leaving a total of 46 incidents. The sample included nine incidents for which reporting was delayed until licence issuance; these were retained for analysis but were excluded from calculations related to timeliness of notification.

Exposure and/or laboratory-acquired infection incidents occurred in 3.4% of all regulated containment zones. The majority of reported incidents involved exposure only (n=42; 91.3%), while four incidents led to a suspected (n=3; 6.5%) or confirmed (n=1; 2.2%) laboratory-acquired infection. Most incidents involved HPTs classified at a risk group 2 level that were manipulated in a biosafety containment level 2 laboratory (91.3%). Three incidents occurred in a containment level 3 designated facility and one incident occurred in a containment level 4 designated facility.

Distribution of incidents by sector

The highest number of reported incidents occurred in the academic (n=16; 34.8%) and hospital (n=12; 26.1%) sectors, which was proportionate to the distribution of containment zones by sector (**Table 1**). Private industry represented 32.2% of all containment zones, but only 17.4% of reported exposure incidents.

Table 1: Reported human pathogen or toxin exposure incidents by sector, Canada 2016

Sector	Number of active licences		Number of containment zones		Number of exposure incidents	
	n	%	n	%	n	%
Academic	168	20.1	436	32.2	16	34.8
Hospital	186	22.3	290	21.4	12	26.1
Private industry/ business	376	45.0	436	32.2	8	17.4
Public health (government)	25	3.0	64	4.7	4	8.7
Veterinary/ animal health (government)	18	2.2	38	2.8	4	8.7
Environmental (government)	32	3.8	37	2.7	0	0
Other government	30	3.6	51	3.8	2	4.3
TOTAL	835	100	1,352	100	46	100

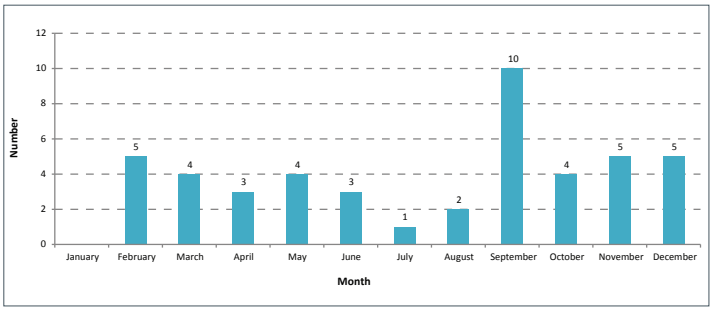
Table 1: Footnotes

Abbreviation: n, number
NOTES: Data are from the Laboratory Incident Notification Canada (LINC) surveillance system (Canada, retrieved 2017-05-26)
'Containment zone' is defined as a physical area that meets the minimum physical and operational practice requirements for the handling of infectious material or toxins categorized at a specific risk group level safely in laboratory and animal work environments
'Academic' includes university, veterinary college, college, CEGEP and others
'Hospital' includes academic-affiliated and non-academic affiliated hospitals
'Private industry/business' includes animal health, human health, biotechnology, pharmaceutical, food industry and pathogen or toxin distributors
'Public health', 'veterinary/animal health', 'environmental' and 'other' include federal, provincial, territorial and municipal governments

Incident frequency and timeliness of reporting

Typically, four to five incidents occurred each month, with lower numbers seen in the summer (**Figure 1**). The month of September presented as an outlier, with 10 exposure incidents reported to PHAC. Upon examination, all September incidents were unrelated in terms of location, licence holder or implicated HPT. In addition, the characteristics of the incidents occurring in September were similar to that of all incidents when analysed by containment level, sector and pathogen type.

Figure 1: Reported human pathogen or toxin exposure incidents by month of incident, Canada 2016



NOTE: Data are from the Laboratory Incident Notification Canada (LINC) surveillance system (Canada, retrieved 2017-05-26)

For incidents not involving a security sensitive biological agent, the number of days between incident occurrence and initial notification to PHAC ranged from 1 to 119 days, with an average lag of 23.5 days (based on calendar days and including non-business days) (**Table 2**). Although not shown in Table 2, half of incidents were first reported to PHAC within approximately one week of occurrence, while nine incidents were reported more than one month after occurrence. Reasons for delay included a lack of awareness regarding reporting requirements (n=4) and the need for assistance in report submission (n=3). On average, follow-up reports were submitted 18.4 days after the initial report, with 89.3% of reports meeting the target deadline of 30 days.

For incidents involving a security sensitive biological agent, the number of days between incident occurrence and initial notification to PHAC ranged from 0 to 65 days, with an average lag of 17.1 days (based on calendar days and including non-business days) (Table 2). The deadline for submission of a follow-up report after initial notification was 15 days; 77.4% of follow-up reports met this deadline. For the two incidents submitted past the target deadline, no clear reasons were available for the reporting delay. The observed delays in reporting are not uncommon with new regulatory systems, as

Table 2: Timeliness of reported exposure incidents, Canada 2016

Incident type	Time interval		Target interval	Actual interval		Number of incidents submitted before deadline		Number of incidents submitted past deadline	
	From	To	Number of days	Range of days	Average number of days	n	%	n	%
Not involving a security sensitive biological agent*	Incident occurrence	Initial notification	Without delay	1 – 119	23.5	N/A	N/A	N/A	N/A
	Initial notification†	Follow-up report	30	0 – 39	18.4	25	89.3	3	10.7
Involving a security sensitive biological agent	Incident occurrence	Initial notification	Without delay	0 – 65	17.1	N/A	N/A	N/A	N/A
	Initial notification†	Follow-up report	15	0 – 39	15.9	7	77.4	2	22.2

Abbreviations: n, number; N/A, not applicable
NOTES: Data are from the Laboratory Incident Notification Canada (LINC) surveillance system (Canada, retrieved 2017-05-26)
Based on calendar days (includes non-business days) from original notification to first follow-up report
Excludes n=9 incidents that could not be reported until licence issuance
* Includes incidents where biological agent is unknown (n=5)
† Initial notification to the Public Health Agency of Canada, as required through regulatory legislation

there is a lag period while regulated parties become increasingly aware of their reporting obligations.

Number of affected persons

As a result of 46 incidents, 100 people were exposed to an HPT. In the majority (84.8%) of incidents, a single person was exposed; in two incidents, two people were exposed and in five incidents, three or more people were exposed. All incidents involving two or more exposed individuals occurred in a hospital or diagnostic setting. Of the 100 people affected, four were diagnosed with a suspected or confirmed laboratory-acquired infection. No secondary exposures were reported.

Human pathogens and toxins involved

With over 22 different species of HPTs implicated in the incidents, bacteria were the most frequently involved, with 16 (34.8%) incidents involving a bacterium at either the risk group 2 (n=14) or risk group 3 (n=2) level, excluding bacteria classified as a security sensitive biological agent (**Table 3**). A total of 11 (23.9%) incidents involved a security sensitive biological agent at the risk group 3 (n=10) or risk group 4 (n=1) level. The

Table 3: Reported human pathogens or toxins involved in exposure incidents by risk group level and biological agent type, Canada 2016

Biological agent type	Risk group 2		Risk group 3		Risk group 4		Unknown		Total	
	n	%	n	%	n	%	n	%	n	%
Bacterium	14	51.9	2	15.4	0	0	0	0	16	34.8
Virus	11	40.7	1	7.7	0	0	0	0	12	26.1

Table 3: Reported human pathogens or toxins involved in exposure incidents by risk group level and biological agent type, Canada 2016 (continued)

Biological agent type	Risk group 2		Risk group 3		Risk group 4		Unknown		Total	
	n	%	n	%	n	%	n	%	n	%
Fungus	1	3.7	0	0	0	0	0	0	1	2.2
Parasite	1	3.7	0	0	0	0	0	0	1	2.2
Security sensitive biological agent	0	0	10	76.9	1	100	0	0	11	23.9
Unknown	0	0	0	0	0	0	5	100	5	10.9
TOTAL	27	100	13	100	1	100	5	100	46	100

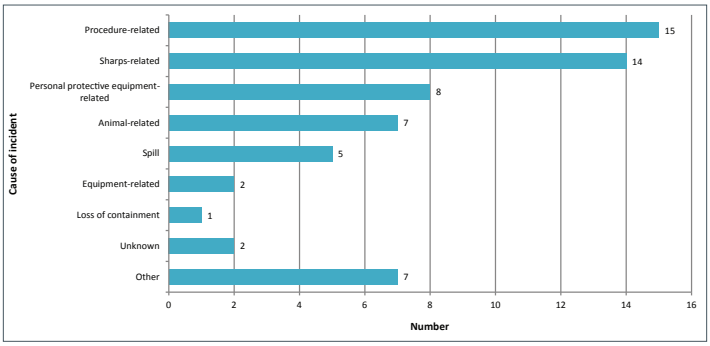
Abbreviation: n, number
NOTES: Data are from the Laboratory Incident Notification Canada (LINC) surveillance system (Canada, retrieved 2017-05-30)
Work at the risk group 1 level is not regulated by the federal government
'Security sensitive biological agent' involved in reported incidents includes bacteria and viruses
'Unknown' includes situations where the biological agent implicated in the incident was never identified

most commonly reported HPT (n=5) was the bacterial species *Brucella* spp., which is classified as a risk group 3 security sensitive biological agent.

Causes of incidents

The most common occurrences leading to an incident were procedure- (n=15) and sharps-related (n=14) (**Figure 2**); however, issues related to personal protective equipment, animal handling, spills, equipment and loss of containment were also cited. Upon review, the seven cases reported under the 'other' category were likely better classified within one or more of the existing categories. Notably, in 10 (21.7%) cases, the inadvertent possession or isolation of a biological agent during the course of routine work played a role in exposure (data not shown). As risk group 2 licence holders are only licensed to work with risk group 2 human pathogens and/or toxins below trigger quantity, any HPT that a licence holder may come across that is at a risk group 3 or risk group 4 level or toxins above trigger quantity

Figure 2: Reported causes of human pathogen or toxin exposure incidents, Canada 2016



NOTES: Data are from the Laboratory Incident Notification Canada (LINC) surveillance system (Canada, retrieved 2017-05-26)
'Sharps-related' includes needle sticks and other sharp injuries
'Personal protective equipment-related' includes inadequate or failure of personal protective equipment
'Animal-related' includes bites and scratches

would result in an inadvertent possession, and may pose an increased risk to staff.

Corrective actions to improve safety in laboratory settings

As a result of the investigatory process, most reporters were able to identify root causes or areas for improvement in existing systems and processes that could avert a future similar incident. The most cited area for improvement centred on standards/standard operating procedures, policies, rules or electronic procedures (71.7%) (**Table 4**). Issues in communication were recognized in a quarter (26.1%) of incidents and issues in management or oversight were cited in 11 (23.9%) incidents. Upon analysis, the 15 'other' root causes could have been categorized within existing categories, as they included issues with communication, equipment and human error.

