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Obstacles to Developing a Multinational Report Card on Antimicrobial Resistance for Canada: An Evidence-Based Review

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ABSTRACT

Many countries want to compare the results of their antimicrobial resistance programs to those of others nations to help gauge the effectiveness of their prevention and control practices. In our attempt to compare Canada with other nations, we encountered several challenges that must be addressed before meaningful multinational comparisons can be made. The fundamental barriers to comparison were the lack of shared targets for performance and predictive measures of success. Unique problems and policies within countries resulted in variations in goals, methods, pathogens, drugs, and priorities within and between jurisdictions. Other obstacles included: (1) lack of information on potential biases associated with different microbiological testing and sampling methods; (2) lack of information with which to conclude whether or not different programs examined comparable spectra of patients or outcomes; (3) inadequate description of the epidemiological rationale for sampling strategies; (4) use of aggregated national data that can hide regional or local variations; (5) rarity of studies designed explicitly for multinational comparison; and (6) lack of international agreement on methods, continuing education, and quality control needed to ensure program comparability. Comparison based on a country's ability to meet its internal goals for antimicrobial resistance control may be a more informative basis for a report card than specific resistance or drug use rates.

INTRODUCTION

INCREASINGLY, NATIONS WANT TO COMPARE the results of their antimicrobial resistance (AMR) programs to those of other countries to gauge the effectiveness of their AMR prevention and control practices.[5] Comparison between countries is challenging because most data have historically been generated by short-term surveys in select areas from projects with varying objectives and/or have been generated in a nonsystematic, noncontinuous, and nonintegrated manner.[21,28] Although it is tempting to combine the "best available information" to examine international trends or to compare the impact of interventions, such evaluations are open to significant bias when several factors contribute to the patterns described in the data.[13] Any attempt to create a multinational report card requires that differences seen between countries reflect differences in the true patterns of drug use and resistance rather than differences in how data are collected and measured.

Given this background, we undertook a project to determine if Canadian AMR data would be suited to comparison with other countries and if there were indeed countries that were comparable to Canada with respect to surveillance outputs related to antimicrobial use and resistance in people and animals. In doing so, we discovered several obstacles that prevented comparison.

MATERIALS AND METHODS

The peer-reviewed and grey literature as well as internet-accessible reports of AMR and drug use surveillance programs were searched using MEDLINE, PubMed, PubMed Central, Highwire Press, and Science Direct. Google was used as an internet search engine. Approximately 200 keywords were used alone and in combination for these searches. Keywords were based on pathogen names, names of investigators active in sur-

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veillance, surveillance program names, methodological terms, and country names. One hundred and thirty-six Web sites on AMR and drug use surveillance around the world were reviewed. This was supplemented with telephone or e-mail interviews with 20 people associated with Canadian AMR programs. Information on AMR in the medical (hospital and community-based) and veterinary sector was included in this report. All information was collected in the summer of 2005.

A report card seeking to evaluate and improve the Canadian system would benefit little by comparison with countries with limited diagnostic options, lack of infrastructure and expertise, and lack of strong national policy and support. Although paying attention to patterns in Africa, Asia, and South America may be an important component of international surveillance intended to detect emerging risks, we limited our collection of information largely to North America and Europe, because many other countries lacked the necessary surveillance and laboratory capacity.[12,27] Because program structure and outcomes could be expected to vary from year to year, we sought annual reports from surveillance programs for the same year when possible or within 5 years when the same years results were not available for specific programs being compared. Table 1 provides some questions and features that guided our search for comparable programs and data.

RESULTS

Goals, methodologies, and reporting

In this project, we rarely found sufficient information to allow us to answer the questions in Table 1. There was significant variation in national goals, capacities, and methods. Canadian program objectives had not been precisely articulated.[23] The most common, albeit general, objectives found were either to sustain a certain therapeutic capacity for a specific population or to reduce obstacles to effective antimicrobial therapy in a population over time. These goals did not prescribe measurable performance expectations in a manner that was comparable between countries. Thresholds for program success or failure were most often clinically meaningful at the local level and, therefore, varied within and between countries over time. "Although much contemporary work [was] focused on international programmes, antimicrobial resistance surveillance remain[ed] peppered with numerous disparate local as well as multinational studies."[22]