Table 4: Areas for improvement in reported human pathogen or toxin exposure incidents, Canada 2016

Root cause	Areas of concern	Citations	Proportion of incidents citing root cause
		n	%
Standard operating procedure	Documents were known but not followed	33	71.7
	Documents were not known by user		
	Documents were not followed correctly		
	Documents were not correct for the task/activity		
	Documents were not in place but should have been in place		
Training	Training was not developed or implemented	7	15.2
	Training was inappropriate or insufficient		
	Training was available, but not completed		
	Staff were not qualified or proficient in performing the task		
Communication	There was no method or system for communication	12	26.1
	Communication did not occur		
	Communication was unclear, ambiguous or misunderstood		
Management and oversight	Supervision needed improvement	11	23.9
	Auditing/evaluation/enforcement of standard operating procedure needed improvement		

Table 4: Areas for improvement in reported human pathogen or toxin exposure incidents, Canada 2016 (continued)

Root cause	Areas of concern	Citations	Proportion of incidents citing root cause
		n	%
Management and oversight (continued)	Auditing/evaluation/enforcement of training needed improvement	11	23.9
	Preparation needed improvement		
	Human factors needed improvement		
	Risk assessment needed improvement		
	Worker selection needed improvement		
Equipment	Equipment design needed improvement	8	17.4
	Equipment was not properly maintained		
	Equipment failed		
	Equipment was not fit for purpose		
	Quality control was not performed/needed improvement		
Human interaction	Labelling/placement/operation/displays of tools/equipment needed improvement	8	17.4
	Environmental factors within the work area needed improvement		
	Workload constraints/pressures/demands needed improvement		
Other		15	32.6

Abbreviation: n, number
NOTES: More than one root cause can be identified in an incident.
Data are from the Laboratory Incident Notification Canada (LINC) surveillance system (Canada, retrieved 2017-05-26)
'Standard operating procedure' include standards, policies, procedures or other expected practice documents that guided the work/activities

Discussion

This is the initial report of the first comprehensive national surveillance system on laboratory exposures to HPTs. Overall, exposures to HPTs from laboratory incidents were low. In the first year of data based on regulations requiring mandatory reporting of incidents, 46 exposure incidents were reported. One hundred workers were exposed to an HPT, which resulted in four suspected or confirmed laboratory-acquired infections. There were no reports of secondary exposure beyond the laboratory setting. These findings, including the peak in the number of incidents that occurred in September as well as a higher number of incidents in academic laboratories, will need to be further assessed with future years of data. Many of the key findings reinforce what has already been reported in the literature; for example, implicated biological agents were mainly bacteria

(1,17,18), with *Brucella* spp. being a frequently reported cause of laboratory-acquired infection (2,19,20). In addition, common causes of exposure were the mishandling of sharps or the inadvertent possession of an HPT; these causes have also been commonly described elsewhere (21-25).

The strength of this research is that it is based on a mandatory reporting system with standardized and often mandatory reporting fields; however, there are some limitations that should also be considered. Data for 2016 are unlikely to include all reportable incidents due to several factors. First, the system was still in its infancy with licence issuance ongoing throughout the year of data collection. Data may also be incomplete due to self-selection or non-response bias resulting in incidents that are not reported, which may include undetected incidents, incidents not reported due to a lack of awareness or understanding of the regulatory requirements or reluctance to report incidents due to the negative connotation associated with 'accidents' and 'incidents'. Of the reported data, certain biases may exist. Self-reported data can be influenced by many factors, including recall bias, mode of data collection, experience of the reporter/staff and proxy respondent bias. Recall bias would be particularly notable in situations where new information or symptoms occur, forcing reporters to work backwards to identify the incident that likely precipitated the outcome. Changes are continually being made to the LINC system to improve clarity for reporters, with the aim of improving timeliness in reporting and standardization of data.

The information derived from these data can be used as a reference point to inform researchers, regulated parties and the public about the current landscape of laboratory biosafety in Canada and the performance of the LINC system to date. Findings related to data quality can be used to inform the development of similar surveillance systems elsewhere, while the data can be used internally by PHAC to enforce safety standards, improve prevention strategies and promote best practices. Based on these generalized findings, PHAC has already implemented outreach initiatives to improve awareness of commonly occurring incidents, including a notice sent to stakeholders regarding sharps injuries associated with the use of disposable scalpel blades (*Biosafety and Biosecurity for Pathogens and Toxins Newsletter, Are You Using Scalpels with Disposable Blades?, May 2017, unpublished newsletter*), as well as an advisory regarding an increasing trend of inadvertent isolations of *Coccidioides* spp., perhaps due to travellers returning to Canada from southwestern United States, northern Mexico and areas of Central and South America (*Biosafety and Biosecurity for Pathogens and Toxins Newsletter, Laboratory Incident Notification Canada (LINC) Feature Report: Coccidioides, September 2016, unpublished newsletter*).

Conclusion

In Canada, the *HPT Act and Regulations* require mandatory reporting of laboratory exposures to human pathogens and toxins in close to real time. Mandatory reporting requirements support comprehensive, timely and standardized data collection. Reporting incidents to a federal agency serves a wider purpose of strengthening the biosafety and biosecurity of Canadian laboratories through the understanding of potential risks experienced in practice that can lead to systematic change to benefit all regulated parties.

Authors' statement

AB, MH, and MS participate in laboratory incident monitoring. All authors worked on the conceptualization together; AB prepared the original draft and AB, MH, MS contributed to multiple draft review and editing and sign off on the final version. MS and MH also played a supervisory role.

Conflict of interest

None.

Acknowledgements

We would like to thank Ken Turcotte, Ismahan Hussein, Cindy Evans, Craig Brooks, Marnie Fiebig and Jennifer Mihowich at the Centre for Biosecurity for their expertise and provision of supplementary data. We would also like to extend our appreciation to all the licence holders and biological safety officers across Canada for providing high quality reports.

Funding

This work was supported by Public Health Agency of Canada as part of its core mandate.

References

1. Harding AL, Brandt Byers K. Epidemiology of Laboratory-Associated Infections. In: Fleming DO, Hunt DL, editors. Biological Safety: Principles and Practices, 4th Edition. Washington DC: ASM Press; 2006. p. 53-77. DOI (http://dx.doi.org/10.1128/9781555815899).
2. Coelho AC, Diez JG. Biological Risks and Laboratory-Acquired Infections: A Reality that Cannot be Ignored in Health Biotechnology. Front Bioeng Biotechnol 2015. 3(56):1-10. DOI (http://dx.doi.org/10.3389/fbioe.2015.00056). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=25973418&dopt=Abstract).
3. Centers for Disease Control and Prevention. Human Salmonella Typhimurium Infections Linked to Exposure to Clinical and Teaching Microbiology Laboratories (Final Update). Atlanta: Centers for Disease Control and Prevention; 2014. https://www.cdc.gov/salmonella/typhimurium-labs-06-14/index.html
4. Centers for Disease Control and Prevention. Human Salmonella Typhimurium Infections Linked to Exposure to Clinical and Teaching Microbiology Laboratories. Atlanta: Centers for Disease Control and Prevention; 2017. https://www.cdc.gov/salmonella/typhimurium-07-17/index.html
5. Centers for Disease Control and Prevention (CDC). Fatal Laboratory-Acquired Infection with an Attenuated

Yersinia Pestis Strain. MMWR Morb. Mortal. Wkly. Rep. 2011;60(7):201-5. PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=21346706&dopt=Abstract).

6. Hawkes N. Smallpox Death in Britain Challenges Presumption of Laboratory Safety. Science. 1979 March 2;203(4383):855-6. DOI (http://dx.doi.org/10.1126/science.419409). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=419409&dopt=Abstract).
7. RIDDOR - Reporting of Injuries, Diseases and Dangerous Occurrences Regulations. London: Health and Safety Executive; 2013. http://www.hse.gov.uk/riddor/
8. Health Protection Agency. Eye of the Needle: United Kingdom Surveillance of Significant Occupational Exposures to Blood Borne Viruses in Healthcare Workers. London: Health Protection Agency; 2006. http://webarchive.nationalarchives.gov.uk/20140714113638/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1205394781623
9. Wurtz N, Papa A, Hukic M, Di Caro A, Leparc-Goffart I, Leroy E, Landini MP, Sekeyova Z, Drumler JS, Badescu D, Busquets N, Calistri A, Parolin C, Palu G, Christova I, Maurin M, La Scola B, Raoult D. Survey of Laboratory-Acquired Infections Around the World in Biosafety Level 3 and 4 Laboratories. Eur. J. Clin. Microbiol. Infec. Dis. 2016;35(8):1247-58. DOI (http://dx.doi.org/10.1007/s10096-016-2657-1). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=27234593&dopt=Abstract).
10. Willemarck N, Van Vaerenbergh B, Descamps E, Brosius B, Dai Do Thi C, Leunda A, Baldo A. Survey of Laboratory-Acquired Infections in Belgium (2007-2012): An Online Survey. Wetenschappelijk Instituut Volkgezondheid. 2015 February;1-49. http://www.biosafety.be/CU/PDF/2015_Willemarck_LAI%20report%20Belgium_2007_2012_Final.pdf
11. Singh K, Weinstein RA. Laboratory-Acquired Infections. Clinical Infectious Diseases. 2009 July 1;49(1):142-7. DOI (https://doi.org/10.1086/599104). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=19480580&dopt=Abstract).
12. Government of Canada. Human Pathogens and Toxins Regulations, SOR/2015/44, Licenses (December 1, 2015). http://laws.justice.gc.ca/eng/regulations/SOR-2015-44/index.html
13. Public Health Agency of Canada. Canadian Biosafety Standard: for Facilities Handling or Storing Human and Terrestrial Animal Pathogens and Toxins. 2nd Edition. Ottawa ON: Public Health Agency of Canada. 2015. https://www.canada.ca/content/dam/phac-aspc/migration/cbsg-nldcb/cbs-ncb/assets/pdf/cbsg-nldcb-eng.pdf
14. Labrie C, Lecordier S. Regulatory Oversight of Human Pathogens and Toxins in Canada. Can Commun Dis Rep. 2015 December 17;41(S6):14-8. https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2015-41/ccdr-volume-41s-6-december-17-2015/ccdr-volume-41s-6-december-17-2015-3.html
15. Government of Canada. Human Pathogens and Toxins Act, S.C. 2009, c.24, Obligation to Inform Minister (December 1, 2015). http://laws.justice.gc.ca/eng/acts/H-5.67/page-2.html#h-10
16. Public Health Agency of Canada. Canadian Biosafety Handbook. 2nd Edition. Ottawa: Public Health Agency of Canada. 2016. https://www.canada.ca/en/public-health/services/canadian-biosafety-standards-guidelines/handbook-second-edition.html
17. Pike RM. Laboratory-Associated Infections: Summary and Analysis of 3921 Cases. Health Lab Sci. 1976;13(2):105-14. PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=946794&dopt=Abstract).
18. Lacroix G. Literature Review of Laboratory-Acquired Infections in Canada and the United-States between 2000 and 2009. Office of Laboratory Security, Public Health Agency of Canada. 2009. http://biosafety.icid.com/en/files/presentations/Literature-Review-%20Laboratory-Acquired-Infections-Canada-US-2000-2009.pdf
19. Traxler RM, Lehman MW, Bosserman EA, Guerra MA, Smith TL. A Literature Review of Laboratory-Acquired Brucellosis. J Clin Microbiol. 2013;51(9): 3055-62. DOI (dx.doi.org/10.1128/JCM.00135-13). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=23824774&dopt=Abstract)
20. Baron EJ, Miller JM. Bacterial and Fungal Infections Among Diagnostic Laboratory Workers: Evaluating the Risks. Diagn Microbiol Infect Dis. 2008;60(3):241-6. DOI (http://dx.doi.org/10.1016/j.diagmicrobio.2007.09.016). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=17997259&dopt=Abstract).
21. Main CL, Carusone SC, David K, Loeb M. Compliance with Personal Precautions Against Exposure to Bloodborne Pathogens Among Laboratory Workers: A Canadian Survey. Infect Control Hosp Epidemiol. 2008;29(1):66-8. DOI (http://dx.doi.org/10.1086/524325). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=18171190&dopt=Abstract).
22. De Carli G, Abiteboul D, Puro V. The Importance of Implementing Safe Sharps Practices in the Laboratory Setting in Europe. Biochem Med (Zagreb). 2014;24(1): 45-56. DOI (http://dx.doi.org/10.11613/BM.2014.007). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=24627714&dopt=Abstract).
23. Shoaei P, Najafi S, Lotfi N, Vakili B, Ataei B, Yaran M, Shafiei R. Seroprevalence of Hepatitis B Virus Infection and Hepatitis B Surface Antibody Status Among Laboratory Health Care Workers in Isfahan, Iran. Asian J Transfus Sci. 2015;9(2): 138-40. DOI (http://dx.doi.org/10.4103/0973-6247.162701).
24. Peacock SJ, Schweizer HP, Dance DAB, Smith TL. Gee JE, Wuthiekanun V, DeShazer D, Steinmetz I, Tan P, Currie BJ. Management of Accidental Laboratory Exposure to Burkholderia pseudomallei and B. mallei. Emerg Infect Dis. 2008;14(7):e2. DOI (http://dx.doi.org/10.3201/eid1407.071501). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=18598617&dopt=Abstract).
25. Yagupsky P. Brucellae Growing on Thayer-Martin Medium: A Source of Inadvertent Exposure for Laboratory Personnel in Endemic Areas. J Med Microbiol . 2014;63(Pt 1): 148-9. DOI (http://dx.doi.org/10.1099/jmm.0.064121-0). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=24072760&dopt=Abstract).