Published evaluations of national AMR surveillance mostly focussed on the structure and methods of the surveillance system, seeing if they meet a minimum standard for microbiological methods, population sampling, and data analysis,[2,30] rather than seeing if countries met or exceeded thresholds for performance, such as the proportion of isolates resistant to a drug. No evidence was found to suggest the structure and methods of a surveillance system could serve as a surrogate for a country's ability to meet AMR management objectives. There was evidence that surveillance system structure could potentially distort associations between outcomes and actions. For example, differences in the patient source between two multinational programs, particularly the contributions of intensive care units to their sampling frame, affected reported *Escherichia coli* nonsusceptibility data.[28]

Few programs or papers tracked risk factors for AMR emergence, apart from drug use patterns and patterns of AMR in bacteria from foods of animal origin. Where they existed, such comparisons could be best described as ecological studies wherein population level outcomes of resistance were compared to population level drug use patterns—a study design poorly suited to making cause–effect associations and susceptible to considerable bias. Harbarth and Samore[8] listed a suite of 16 variables that influence the emergence of AMR, including microbial ecological factors, prescribing behavior variables, population characteristics, and health policies. The majority of the reports we found focussed largely on two of these determinants, namely laboratory detection and identification of resistant bacteria, and antimicrobial drug usage patterns. We failed to find any program that examined and/or integrated multiple determinates of resistance dissemination and control. Reports were primarily focused on detecting emerging or unexpected changes in patterns of resistance in a limited set of microorganisms and, to a lesser extent, describing drug use patterns. We found no reports that quantified the predictive value of emergence in one jurisdiction for emergence in another, and we did not find reports quantifying or tracking the frequency of emergence within and between countries in a systematic manner.

Most published data were based on short-term surveys of specific organisms and drugs in limited geographic areas.[28] Programs typically reported their findings at a group level (hospital, region, nation). Such data were typically disconnected from patient data, and there were delays between obtaining data on resistance and drug use.[17,21] Biases arising from using locally acquired data as an estimate of national trends were not evaluated and were especially concerning when resistance and drug use patterns were highly variable or locally clustered. We found insufficient detail in most reports to account for threats to international comparability that arose from the trade-offs, variation, and compromises that were made when balancing the biases and advantages that occurred at the local and national levels of data collection.

The breadth and types of data collected by the vast majority of surveillance systems were too limited to account for confounding and causal variables in the relationship between drug use and resistance patterns. Major differences in how countries accounted for drug use and how well they could estimate population exposure arose due to different reporting requirements, different availability of drugs, and different means of providing drugs. Few countries could account for the defined daily dose (DDD) in adults; many had problems extrapolating that measure to children, and most were unclear on how to calculate similar measures for animals.[14,24] Even if the DDD could be calculated, tracking whether or not the prescription was adhered to and completed by the individual providing the isolate was virtually impossible for the programs we evaluated. Hence, measures of drug use were inherently indirect and open to bias, leading to controversy as to how well they reflect or predict changing risk of a resistant strain emerging.[26]

Our attempts to gather information on who was doing what, the methodologies employed, and their results and interpretation thereof were extremely time consuming and would serve as a significant obstacle to anyone wishing to perform a comprehensive evaluation of a nation's AMR status. Information for Canada and other countries was dispersed throughout vari-

TABLE 1. MAIN FEATURES OF AN ANTIMICROBIAL USE OR BACTERIAL DRUG RESISTANCE PATTERN SURVEILLANCE SYSTEM THAT MUST BE CONSIDERED WHEN COMPARING SURVEILLANCE PROGRAMS[1,15,25,28,30]