Appendix: Definitions relating to the *Human Pathogens and Toxins Act*

Term	Definition
Biological safety officer (BSO):	An individual designated for overseeing the facility's biosafety and biosecurity practices.
Containment level (CL):	Minimum physical containment and operational practice requirements for handling human pathogens or toxins safely in laboratory environments. There are four containment levels, ranging from a basic to the highest level of containment (1 to 4).
Containment zone:	A physical area that meets the requirements for a specified containment level. A containment zone can be a single room, a series of co-located rooms or several adjoining rooms. Dedicated support areas, including anterooms (with showers and 'clean' and 'dirty' change areas, where required), are considered to be part of the containment zone.
Exposure:	Contact with, or close proximity to, human pathogens or toxins that may result in infection or intoxication, respectively. Routes of exposure include inhalation, ingestion, inoculation and absorption.
Exposure follow-up report:	A tool used to report and document incident occurrence and investigation information for an exposure incident previously notified to the Public Health Agency of Canada.
Exposure notification report:	A tool used to notify and document preliminary information to the Public Health Agency of Canada of an exposure incident.
Incident:	An event or occurrence with the potential of causing injury, harm, infection, intoxication, disease or damage. Incidents can involve infectious material, infected animals or toxins, including a spill, exposure, release of human pathogens or toxins, animal escape, personnel injury or illness, missing human pathogens or toxins, unauthorized entry into the containment zone, power failure, fire, explosion, flood or other crisis situations (e.g., earthquake, hurricane). Incidents include accidents and near misses.
Laboratory:	An area within a facility or the facility itself where biological material is handled for scientific or medical purposes.
Licence:	An authorization to conduct one or more controlled activities with human pathogens or toxins issued by the Public Health Agency of Canada under Section 18 of the *Human Pathogens and Toxins Act*. One licence can cover many containment zones.
Risk group (RG):	The classification of biological material based on its inherent characteristics, including pathogenicity, virulence, risk of spread and availability of effective prophylactic or therapeutic treatments, that describes the risk to the health of individuals and the public as well as the health of animals and the animal population.
Security sensitive biological agents (SSBAs):	The subset of human pathogens and toxins that have been determined to pose an increased biosecurity risk due to their potential for use as a biological weapon. Security sensitive biological agents are identified as prescribed human pathogens and toxins by Section 10 of the *Human Pathogens and Toxins Regulations*. This includes all risk group 3 and 4 human pathogens that are in the *List of Human and Animal Pathogens for Export Control*, published by the Australia Group, as amended from time to time, with the exception of Duvenhage virus, Rabies virus and all other members of the Lyssavirus genus, Vesicular stomatitis virus, and Lymphocytic choriomeningitis virus. This also includes all toxins listed in Schedule 1 of the *Human Pathogens and Toxins Act* that are listed on the *List of Human and Animal Pathogens for Export Control* when in a quantity greater than that specified in Section 10(2) of the H*uman Pathogens and Toxins Regulations.*

For more definitions, please see the *Canadian Biosafety Standard, Second Edition* (16).

Tuberculosis drug resistance in Canada: 2006–2016

V Gallant[1], J Vachon[1]*, W Siu[1]

Abstract

Background: Drug-resistant strains of tuberculosis (TB) pose a serious threat to TB prevention and control efforts. The Canadian Tuberculosis Laboratory Surveillance System (CTBLSS) was created in 1998 to monitor emerging trends and patterns in TB drug resistance in Canada.

Objective: To present a descriptive overview of TB drug resistance data collected through the CTBLSS for the years 2006 to 2016 in Canada, with a focus on 2016.

Methods: The CTBLSS is an isolate-based surveillance system designed to collect data on TB drug resistance across Canada. Each year, data are collected and analyzed by the Public Health Agency of Canada (PHAC) and then validated by the submitting laboratory.

Results: In 2016, anti-tuberculosis drug susceptibility test results were reported for 1,452 isolates. The proportion of TB drug-resistant strains remained relatively stable with 108 (7.4%) of the isolates classified as monoresistant, five (0.3%) isolates as polyresistant and 17 (1.2%) as multidrug-resistant TB (MDR-TB) strains. In 2016, there were no extensively drug-resistant TB (XDR-TB) isolates identified. Males accounted for 792 (54.5%) of all reported isolates and 64 (49.2%) of the resistant strains and females accounted for 11 (64.7%) of the MDR-TB strains. Between 2006 and 2016, individuals between 15 and 44 years of age comprised 47.4% of all reported isolates, 54.0% of isolates showing any resistance and 72.3% of MDR-TB strains.

Conclusion: TB drug resistance levels have been relatively low and stable over the past 11 years and have remained below the global average since national surveillance began. However, with growing worldwide concern about drug resistance and the emergence of XDR-TB, the CTBLSS will remain vital to the monitoring of TB drug resistance in Canada.

Affiliation

[1] Centre for Communicable Disease and Infection Control, Public Health Agency of Canada, Ottawa, ON

***Correspondence:** tb_surveillance@phac-aspc.gc.ca

Suggested citation: Gallant V, Vachon J, Siu W. Tuberculosis drug resistance in Canada: 2006–2016. Can Commun Dis Rep. 2017;43(11):236-41. https://doi.org/10.14745/ccdr.v43i11a05

Introduction

Tuberculosis (TB), an airborne infectious disease caused by the bacterium *Mycobacterium tuberculosis*, remains a major cause of morbidity and mortality in many parts of the world. In 2015, there were an estimated 10.4 million new TB cases worldwide, and 1.8 million people died from this curable disease (1). While the majority of TB cases are caused by strains that are susceptible to the best available TB drugs, drug resistance is a major concern for TB control. Whereas the average length of time to treat a person with fully susceptible TB is between six and nine months, treatment of drug-resistant TB may require 12 to 18 months (and possibly longer) with drugs that are more expensive but less effective and potentially more toxic (2).

Drug-resistant strains of tuberculosis (TB) pose a serious threat to TB prevention and control efforts. Although it has not been a major public health issue in Canada, drug resistance has the potential to become one as Canadians frequently travel abroad and many individuals immigrate to Canada from countries with high TB rates and associated drug resistance.

The Canadian Tuberculosis Laboratory Surveillance System (CTBLSS) was established in 1998. It is a collaboration between federal, provincial and territorial governments and the Canadian Tuberculosis Laboratory Technical Network (CTLTN), a pan-Canadian network of technical and scientific heads of provincial and territorial TB laboratories. The CTBLSS is managed by the Centre for Communicable Diseases and Infection Control (CCDIC) within the Public Health Agency of Canada (PHAC).

The primary objective of the CTBLSS is to monitor emerging trends and patterns in TB drug resistance in Canada. This surveillance report presents a descriptive overview of data for the years 2006 to 2016, with a focus on 2016, on resistance to first- and second-line TB drugs in Canada. The results are disaggregated by province/territory and, where feasible, by sex and/or age group. The CTBLSS captures minimal demographic information (age, sex and province or territory only). Therefore, no direct observations about drug resistance related to other demographic factors, including ethnicity, are made. As the primary source of national data on TB drug resistance in

Canada, the data presented here are intended to inform public health action as well as policy and program development and assessment.

Previously, these data were published annually in a stand-alone report entitled *Tuberculosis: Drug Resistance in Canada*. This is the first iteration of the report to be published in the *Canada Communicable Disease Report* (CCDR). The data presented in this report are the most up-to-date at the time of publication and replace those previously published. Supplementary data tables are available online (3).

Methods

The CTBLSS is an isolate-based surveillance system designed to collect data on TB drug resistance across Canada. TB drug resistance is identified through susceptibility testing of biological specimens (isolates) collected from individuals with culture-positive TB (2). Details on the CTBLSS methods of data collection, data management and other laboratory processes have been previously described (4). As well, a list of recommended first- and second-line anti-tuberculosis drugs and the recommended critical concentrations to be used for routine testing are presented (4).

All participating laboratories tested for resistance to the four first-line antibiotics (isoniazid, ethambutol, rifampin and pyrazinamide) except for the Public Health and Microbiology Reference Laboratory in British Columbia, which did not routinely test for resistance to pyrazinamide. If resistance to any of the other three first-line drugs was detected, British Columbia subsequently tested the isolate for resistance to pyrazinamide. For all laboratories, results for second-line drug susceptibility testing were submitted for isolates showing resistance to isoniazid and rifampin in order to identify extensively drug-resistant TB (XDR-TB) isolates. **Table 1** describes TB drug resistance patterns as defined in the *Canadian Tuberculosis Standards* (2).

Table 1: Definitions of tuberculosis drug resistance patterns (2)

Resistance pattern	Definition
Monoresistance	Resistance to one first-line anti-tuberculosis drug only (isoniazid, rifampin, ethambutol or pyrazinamide).
Polyresistance	Resistance to more than one first-line anti-tuberculosis drug, not including the combination of isoniazid and rifampin.
Multidrug-resistant tuberculosis (MDR-TB)	Resistance to isoniazid AND rifampin with or without resistance to other anti-tuberculosis drugs.
Extensively drug-resistant tuberculosis (XDR-TB)	Resistance to isoniazid AND rifampin AND any fluoroquinolone AND at least one of the three injectable second-line drugs (amikacin, capreomycin or kanamycin).

Drug susceptibility test (DST) results (sensitive/resistant/not done) for all *Mycobacterium tuberculosis* complex (MTBC) isolates demonstrated on culture, specifically *M. tuberculosis*, *M. africanum*, *M. canetti*, *M. caprae*, *M. microti*, *M. pinnipedii* or *M. bovis*, were voluntarily submitted to PHAC by provincial TB laboratories for inclusion in the CTBLSS. Data were submitted to PHAC either through the manual completion of a standard reporting form (M. tuberculosis Complex Antimicrobial Susceptibility Reporting Form) or electronically (5).

Standardized data recoding procedures were applied to all data to create a national dataset. All raw data (paper forms and electronic datasets) were retained in compliance with PHAC's directive for the collection, use and dissemination of information relating to public health.

No statistical procedures were used for comparative analyses, nor were any statistical techniques applied to account for missing data. Data in tables with small cell sizes (n=<5) were not suppressed, since disclosure was not deemed to pose any risk of identifying individual cases. These procedures were in line with the directive for the collection, use and dissemination of information relating to public health. The data presented in this report were extracted from the CTBLSS database on March 2017 and have been validated by the reporting laboratories. Microsoft Excel 2010 and SAS Enterprise Guide (SAS EG) v5.1 software were used for data cleaning and analysis.

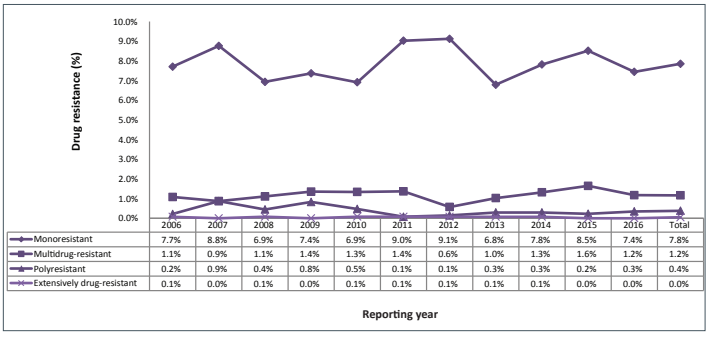
Results

In 2016, anti-tuberculosis DST results for 1,463 isolates were reported to PHAC. Of these, 11 (0.8%) isolates were identified as *M. bovis* Bacillus Calmette-Guerin and were excluded from further analyses. Of the remaining 1,452 isolates analyzed, 843 (58.1%) were reported as MTBC where the species were known (830 were *M. tuberculosis*, nine were *M. africanum* and four were *M. bovis*) and 609 (41.9%) were MTBC of an unknown species (data not shown) (**Supplementary Table 1**).

TB drug resistance patterns

In 2016, 1,322 (91.0%) of the tested isolated were sensitive to all four first-line TB drugs. The proportion of TB drug-resistant isolates remained low with 108 (7.4%) of the isolates classified as monoresistant, five (0.3%) as polyresistant and 17 (1.2%) as multidrug-resistant TB (MDR-TB) strains (**Figure 1).**

Figure 1: Tuberculosis drug resistance patterns as a percentage of isolates tested, Canada, 2006 to 2016

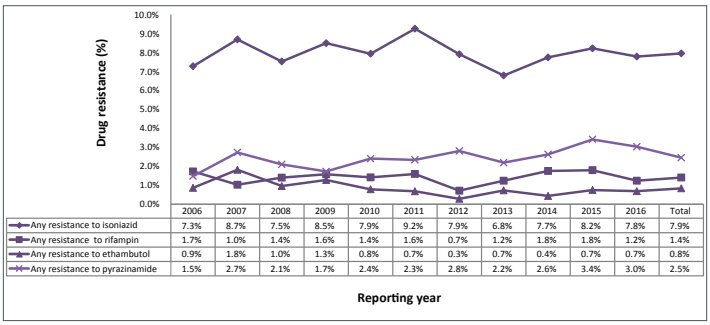


	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Monoresistant	7.7%	8.8%	6.9%	7.4%	6.9%	9.0%	9.1%	6.8%	7.8%	8.5%	7.4%	7.8%
Multidrug-resistant	1.1%	0.9%	1.1%	1.4%	1.3%	1.4%	0.6%	1.0%	1.3%	1.6%	1.2%	1.2%
Polyresistant	0.2%	0.9%	0.4%	0.8%	0.5%	0.1%	0.1%	0.3%	0.3%	0.2%	0.3%	0.4%
Extensively drug-resistant	0.1%	0.0%	0.1%	0.0%	0.1%	0.1%	0.1%	0.1%	0.1%	0.0%	0.0%	0.0%

For the period 2006 to 2016, DST results were reported for 14,872 isolates (Supplementary Table 1). Monoresistance was the most frequent pattern reported, representing approximately 1,167 (7.8%) of all the isolates tested over the period. In total, 173 (1.2%) of the isolates were identified as MDR-TB (excluding XDR-TB) and seven (<0.1%) of the isolates were identified

as XDR-TB. While there have been small fluctuations in the proportion of isolates showing various resistance patterns, the results have remained consistent during the 11-year period from 2006 to 2016 (**Figure 2; Supplementary Table 2**).

Figure 2: Percentage of isolates tested with any resistance to isoniazid, pyrazinamide, rifampin or ethambutol, Canada, 2006 to 2016



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Any resistance to isoniazid	7.3%	8.7%	7.5%	8.5%	7.9%	9.2%	7.9%	6.8%	7.7%	8.2%	7.8%	7.9%
Any resistance to rifampin	1.7%	1.0%	1.4%	1.6%	1.4%	1.6%	0.7%	1.2%	1.8%	1.8%	1.2%	1.4%
Any resistance to ethambutol	0.9%	1.8%	1.0%	1.3%	0.8%	0.7%	0.3%	0.7%	0.4%	0.7%	0.7%	0.8%
Any resistance to pyrazinamide	1.5%	2.7%	2.1%	1.7%	2.4%	2.3%	2.8%	2.2%	2.6%	3.4%	3.0%	2.5%

Any first-line drug resistance

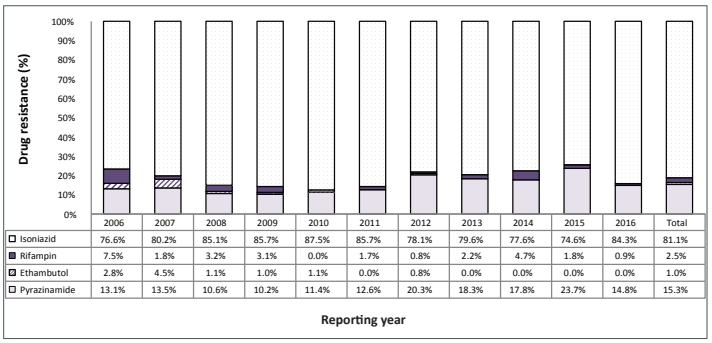
In 2016, ethambutol, isoniazid and rifampin susceptibility results were available for all 1,452 isolates. The drug susceptibility test results to pyrazinamide were reported for 1,254 (86.4%) isolates. As a proportion of those tested, 113 (7.8%) were resistant to isoniazid, 38 (3.0%) were resistant to pyrazinamide, 18 (1.2%) were resistant to rifampin and 10 (0.7%) were resistant to ethambutol (Supplementary Table 2). Overall, 130 (9.0%) of the isolates were resistant to at least one of the first-line drugs. Between 2006 and 2016, the proportion of reported isolates with resistance to at least one of the four first-line tuberculosis medications was stable over time (Figure 2). Resistance to isoniazid alone or in combination with other drugs varied between 7.5 and 9.2% of isolates tested. Resistance to ethambutol, rifampin or pyrazinamide remained below 3.5% (Figure 2).

Monoresistance

In 2016, 130 (9.0%) of the total TB isolates were reported to be resistant to at least one of the four first-line drugs. Of those, 108 (83.1%) were monoresistant. Of the monoresistant isolates, 91 (84.3%) were resistant to isoniazid, 16 (14.8%) were resistant to pyrazinamide and one (0.9%) was resistant to rifampin. No isolates were found to be monoresistant to ethambutol (**Supplementary Table 3 - Table 15**; data not tabulated across tables).

Between 2006 and 2016, 1,167 (7.8%) isolates were found to be monoresistant to one of the four first-line TB drugs. Of these, isoniazid resistance was the most frequently reported with 946 (81.1%) of the isolates (**Figure 3**). During this period, 29 (2.5%) of the monoresistant isolates were found to be resistant to rifampin. On average, one to three rifampin monoresistant isolates were reported each year from 2006 to 2016 (Figure 3; Supplementary Table 3 - Table 15; data not tabulated across tables).

Figure 3: Percentage of monoresistant isolates resistant to isoniazid, pyrazinamide, rifampin, or ethambutol, Canada, 2006 to 2016



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Isoniazid	76.6%	80.2%	85.1%	85.7%	87.5%	85.7%	78.1%	79.6%	77.6%	74.6%	84.3%	81.1%
Rifampin	7.5%	1.8%	3.2%	3.1%	0.0%	1.7%	0.8%	2.2%	4.7%	1.8%	0.9%	2.5%
Ethambutol	2.8%	4.5%	1.1%	1.0%	1.1%	0.0%	0.8%	0.0%	0.0%	0.0%	0.0%	1.0%
Pyrazinamide	13.1%	13.5%	10.6%	10.2%	11.4%	12.6%	20.3%	18.3%	17.8%	23.7%	14.8%	15.3%

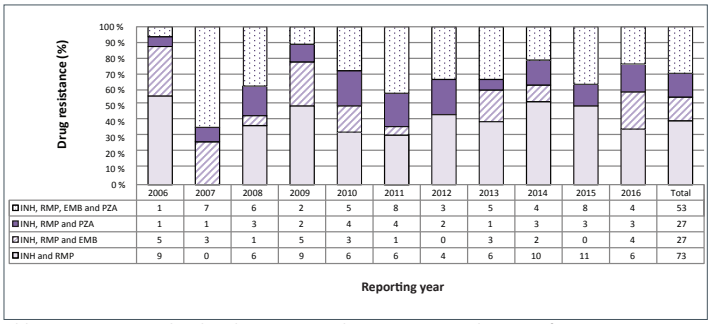
Polyresistant, multidrug-resistant and extensively drug-resistant TB

In 2016, five (0.2%) of the isolates were resistant to two or more of the first-line drugs (excluding the combination of isoniazid and rifampin) and were therefore classified as polyresistant. Two isolates were resistant to isoniazid and ethambutol and three were resistant to isoniazid and pyrazinamide.

Between 2006 and 2016, 54 (0.4%) of the isolates were identified as polyresistant. Of these, 23 (42.6%) were resistant to isoniazid and ethambutol, 24 (44.4%) were resistant to isoniazid and pyrazinamide and one was resistant to ethambutol and pyrazinamide. The remaining six (11.1%) isolates were resistant to isoniazid, ethambutol and pyrazinamide (Supplementary Table 3 - Table 15; data not tabulated across tables).