Features of the program	*Key questions for assessment of comparability*
Requirement to report	• Are legislation or collaborator agreements similar with respect to the requirements to contribute samples or data to central programs?
Study objectives	• Are data collected on the basis of the pathogen, disease or group of diseases? • Is this a single survey or ongoing surveillance? • Is the objective to show local patterns or national average trends?
Host population composition and sampling	• Is the population sampled specifically for surveillance purposes or as by-products of clinical practice? • Is more than one population source used to create the sample? • Are the settings from which isolates derived similar? • Can an individual within a system be counted more than once within the same clinical course of infection? • Are the sample size adequate to describe the variation and central tendency of rates and proportions? • Is the unit of analysis the individual or group (e.g., herd)?
Population demography	• Are denominator data used to report sampling outcomes as rates and/or proportions? • Can the sample population be related to the national population based on the sample selection? • How does the number of samples per site and sites per nation compare when standardized for differences in demography between nations or regions? • Are demographic changes tracked and accounted for?
Organism	• Are the methods used to isolate and identify representative colonies from cultures consistent and comparable? • Are species of pathogens identified by internationally accepted methods for taxonomic identification of isolates? • Is there a consistent set of organisms tracked by the system? • To what taxonomic level are isolates identified? • Is there a program of quality control to validate identification?
Isolate collection	• Are the sources of the isolates meaningful and interpretable? • Does the program allow for more than the first positive culture from a patient to be included in the dataset? • Are isolates collected before antibiotic treatment? • Does the sample size, temporal and spatial distribution of isolate collection allow for description of national annual trends?
Susceptibility testing	• Are the standards, methods and thresholds used to classify resistance consistent and internationally accepted? • Are results reported quantitatively or qualitatively? • Is there a program of quality control to validate susceptibility classification? • Is there overlap in the drugs used for screening between programs? • Are the number and frequency of isolates reported in the same manner along with data on the denominator used to calculate incidence and prevalence rates? • Is there a sufficient number of isolates sampled to create reliable estimates of population trends? • Are methods for population sampling epidemiologically valid and sample populations with the same average treatment history? • Are the regulations and laws requiring (or not) reporting of surveillance data the same across programs?
Drug use	• Is drug usage or sales measured on a per capita basis? • Are the same sectors of the population kept under surveillance? • Are internationally recognized standards such as the Anatomical Therapeutic Chemical (ATC) Classification and the Defined Daily Dose (DDD) units used? • Is there a list of antimicrobial drugs available for use in the country? • Are differences in drug availability and reporting requirements accounted for? • Are drug sales put into the context of usage so as to control for different population sizes and different drug use regulations?
Data handling and analysis	• Is reporting of the data of similar standards, timing, quality and consistency? • Have comparisons accounted for lack of independence or clustering of data typical for this form of surveillance? • Do the reported results cover the same time frame? • Have data been collected long enough to differentiate temporal trends from inter-annual variation with the expected range of variation?

ous locations (Web sites, peer-reviewed press, and institutional memory) and often required personal communications to gather the necessary information to understand the objectives, design, and intent of a program. Whereas many of the individual programs provided useful data on specific issues for specific times and locations, differences in methods, funding, and infrastructure created significant obstacles to integrating all results into a single comprehensive national picture. Few programs collected data on both changes in populations across space and time (such as the history of individual patient treatment, history of AMR programs in a population, and history of drug availability), thus requiring one to assume all compared countries were at the same stage in their AMR status and response.

The lack of explicit thresholds or targets for success in Canadian and most international AMR programs made it impossible to determine if a country was more or less effective or efficient in meeting their goals when compared to Canada. Some programs were beginning to make interannual comparisons to look for significant trends or clusters, but many were relatively young, making it hard to determine if year-to-year variation was more than expected background variation.

Canadian AMR reporting

We found a large number and variety of local and regional Canadian programs. Many hospitals had in-house AMR surveillance as well as infection control programs tracking nosocomial infections. Private and provincial veterinary and medical diagnostic labs routinely generated data on pathogen sensitivity patterns. Federally inspected abattoirs provided samples from food of animal origin for AMR monitoring. Some provinces had projects tracking patterns of AMR in animal clinical isolates as well as surveys for veterinary drug use while industry and government collected data on drug sales.[6] Unfortunately, the great variety of programs led to a diversity of objectives and subpopulations sampled. Agencies or individuals generating AMR data did so to support clinical decision making, to modify local or provincial policy and practices, for research, or to meet regulatory requirements, hence the methods used varied significantly. Programs developed for local or provincial planning tended not to be well connected with similar programs in other Canadian jurisdictions. The lack of coordination was a fundamental obstacle to developing a comprehensive, ongoing national picture.

Canadian programs national in scope were restricted to five issues: (1) respiratory tract infections; (2) nosocomial infections emphasizing methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE); (3) foodborne enteric pathogens focussed largely on *Salmonella* spp and *E. coli* from humans and from animals at slaughter or meat products; (4) *Neisseria gonorrheae*; and (5) *Mycobacterium tuberculosis*. We found six programs explicitly intended to examine national trends and to relate national actions with outcomes: Canadian Nosocomial Infection Surveillance Program (CNISP), Canadian Bacterial Surveillance Network (CBSN), Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS), Canadian Respiratory Organism Susceptibility Study Group (CROSS), Canadian Tuberculosis Laboratory Surveillance System, and Canadian *Neisseria gonorrheae* Antimicrobial Susceptibility Network (Table 2). Only CIPARS attempted to examine patterns of AMR in different settings (human and animal clinical isolates, animals at slaughter, and food) along with data on drug use. We were unable to find sufficient information to describe the national representativeness of the National Centre for Streptococcus.