In 2016, 17 (1.2%) of the isolates tested were resistant to isoniazid and rifampin. Of these, six (35.3%) were resistant to only isoniazid and rifampin, four (23.5%) were resistant to isoniazid, rifampin and ethambutol, and three (17.6%) were resistant to isoniazid, rifampin and pyrazinamide. Finally, four (23.5%) of the isolates were resistant to all four of the first-line drugs (**Figure 4; Supplementary Table 17**).

Figure 4: Number and percentage of isolates resistant to isoniazid and rifampin with or without resistance to ethambutol and/or pyrazinamide, Canada, 2006 to 2016



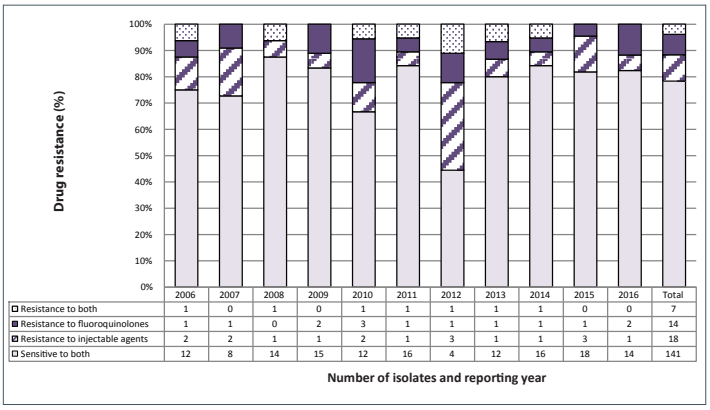
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
INH, RMP, EMB and PZA	1	7	6	2	5	8	3	5	4	8	4	53
INH, RMP and PZA	1	1	3	2	4	4	2	1	3	3	3	27
INH, RMP and EMB	5	3	1	5	3	1	0	3	2	0	4	27
INH and RMP	9	0	6	9	6	6	4	6	10	11	6	73

Abbreviations: EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RMP, rifampin

For the period 2006 to 2016, 180 (1.2%) of the isolates tested were resistant to both isoniazid and rifampin. During that time, 73 (40.6%) were resistant only to isoniazid and rifampin, 27 (15.0%) were also resistant to ethambutol and an additional 27 (15.0%) were resistant to pyrazinamide. The remaining 53 (29.4%) isolates were resistant to all four of the first-line TB medications (Figure 4; Supplementary Table 3 - Table 15; data not tabulated across tables).

To determine XDR-TB, all isolates that were found to be resistant to both isoniazid and rifampin were subsequently tested for resistance to select second-line drugs. In 2016, of the 17 isolates identified as resistant to both isoniazid and rifampin, one was resistant to at least one of the injectable agents (amikacin, capreomycin or kanamycin) but susceptible to the fluoroquinolones, and two isolates were resistant to at least one fluoroquinolone but susceptible to all of the injectable agents. The remaining 14 isolates were all susceptible to both the injectable agents and the fluoroquinolones. As none of the 17 isoniazid- and rifampin-resistant isolates were resistant to both an injectable agent and a fluoroquinolone, no isolates were classified as XDR-TB. 2016 was the second year in a row with no reported XDR-TB isolates.

Figure 5: Number and percentage of isolates resistant to isoniazid and rifampin with or without resistance to fluoroquinolones and/or injectable agents, Canada, 2006 to 2016



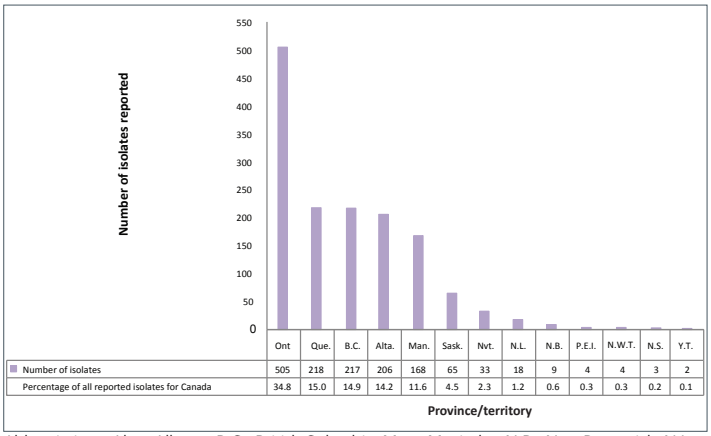
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Resistance to both	1	0	1	0	1	1	1	1	1	0	0	7
Resistance to fluoroquinolones	1	1	0	2	3	1	1	1	1	1	2	14
Resistance to injectable agents	2	2	1	1	2	1	3	1	1	3	1	18
Sensitive to both	12	8	14	15	12	16	4	12	16	18	14	141

Between 2006 and 2016, of the 180 isolates resistant to both isoniazid and rifampin, 141 (78.3%) were found to be sensitive to both the injectable agents and the fluoroquinolones (**Figure 5**). Additionally, 18 (10.0%) were resistant to the injectable agents but susceptible to the fluoroquinolones and 14 (7.8%) were resistant to the fluoroquinolones but susceptible to the injectable agents. Finally, seven (3.9%) of the isolates were found to be resistant to both the fluoroquinolones and the injectable agents, identifying them as XDR-TB (Figure 5).

Geographical distribution

In 2016, 1,314 (90.4%) of the isolates originated from five provinces: Ontario, Quebec, British Columbia, Alberta and Manitoba (**Figure 6**; **Supplementary Table 16**). Saskatchewan accounted for fewer than 5% of reported isolates while the northern territories (Northwest Territories, Nunavut and Yukon) and the Atlantic provinces (New Brunswick, Newfoundland and Labrador, Nova Scotia and Prince Edward Island) together accounted for 5% of the reported isolates. In 2016, all isolates reported from Nunavut, the Northwest Territories, Yukon, Newfoundland and Labrador, New Brunswick and Prince Edward Island were susceptible to all first-line drugs tested. Of the 17 MDR-TB isolates, seven (41.2%) originated from Ontario, four (23.5%) from Alberta and two (11.8%) each from British Columbia, Quebec and Manitoba.

Figure 6: Number of *Mycobacterium tuberculosis* complex isolates reported, by province or territory of origin and as a percentage of all isolates reported in Canada, 2016



	Ont	Que.	B.C.	Alta.	Man.	Sask.	Nvt.	N.L.	N.B.	P.E.I.	N.W.T.	N.S.	Y.T.
Number of isolates	505	218	217	206	168	65	33	18	9	4	4	3	2
Percentage of all reported isolates for Canada	34.8	15.0	14.9	14.2	11.6	4.5	2.3	1.2	0.6	0.3	0.3	0.2	0.1

Abbreviations: Alta., Alberta; B.C., British Columbia; Man., Manitoba; N.B., New Brunswick; N.L., Newfoundland and Labrador; N.S., Nova Scotia; Nvt., Nunavut; N.W.T., Northwest Territories; Ont., Ontario; P.E.I., Prince Edward Island; Que., Quebec; Sask., Saskatchewan; Y.T., Yukon

Between 2006 and 2016, the 173 MDR-TB isolates originated from seven provinces: Alberta, British Columbia, Manitoba, New Brunswick, Ontario, Quebec and Saskatchewan. Ontario accounted for 97 (56.1%) of all reported MDR-TB isolates and has reported an average of nine MDR-TB isolates per year (range: 614) (**Supplementary Table 11**). Alberta accounted for 24 (13.9%) of the reported MDR-TB isolates, of which more than 10 (41.6%) were reported between 2014 and 2016 (**Supplementary Table 3**).

Between 2006 and 2016, both British Columbia and Quebec consistently reported, on average, fewer than two MDR-TB isolates per year. Manitoba reported seven MDR-TB isolates over the past 11 years, averaging less than one per year. New Brunswick and Saskatchewan reported one and two MDR-TB isolates respectively, between 2006 and 2016 (**Supplementary Table 18**).

Between 2006 and 2016, there were seven XDR-TB isolates reported. Of the seven, five originated from Ontario, one from Manitoba and one from Quebec (Supplementary Table 18).

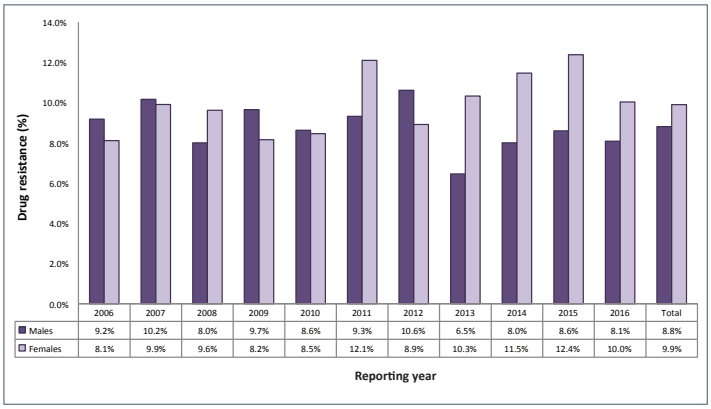
Demographic information

In 2016, sex was known for 1,450 (99.9%) of the 1,452 individuals from whom isolates were collected (**Supplementary Table 19**). While males accounted for 732 (54.5%) of all reported isolates and 64 (49.2%) of the resistant isolates, females represented 11 (64.7%) of the MDR-TB isolates.

Between 2006 and 2016, males accounted for 8,265 (56.3%) of all the isolates reported, 726 (53.1%) of isolates with any

resistance and 85 (50.0%) of the MDR-TB isolates (data not shown). Although there were only seven XDR-TB isolates reported between 2006 and 2016, five were from females. The proportion of females whose TB showed any drug resistance increased slightly during the 11-year period (from 8.1% in 2006 to 10.0% in 2016) and was higher than males (at 8.1%) in 2016 (**Figure 7**).

Figure 7: Percentage of isolates showing any resistance among all isolates tested, by sex, Canada, 2006 to 2016

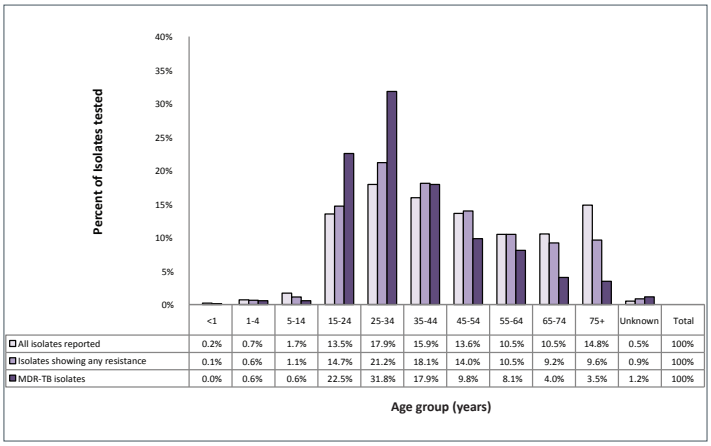


	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Males	9.2%	10.2%	8.0%	9.7%	8.6%	9.3%	10.6%	6.5%	8.0%	8.6%	8.1%	8.8%
Females	8.1%	9.9%	9.6%	8.2%	8.5%	12.1%	8.9%	10.3%	11.5%	12.4%	10.0%	9.9%

In 2016, age and/or date of birth was reported for all 1,452 individuals from whom isolates were collected (**Supplementary Table 19**). Of the 130 drug-resistant isolates, 26 (20.0%) of those with any resistance were from individuals between 25 and 34 years of age and 25 (19.2%) were among those between 15 and 24 years of age (Supplementary Table 19). Five isolates with any resistance were from individuals under the age of 15 years. In 2016, of the 17 MDR-TB cases, 16 (94.1%) were among individuals aged between 15 and 64 years of age and only one case was found in an individual between five and 14 years of age (Supplementary Table 19).

Between 2006 and 2016, individuals between 15 and 44 years of age accounted for 7,045 (47.4%) of all reported isolates, 757 (54.0%) of the isolates showing any resistance and 125 (72.3%) of MDR-TB isolates (**Figure 8**).

Figure 8: Proportion of reported isolates by resistance pattern and age group, Canada, 2006 to 2016



	<1	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75+	Unknown	Total
All isolates reported	0.2%	0.7%	1.7%	13.5%	17.9%	15.9%	13.6%	10.5%	10.5%	14.8%	0.5%	100%
Isolates showing any resistance	0.1%	0.6%	1.1%	14.7%	21.2%	18.1%	14.0%	10.5%	9.2%	9.6%	0.9%	100%
MDR-TB isolates	0.0%	0.6%	0.6%	22.5%	31.8%	17.9%	9.8%	8.1%	4.0%	3.5%	1.2%	100%

Abbreviation: Alta., Alberta; B.C., British Columbia; Man., Manitoba; MDR-TB, multidrug-resistant tuberculosis; N.B., New Brunswick; N.L., Newfoundland and Labrador; N.S., Nova Scotia; Nvt., Nunavut; N.W.T., Northwest Territories; Ont., Ontario; P.E.I., Prince Edward Island; Que., Quebec; Sask., Saskatchewan; Y.T., Yukon

Discussion

In Canada, between 2006 and 2016, trends in TB drug resistance remained relatively low and stable. In 2016, although there was a slight increase in the number of isolates reported as compared with previous years, this did not translate into an increased proportion of drug resistance. Of the results submitted in 2016, 9.0% of all isolates tested were resistant to at least one of the four first-line drugs; the majority (83.1%) of those were resistant to only one drug. Of isolates tested, MDR-TB was identified in only 1.2% and XDR-TB was not identified among any results reported in 2016.

Isoniazid monoresistance was the most commonly reported pattern in Canada. Rifampin, along with isoniazid, is one of the most effective first-line medications; fortunately, rifampin monoresistance remains low but ongoing surveillance will continue to be important to identify any changes in resistance patterns to this drug.

In 2016, the data showed some regional variation, including slightly increased levels of MDR-TB in Alberta. As well, the proportion of females with resistance appeared to slightly increase over time and was higher than the proportion of males with resistance.

In many parts of the world, drug resistance is a major challenge to preventing and controlling TB. Eastern Europe and Central Asia continue to have the world's highest proportion of MDR-TB cases (1). Such cases pose a considerable challenge to treatment and prevention efforts because the availability of effective anti-tuberculosis drugs becomes limited.

As reported in *Tuberculosis in Canada - Summary 2015*, foreign-born individuals continued to account for the majority of reported cases, at 71% of active TB cases diagnosed in Canada (6) and it is likely that these individuals acquired the infection outside of Canada. Therefore, although data on country of origin is not collected in the CTBLSS, TB drug-resistance patterns in Canada are probably affected by drug-resistance patterns elsewhere in the world.

Data published by the World Health Organization show that, globally, in 2015, about 3.9% (95% CI: 2.7%–5.1%) of new TB cases and 21% (95% CI: 15%–28%) of previously-treated TB cases were MDR-TB (1). Although the data captured through the CTBLSS do not distinguish between isolates from new versus previously-treated cases of TB, it is reassuring that only 1.2% of isolates tested in 2016 were MDR-TB (which is considerably lower than global estimates). In addition, only seven XDR-TB cases were identified between 2006 and 2016 indicating that XDR-TB in Canada remains rare.

A few limitations should be considered. Although efforts were made to ensure that multiple records for any one individual in a given year were removed, given the minimal identifying information available for each isolate (age and sex), it is possible that multiple isolates from one individual were included in the database. This bias is likely minimal given the validation process with provincial and territorial data providers.

Demographic and clinical data collected through the CTBLSS were limited, and no data were collected on the ethnic origin, diagnostic/clinical status or treatment outcome of the individual from whom the sample was collected. Additional demographic

and clinical information would facilitate a more in-depth epidemiological assessment of drug resistance patterns in Canada. Differentiation between primary and acquired drug resistance (1) and differing resistance patterns among new cases in comparison to re-treatment cases was not possible based on data collected through this surveillance system. However, the Tuberculosis in Canada—Summary 2015 (6) and Tuberculosis in Canada 2012 (7) surveillance reports provide an overview of the overall reported active TB cases and corresponding incidence rates in Canada by select demographic and clinical characteristics, and present case-based (vs. isolate-based) data on primary and acquired drug resistance in Canada that were not presented here. Together, these reports provide a comprehensive overview of TB case and drug resistance surveillance data from a national perspective.

Typically, only MDR-TB isolates or other extensive resistance patterns will undergo select second-line drug sensitivity testing. Although the Clinical and Laboratory Standards Institute (CLSI) recommends that isoniazid-monoresistant isolates as well as other polyresistant non-MDR isolates be tested for second-line drug resistance (8), this is not universally reported in Canada. Other isolates that are not MDR-TB may be resistant to fluoroquinolones because of the widespread use of these antibiotics for other respiratory infections. To some extent, this limits our understanding of the emergence of second-line drug resistance within Canada.

The Public Health Agency of Canada continues to work with its provincial and territorial partners to achieve the goal of TB elimination in Canada. With the growing worldwide concern about drug resistance and the emergence of XDR-TB, the CTBLSS remains vital to the monitoring of TB drug resistance in Canada.

Authors' statement

VG – Conceptualization, Methodology, Software, Validation, Formal Analysis, Writing – Original Draft

JV – Conceptualization, Writing – Review & Editing

WS – Writing – Review & Editing, Supervision

Conflict of interest

None.

Acknowledgements

The Surveillance and Epidemiology Division, Centre for Communicable Diseases and Infection Control at the Public Health Agency of Canada would like to acknowledge the members of the Canadian Tuberculosis Laboratory Technical Network and their teams as well as colleagues at The National Microbiology Laboratory for their contribution to and participation in the Canadian Tuberculosis Laboratory Surveillance System.

Funding

This work was supported by the Public Health Agency of Canada as part of its core mandate.

References

1. World Health Organization. Global tuberculosis report 2016. Geneva: WHO Press; 2017. http://www.who.int/tb/publications/global_report/en/
2. Menzies R, Wong T (eds). Canadian Tuberculosis Standards, 7th Edition. Canadian Thoracic Society. Canadian Lung Association Public Health Agency of Canada; 2014. http://strauss.ca/OEMAC/wp-content/uploads/2013/11/Canadian_TB_Standards_7th-edition_English.pdf
3. V Gallant, J Vachon, W Siu. Tuberculosis drug resistance in Canada:2006—2016 Supplementary data [Internet]. Can Commun Dis Rep. 2017;43(11). https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2017-43/ccdr-volume-43-11-november-2-2017/tuberculosis-drug-resistance-canada-2006–2016-supplementary-data.html
4. Public Health Agency of Canada. Tuberculosis: Drug resistance in Canada 2015, Ottawa (Canada): Minister of Public Works and Government Services Canada; 2017. https://www.canada.ca/en/public-health/services/publications/diseases-conditions/tuberculosis-drug-resistance-canada-2015.html
5. Public Health Agency of Canada. M. tuberculosis Complex Antimicrobial Susceptibility Reporting Form. https://www.canada.ca/content/dam/phac-aspc/documents/services/diseases/tuberculosis/m-tuberculosis-complex-antimicrobial-susceptability-reporting-form-eng.pdf
6. Gallant V, Duvvuri V, McGuire M. Tuberculosis in Canada—Summary 2015. Can Commun Dis Rep. 2017;43(3):77-82. https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/publicat/ccdr-rmtc/17vol43/dr-rm43-3-4/assets/pdf/17vol43_3_4-ar-04-eng.pdf
7. Public Health Agency of Canada. Tuberculosis in Canada 2012. Ottawa (Canada) Date modified: 2015-05-29. https://www.canada.ca/en/public-health/services/infectious-diseases/tuberculosis-canada-2012.html
8. Woods GL, Brown-Elliott BA, Conville PS, Desmond EP, Lin G, Pfyffer GE, Ridderhof JC, Siddiqi SH, Wallace RJ, Warren NG, Witebsky FG. Susceptibility testing of mycobacteria, nocardiae, and other aerobic actinomycetes; approved standard–Second Edition. Wayne, PA: Clinical and Laboratory Standards Institute; 2011:31(5).

New vaccine administration practice recommendations from the Canadian Immunization Guide

C Jensen[1], D Moore[2], C Mah[3], O Baclic[1], S Marchant-Short[4] on behalf of the National Committee on Immunization (NACI)*

Abstract

Background: The *Canadian Immunization Guide* (CIG) is published online by the Public Health Agency of Canada and summarizes guidance on vaccines for human use into a single resource. Chapters are reviewed and updated on a regular basis. Vaccine administration is a critical part of any immunization program. Recently, the CIG chapter on vaccine administration practices was updated.

Objective: To provide highlights of recent changes to the Vaccine Administration Practices chapter of the CIG.

Approach: Vaccine-specific guidance in the CIG is based on National Committee on Immunization (NACI) and Committee to Advise on Tropical Medicine and Travel (CATMAT) recommendations as well as new recommendations developed by the CIG Working Group members and NACI Secretariat technical staff. New recommendations are based on a review of the literature, including systematic reviews when available, a review of guidance provided by other National Immunization Technical Advisory Groups and expert opinion. The revisions are approved by the Working Group chair, as well as NACI.

Results: Highlights of new recommendations include the following: vaccine providers should adhere to jurisdictional or organizational policies and procedures regarding combining the contents of multi-dose vials; clinical judgement should be used when selecting needle length for intramuscular injections that takes into account the vaccine recipient's weight, gender and age; filter needles are not recommended for vaccine administration as they may filter out active ingredients such as adjuvants; an injection site other than in an area where lymphatic drainage may be impaired should be considered; there is no evidence or theoretical rationale for avoiding injection through a tattoo or superficial birthmark; and immunization pain management strategies have now been developed for all ages.

Conclusion: Recommendations in vaccine administration practices have recently been changed in some important ways. The Public Health Agency of Canada is committed to providing information on immunization in an easily accessible, reader-friendly format for healthcare providers and policy-makers.