The source of isolates for Canadian national programs varied by organism and within and between programs. Information collected on the sample population, sources of samples, case definitions, and classification of isolate susceptibility status varied among Canadian programs. There was insufficient background information to determine how well the programs reflected the populations at risk. Some Canadian efforts were ongoing, some were pilot studies, and the rest were targeted, time-limited surveys, complicating efforts to see temporal trends. In some cases, isolates were simply collected and stored until funding becomes available for testing. Some programs, such as CBSN, relied exclusively on external funding from the pharmaceutical industry rather than ongoing government financial support, creating the potential for perceived conflicts of interest and program instability. Despite these limitations, these programs presented national summaries of AMR trends on program Web sites, in government reports, or in the peer-reviewed

Table 2. Web Site Addresses for National Antimicrobial Resistance and Use Surveillance Programs[a]

Program name	*Web site address*
Canadian Integrated Program for Antimicrobial Surveillance (CIPARS)	http://www.phac-aspc.gc.ca/cipars-picra/index.html
Canadian Bacterial Surveillance Network (CBSN)	http://microbiology.mtsinai.on.ca/research/cbsn/default.asp
Canadian Nosocomial Infection Surveillance Program (CNISP)	http://www.phac-aspc.gc.ca/nois-sinp/survprog_e.html
(Canadian) National Centre for Streptococcus	http://www2.provlab.ab.ca/ncs/ncs.htm
Canadian Tuberculosis Laboratory Surveillance System	http://www.phac-aspc.gc.ca/publicat/tbdrc01/index.html
Active Bacterial Core Surveillance (ABC)	http://www.cdc.gov/ncidod/dbmd/abcs/
National Antimicrobial Resistance Monitoring Program (NARMS)	http://www.cdc.gov/narms/
Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP)	http://www.danmap.org/

[a]Cited on June 5, 2007.

literature and hence served as the most accessible summaries of national performance in Canada.

Apart from these six programs, we found few mechanisms by which data generated at a local or provincial level regularly made their way into a national database that could be analyzed and results communicated. Individual hospital laboratory surveillance programs were often not linked or integrated between hospitals nor did hospital or veterinary government laboratories effectively or regularly link to private laboratories in Canada. This is not to suggest there were no attempts to pull data together on a provincial or regional level. For example, the British Columbia Centre for Disease Control (BCCDC) along with the Association of Medical Microbiology and Infectious Disease Canada coordinated data from 19 sites on MRSA and VRE, the results of which are summarized in the BCCDC's annual reports. Summaries of MRSA and VRE from Ontario hospitals have also been published.[20]

We failed to find any program that reported the uptake, application, and success of infection control practices in Canada. We did not look to provincial or federal public health programs that monitor vaccine use and reportable vaccine-preventable diseases as a surrogate for immunization-associated aspects of infection control. Virtually all of the information we found on infection control was associated with educational messages for practitioners. Some papers or Web sites described legislative approaches to infection control, but there were insufficient numbers of similar papers or Web sites in Canada to allow for cross-jurisdictional comparisons.

The most common mechanism for disseminating results outside of a jurisdiction was through the scientific press or at professional meetings. In the latter, only some abstracts were available for external reviewers, precluding easy access to information on methods as well as restricting access to the results to conference participants. We were able to find a wide variety and number of papers in the scientific press regarding patterns of AMR and, to a lesser degree, on drug use in Canada. However, most of these provided little continuity and operated for an insufficient length of time to account for temporal variability. There were significant time delays between identified trends and publication of results.

Multinational AMR reporting

Canada contributed to five multinational programs on a regular basis (Table 3). We could not find details on the specific sources of Canadian isolates for these programs and thus, could not determine if the Canadian data were nationally representative. Therefore, we could not conclude if these programs included a truly national picture of Canada. Despite this potential representation bias, these programs have been used to compare Canada with other nations. SENTRY has been used to describe patterns of resistance in Canadian isolates in a multinational context for enterococci[16] and respiratory and urinary tract pathogens.[18,19]

Multinational programs tracking drug use were few, the number of countries they considered was limited, and Canada was not part of those efforts. The World Health Organization (WHO) had two databases, one to monitor the pharmaceutical situation of member states and the other to monitor key aspects of drug use, but few member states regularly monitored national medication use.[31] North America was lacking intrajurisdictional publicly available data on prescription information for various human populations that could be used to determine trends in antimicrobial use at the population level or to determine key factors driving antimicrobial consumption in people.[24] Only a small portion of veterinary drug use in Canada could be accounted for by publicly accessible data, and no single agency had the mandate to collect and collate all the relevant sources of veterinary drugs.[6]

All countries reported some limitations with capturing representative samples of the national population, consistency of case definitions, and/or resources to ensure quality control and longevity of programs. Some programs were sufficiently internally consistent to allow generation of trend data on selected subpopulations within a region as well as for the detection and tracking of emerging resistance. Others had samples sizes and sampling methods that could not allow reliable and consistent interpretation of reported trends.