Affiliations

[1] Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada, Ottawa, ON

[2] McGill University, Montreal, QC

[3] Dalhousie University, Halifax, NS and University of Toronto, Toronto, ON

[4] Public Health Nursing, Health PEI, Charlottetown, PE

***Correspondence:** naci-ccni@phac-aspc.gc.ca

Suggested citation: Jensen C, Moore D, Mah C, Baclic O, Marchant-Short S on behalf of the National Committee on Immunization (NACI). New vaccine administration practice recommendations from the Canadian Immunization Guide. Can Commun Dis Rep. 2017;43(11):242-4. https://doi.org/10.14745/ccdr.v43i11a06

Introduction

The *Canadian Immunization Guide* (CIG) is published online by the Public Health Agency of Canada (PHAC). It is a trusted, reader-friendly summary of information on immunization and has been used by healthcare providers who administer vaccines to their patients and by policy-makers for the delivery of immunization programs since 1979 (1). The CIG is divided into five parts and summarizes guidance from the National Advisory Committee on Immunization (NACI) and the Committee to Advise on Tropical Medicine and Travel (CATMAT) into a single resource. Chapters are reviewed and updated on a four year cycle or more frequently in the event of a new recommendation or a changing practice. A Table of Updates (2) summarizes key changes as they are made to individual chapters.

Vaccine administration is a critical part of any immunization program. Important considerations in vaccine administration practices are pre-vaccination counselling, vaccine preparation and needle selection, as well as identification of the proper route, site and technique for vaccine administration.

Immunization pain management strategies, postvaccination counselling and observation and infection prevention and control are also integral parts of vaccine administration practices. The objective of this article is to provide highlights of the key changes to the Vaccine Administration Practices chapter in Part 1 of the CIG.

Approach

Vaccine-specific guidance in the CIG is summarized from NACI and CATMAT recommendations as written in the statements and updates (3,4). New recommendations not contained in a NACI or CATMAT statement are written by the CIG Working Group members and NACI Secretariat technical staff at PHAC. The revisions are approved by the Working Group chair, as well as NACI. The Part 1 Working Group was activated to revise the Vaccine Administration Practices chapter in August 2016. The previous version of the Vaccine Administration Practices chapter was published online in 2014. A chapter revision was undertaken prior to the four year cycle as there was new research, particularly in the areas of needle selection and pain management, which prompted a chapter revision.

A full chapter revision was undertaken. Feedback on the existing chapter was solicited by the NACI Liaison Member of the Canadian Immunization Committee from nurse immunizers. Requests for clarification and guidance were considered and the chapter was reviewed to identify issues that required a review of the literature. The revised needle length recommendations provided in "Table 3: Needle selection guidelines" of the Vaccine Administration Practices chapter were based on a review of the literature, a review of guidance provided by other National Immunization Technical Advisory Groups (NITAGs) and expert opinion. The revised recommendations in "Table 4: Immunization pain management strategies, by age groups" of the Vaccine Administration Practices chapter were based on the systematic review of vaccine injection pain reduction strategies by Taddio and colleagues (5). The six systematic reviews, upon which the guidelines were based, were assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) checklist by the NACI Secretariat prior to inclusion in the chapter revision (6).

Table 1: Key changes to Vaccine Administration Practices chapter

Topic	Section Heading - Sub-heading	Previous guidance	Revised/new guidance
Combination of contents of multi-dose vials	Vaccine administration - Vaccine preparation - Vaccine inspection and mixing	In immunization clinics in which only a single vaccine is being administered, the contents of more than one multi-dose vial may be combined to prevent wastage if the vials have the same lot number.	Vaccine providers should adhere to jurisdictional or organizational policies and procedures regarding combining the contents of multi-dose vials.

Table 1: Key changes to Vaccine Administration Practices chapter (continued)

Topic	Section Heading - Sub-heading	Previous guidance	Revised/new guidance
Needle selection for intramuscular injections (IM)	Vaccine administration • Needle selection • Table 3: Needle selection guidelines • Route of administration, Intramuscular (IM)	Needle length: 2.2—2.5 cm (⅞ – 1 inch) for infants, toddlers and older children 2.5 – 3.8 cm (1- 1½ inches) for adolescents and adults	A range of needle lengths are provided in the revised Table 3, as clinical judgement should be used when selecting needle length for IM injections. Consideration should be given to the vaccine recipient's weight, gender and age
Use of filtration needles	Vaccine administration • Needle selection	None	Filtration needles are not recommended for vaccine administration as they may filter out active ingredients such as adjuvants
Vaccine administration into an area where lymphatic circulation may be impaired or through a tattoo or superficial birthmark	Vaccine administration • Route, site and technique for vaccine administration • Parenteral vaccines	None	Injection of a vaccine into an area where lymphatic circulation may be impaired (e.g., local lymphedema, lymphangioma, axillary lymph node dissection, arteriovenous (A-V) fistula, upper limb amputation) could theoretically result in an impaired immune response due to impaired vaccine absorption, although there are no data to support this. Consider an alternative injection site if possible. There is no evidence or theoretical rationale for avoiding injection through a tattoo or superficial birthmark
Techniques to decrease immunization injection pain	Vaccine administration • Techniques to decrease immunization injection pain Table 4: Immunization pain management strategies, by age groups	The previous version of Table 4 contained only immunization pain management strategies for children	Revised version of Table 4 provides immunization pain management strategies for all ages

Summary of updates

The updates are summarized in Table 1. For complete information, please refer to the Vaccine Administration Practices chapter in the CIG (7).

Discussion

Recommendations in vaccine administration practices have changed recently in some important ways; vaccine providers in Canada should consult jurisdictional or organizational policies regarding the combination of contents of multi-dose vials. Now vaccine providers are encouraged to take weight, gender and age into consideration in the selection of needle length for intramuscular injections. Additionally, there are now pain management strategies to decrease injection pain for all ages. These new recommendations may inform upcoming vaccination campaigns in terms of vaccine administration practices.

The Public Health Agency of Canada is committed to providing information on immunization and vaccines available for use in Canada in an easily accessible, reader-friendly format, through timely and ongoing CIG updates. To receive information regarding new NACI recommendations, statements and updates and/or updates to CIG chapters, please subscribe to the mailing list (8).

Authors' statement

This report summary was prepared by the CIG Part 1 Working Group: Marchant-Short S (Chair), Moore D, Mah C, Jensen C and Baclic O. Marchant-Short S is a NACI member. Moore D and Mah C are NACI Liaison members.

Conflict of interest

None.

Acknowledgements

The authors would like to thank the extremely dedicated NACI members and the staff of Public Health Agency of Canada who support the *Canadian Immunization Guide* process.

Funding

The Public Health Agency of Canada supports the activities of NACI as an external advisory body.

References

1. Government of Canada. Canadian Immunization Guide. Ottawa ON: PHAC. https://www.canada.ca/en/public-health/services/canadian-immunization-guide.html [Accessed September 8, 2017].
2. Government of Canada. Canadian Immunization Guide: Table of Updates. Ottawa ON. https://www.canada.ca/en/public-health/services/canadian-immunization-guide/updates.html [Accessed September 8, 2017].
3. Government of Canada. National Advisory Committee on Immunization. Ottawa ON: PHAC. https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci.html [Accessed September 8, 2017].
4. Government of Canada. About CATMAT. Ottawa ON: PHAC. https://www.canada.ca/en/public-health/services/travel-health/about-catmat.html [Accessed September 8, 2017].
5. Taddio A, McMurtry CM, Shah V, Riddell RP, Chambers CT, Noel M, MacDonald NE, Rogers J, Bucci LM, Mousmanis P, Lang E, Halperin SA, Bowles S, Halpert C, Ipp M, Asmundson GJG, Rieder MJ, Robson K, Uleryk E, Antony MM, Dubey V, Hanrahan A, Lockett D, Scott J, Bleeker EV; HELPinKIDS&Adults. Reducing pain during vaccine injections: clinical practice guideline. CMAJ 2015; 187(13):975-82. DOI (http://dx.doi.org/10.1503/cmaj.150391). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=26303247&dopt=Abstract).
6. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology. 2007;7(10):1-7. DOI (https://doi.org/10.1186/1471-2288-7-10). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=17302989&dopt=Abstract).
7. Government of Canada. Canadian Immunization Guide: Vaccine Administration Practices. Ottawa ON. https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-1-key-immunization-information/page-8-vaccine-administration-practices.html [Accessed September 8, 2017].
8. Government of Canada. Canadian Immunization Guide Update – Mailing List. Ottawa ON. http://www.healthycanadians.gc.ca/healthy-living-vie-saine/immunization-immunisation/canadian-immunization-guide-canadien-immunisation/email-subscription-abonnement-courriel-eng.php?_ga=2.266822922.504025174.1504710542-950076339.1489780715 [Accessed September 8, 2017].

RAPID COMMUNICATION

Hepatitis A virus infection associated with cannabis use

C Sikora[1,2]*, G Tipples[2,3], X-L Pang[2,3], A Andonov[4,5]

Abstract

We identified a case of acute Hepatitis A virus (HAV) infection linked to cannabis use. The local Public Health department received report of a man in his mid-20s with a classic presentation of hepatitis – jaundice, abdominal pain, vomiting, general malaise, and dark urine – as well as elevated serum aminotransferase levels and a positive anti-HAV IgM. Upon questioning, he reported no contact with ill individuals, or travel outside his metropolitan area. His exclusive source of water was the local municipal supply. He reported consuming mainly pre-packaged lower risk foods from large chain-style supermarket stores and eating at several local restaurants. While administering the questionnaire, the investigator identified that the patient smoked cannabis. Upon request, the patient agreed to provide a sample of cannabis for testing purposes. A viral elution of fresh cannabis leaves was completed. The sequences derived from the patient's serum sample and the eluate from the cannabis leaves were identical, but did not match any other HAV sub-genotype 1B sequences from Canadian isolates within the National Microbiology Laboratory database. Hepatitis A virus can survive >60 days when dried and kept at room temperature and low humidity; HAV can remain infectious in water at room temperature for 300 days. It cannot be concluded with certainty that the cannabis was the source of the hepatitis A; however, as other sources were excluded, or were of lesser probability, the association of cannabis with his disease acquisition remains strong.

Affiliations

[1] Alberta Health Services, Edmonton, AB

[2] University of Alberta, Edmonton, AB

[3] Provincial Laboratory for Public Health, Alberta Health Services, Edmonton, AB

[4] National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB

[5] University of Manitoba, Winnipeg, MB

***Correspondence:** christopher.sikora@ahs.ca

Suggested citation: Sikora C, Tipples G, Pang X-L, Andonov A. Hepatitis A virus infection associated with cannabis use. Can Commun Dis Rep. 2017;43(11):245-6. https://doi.org/10.14745/ccdr.v43i11a07

The medical literature reports that cannabis can be contaminated by bacteria, mold, and chemicals such as pesticides, lead, ammonia, and formaldehyde (1). We identified a case of acute hepatitis A virus (HAV) infection linked to cannabis use. The local Public Health department received report of a patient with a positive anti-HAV IgM. The patient was a man in his mid- 20s with a classic clinical presentation of hepatitis – jaundice, abdominal pain, vomiting, general malaise, and dark urine – and elevated serum aminotransferase levels (ALT, AST). He reported no contact with ill individuals, or travel outside of the local urban metropolitan area in the previous two years. Subsequent blood testing identified the presence of HAV genotype 1B.

A thorough food history was completed (2). His exclusive source of water was the local municipal supply. Grocery shopping was done at several large chain-style supermarket stores. He reported eating at several local restaurants, and had consumed mainly pre-packaged lower risk foods. No specific exposures or high-risk contacts were identified. While administering the questionnaire, the investigator identified that the patient frequently smoked cannabis during the previous several months. Upon request, the patient agreed to provide a sample of cannabis for testing purposes. A viral elution of fresh cannabis leaves was completed followed by ultracentrifugation to concentrate the eluate, which was done as previously described (3). Hepatitis A virus was extracted by the EasyMag platform (NucliSENS® easyMAG, bioMérieux, Montreal), and amplified by reverse transcription polymerase chain reaction (RT-PCR) (4).

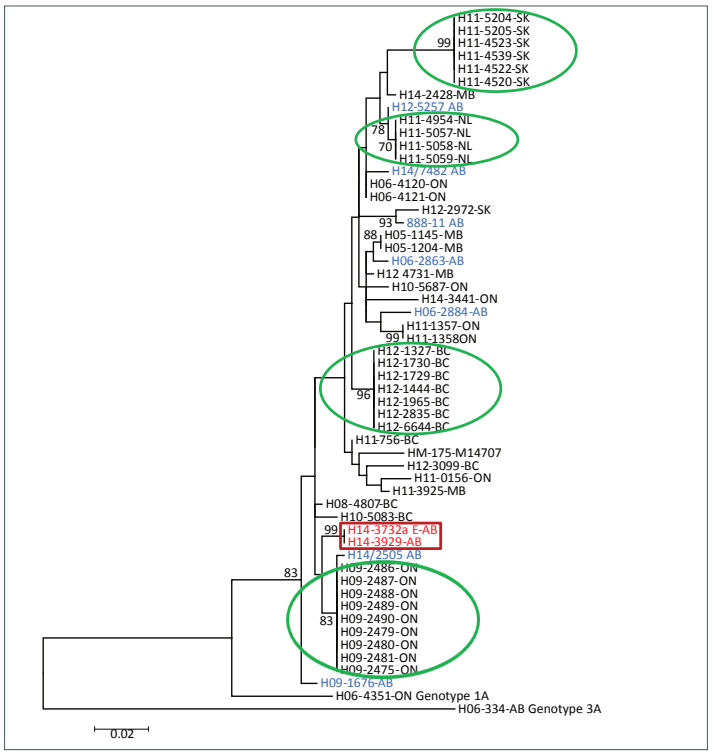
The sequences derived from the patient's serum sample and the eluate from the cannabis leaves were identical. These two sequences were unique and did not match any other HAV subgenotype 1B sequences from Canadian isolates within our database (**Figure 1).**

There are several reports in the literature citing cannabis use as a risk for acquiring hepatitis A (5,6), although simultaneous parenteral drug use and sharing of potentially contaminated paraphernalia have been suggested as a mechanism of transmission. Smoking or handling of fecally-contaminated cannabis has also been implicated in the transmission of salmonellosis (7).

The presentation of this case of locally acquired hepatitis A was unusual. The Edmonton area (population approximately 1.2 million) has approximately 6-28 HAV cases per year, and all but one or two are associated with travel to endemic areas (8). In this case, there were no genetic linkages with other known cases, leading local public health to suspect an unrecognized reservoir. It appears the patient may have been infected by ingesting small particles of cannabis from a hand-rolled cigarette.

Hepatitis A virus is exceptionally sturdy and can survive for a prolonged period of time (> 60 days) when dried and kept at room temperature and low humidity (9). Alternatively an HAV-contaminated water source used for the cannabis grow-op

Figure 1: Maximum likelihood phylogenetic tree of the VP1-P2A junction (nucleotides 2903 to 3275, according to the reference strain HM-175) showing the relationship between Canadian HAV 1B isolates



Legend: The reference HAV 1B strain HM-175-M14707 is in bold font. Numbers indicate the reproducibility after 1,000 bootstraps, and only bootstraps values higher than 70% are shown. Genotypes 1A and 3A are included as outliers. The scale bar indicates 2% sequence diversity. Patient and cannabis leaves eluate isolates (red font) are compared to other 1B isolates from the same (blue font) or other provinces (black font). Epidemiologically linked cases from different outbreak clusters illustrating the genomic sequence identity are encircled

could have contributed to the infection; HAV can remain infectious in water at room temperature for 300 days (10).

It cannot be concluded with certainty that the cannabis was the source of the hepatitis A; however, as other sources were excluded, or were of lesser probability, the association of cannabis with his disease acquisition remains strong.

Given the variable conditions in which cannabis is produced, it is unknown what infectious disease risk may be present. Monitoring and testing of cannabis may be needed for the purposes of safety and quality.

References

1. Guidance for State Medical Cannabis Testing Programs http://www.aphl.org/aboutAPHL/publications/Documents/EH-Guide-State-Med-Cannabis-052016.pdf#search=cannabis [Consulté le 27 octobre 2017]
2. Public Health Agency of Canada's Hepatitis A Hypothesis-Generating Questionnaire. http://www.health.alberta.ca/documents/PHAC-Hepatitis-A-Hypothesis-Generating-Questionnaire-2013.pdf [Consulté le 27 octobre 2017]
3. Sun Y, Laird DT, Shieh YC. Temperature-dependent survival of hepatitis A virus during storage of contaminated onions. Appl Environ Microbiol 2012 Jul;78(14):4976–83. DOI (http://dx.doi.org/10.1128/AEM.00402-12). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=22544253&dopt=Abstract).
4. Swinkels HM, Kuo M, Embree G, Andonov A, Henry B, Buxton JA; Fraser Health Environmental Health Investigation Team. Hepatitis A outbreak in British Columbia, Canada: the roles of established surveillance, consumer loyalty cards and collaboration, February to May 2012. Euro Surveill 2014 May;19(18):20792. DOI (http://dx.doi.org/10.2807/1560-7917.ES2014.19.18.20792). PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=24832119&dopt=Abstract).
5. Harkess J, Gildon B, Istre GR. Outbreaks of hepatitis A among illicit drug users, Oklahoma, 1984-87. Am J Public Health 1989 Apr;79(4):463–6. DOI (http://dx.doi.org/10.2105/AJPH.79.4.463). PubMed (https://www.ncbi.nlm.nih.gov/pubmed/2929804?dopt=Abstract).
6. Shaw DD, Whiteman DC, Merritt AD, el-Saadi DM, Stafford RJ, Heel K, SMith GA. Hepatitis A outbreaks among illicit drug users and their contacts in Queensland, 1997. Med J Aust 1999 Jun;170(12):584–7. PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10416427&dopt=Abstract).
7. Taylor DN, Wachsmuth IK, Shangkuan YH, Schmidt EV, Barrett TJ, Schrader JS et al. Salmonellosis associated with marijuana: a multistate outbreak traced by plasmid fingerprinting. N Engl J Med 1982 May;306(21):1249–53. DOI (http://dx.doi.org/10.1056/NEJM198205273062101).PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7070444&dopt=Abstract).
8. Interactive Health Data Application. http://www.ahw.gov.ab.ca/IHDA_Retrieval/
9. Abad FX, Pintó RM, Bosch A. Survival of enteric viruses on environmental fomites. Appl Environ Microbiol 1994 Oct;60(10):3704–10. PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7986043&dopt=Abstract)
10. Biziagos E, Passagot J, Crance JM, Deloince R. Long-term survival of hepatitis A virus and poliovirus type 1 in mineral water. Appl Environ Microbiol 1988 Nov;54(11):2705–10. PubMed (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2850763&dopt=Abstract).

Canadian Antimicrobial Resistance Surveillance System - 2017 Report highlights

Source: Public Health Agency of Canada. **Canadian Antimicrobial Resistance Surveillance System - 2017 Report highlights**. Ottawa; ON. Available November 2017 online.

In March 2015, the Public Health Agency of Canada (PHAC) launched the Canadian Antimicrobial Resistance Surveillance System (CARSS) as the national focal point for surveillance of antimicrobial resistance (AMR) and antimicrobial use (AMU) in Canada. Each year, CARSS integrates and synthesizes information from PHAC surveillance systems and laboratory reference services to provide data for action in areas such as antimicrobial stewardship, infection prevention and control, and research.

CARSS-2017 Report presents a number of key AMR findings. For example, during 2011 to 2016, overall rates of AMR in Canada were similar to or lower than those in many other developed countries. While rates of infections caused by antimicrobial-resistant organisms fluctuated over recent years, upward trends were seen in the rates of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in pediatric hospitals and vancomycin-resistant *Enterococcus* (VRE) blood stream infections in adult hospitals. In addition, the rate of drug-resistant gonorrhea rose from 2014 to 2015. Conversely, rates of healthcare-associated *Clostridium difficile* infections (CDI) decreased over time.

This year's CARSS report also includes notable findings on human AMU in both the community and hospital setting in Canada. In terms of antimicrobial use in the community, the rate of prescriptions dispensed was relatively stable between 2013 and 2016 and slightly lower than the rates observed between 2010 and 2012. Newfoundland and Labrador had the highest rate of prescriptions dispensed in the community in 2016; British Columbia had the lowest. In 2015, Canada was 13th among 31 countries in consumption of antimicrobials (ranked from lowest to highest), a slightly worse showing than in 2014 when Canada placed 12th among 31 countries in antimicrobial consumption. There was a downward trend in the antimicrobial prescribing rate of physicians and a generally stable rate for dentists, following an increase seen in prescribing by dentists from 2010 to 2012. With respect to antimicrobial use in the hospital setting, the purchasing of antimicrobials remained stable between 2010 and 2016. In 2016, Manitoba, Prince Edward Island, and Newfoundland and Labrador had the highest antimicrobial purchasing rates per capita; Ontario and Alberta had the lowest rates. Of concern, hospitals in 2016 purchased more of some of the antimicrobials considered "last resort" (e.g., daptomycin) than in previous years. Conversely, antimicrobial use in animals has decreased for the first time in 2016. There has been a notable decrease in the use of fluoroquinolones with the overall quantity distributed for use in animals decreasing by approximately 56% between 2015 and 2016.

The Public Health Agency of Canada has made significant progress in strengthening its surveillance activities. However, continuing AMR/AMU data gaps pose challenges to developing a comprehensive picture of AMR/AMU in Canada. The Public Health Agency of Canada continues to collaborate with a range of partners representing public health, health care, agriculture, and other sectors to address identified gaps and to improve AMR and AMU surveillance in Canada. The Executive Summary of the Canadian Antimicrobial Resistance Surveillance System-Report 2017 will be available on-line on November 10, 2017. A copy of the full report can be obtained by emailing carss-scsra@phac-aspc.gc.ca.

Get CCDR delivered to your inbox

- Know the trends
- Get the testing guidelines
- Stay current on new vaccines
- Learn about emerging infections
- Get the table of contents straight to your inbox

SUBSCRIBE TODAY

Web search: CCDR+Subscribe

CCDR

CANADA COMMUNICABLE DISEASE REPORT

Public Health Agency of Canada
130 Colonnade Road
Address Locator 6503B
Ottawa, Ontario K1A 0K9
ccdr-rmtc@phac-aspc.gc.ca

To promote and protect the health of Canadians through leadership, partnership, innovation and action in public health.

Public Health Agency of Canada

Published by authority of the Minister of Health.

This publication is also available online at

http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/17vol43/index-eng.php

Également disponible en français sous le titre :
Relevé des maladies transmissibles au Canada