The 2003 European Antimicrobial Resistance Surveillance System quality control report[4] revealed important intracountry variations in microbiological and epidemiological methods. The

Table 3. Summary of International Programs to Which Canada Contributes Antimicrobial Resistance Data

Program	*Organisms/purpose*	*Canadian involvement*
SENTRY	Nosocomial and community-acquired; sentinel hospitals; blood, respiratory, skin, soft tissue, gastrointestinal and urinary	5 centers report
TSN	Tracks over 580 taxa of bacteria and considers 115 drugs	87 hospitals report
PROTEKT	Community-acquired human respiratory disease	7 centers contribute samples
Enter-Net	Major enteric bacterial pathogens (*Salmonella* spp and verotoxigenic *E. coli*)	National Microbiology Laboratory plus C-Enter-Net sentinels sites
Global Salm-Surv	*Salmonella* spp. from human, veterinary, food, and environmental sources	Public Health Agency of Canada

proportion of contributing sites participating in external quality control programs varied by country. Seventy two percent of the participating laboratories followed National Committee for Clinical Laboratory Standards (NCCLS) guidelines, with 86% using the same method. Overall concordance with reference strains was high (51–99%, 91% on average), but varied among countries, pathogens, and drug. The range in proportion of population covered was from 16 to 100%; the proportion of isolates from patients older than 65 ranged from 4 to 51% and the proportion of isolates from internal medicine wards ranged from 0 to 50%.

Collection methodologies and biases in selected programs

Figure 1 outlines some differentiating features of international *Streptococcus pneumoniae* AMR programs based on how isolates were collected. It illustrates some of the challenges to multinational comparison as differences in isolate source were rarely considered in analysis of multinational datasets.

The Active Bacterial Core Surveillance (ABCs) program is a centrally coordinated U.S. program that uses multiple laboratories or sentinel sites to generate its AMR data. ABCs solicits and actively seeks out all isolates from a smaller number of contributors in an attempt to have a complete description of the AMR pattern in each participating facility (assuming complete case detection). Other *S. pneumoniae* programs relied on subsamples of all available isolates per collection site. For example, Norway collected 50 isolates per site per year between January and March. CBSN requested the first 20 or 100 clinically relevant isolates (depending on laboratory size), whereas CROSS collected the first 100 isolates "deemed significant."

Neither Canadian nor other national programs provided clear epidemiological rationale for selection of collaborating sites that provided *S. pneumoniae* isolates or information. Often readers were left to assume that sites were selected by convenience. Site selection might create some important selection biases, depending on program objectives. For example, CBSN collected 50% of their isolates from Ontario. Although the investigators suggest this reflected a population-weighting scheme and thus the national distribution of *S. pneumoniae*, this assumes the organism was homogeneously distributed throughout the country and that emergence of resistant clones was not clustering according to risk factors unrelated to population distribution. Sampling bias is concerning for sentinel programs where the sentinels are opportunistically selected volunteers as opposed to systematically selected representative sites. Evidence from Sweden shows that there can be significant difference in rates of drug use and AMR between hospitals within the same country, whether due to different policies and practices for infection control and drug use, selection bias, or other methodological issues,[7] suggesting that the features of the sentinel site can affect detected AMR patterns. Gaining data needed to evaluate these biases would require Canadian programs to collect more epidemiological information for each isolate subjected to AMR testing. The resource implications for the volunteer collaborators as well as the central program should not be underestimated due to the demands on local and central staff to collect, enter, and analyze these additional patient and facility data.

With respect to zoonotic enteric agents, *E. coli* tended to be the most commonly tracked enteric pathogen around the world, whereas *Salmonella* and *Campylobacter* were more sporadically monitored. CIPARS was the primary Canadian program reporting on national resistance patterns of *Salmonella* spp. from people, animals, and food, plus data on human antimicrobials. CIPARS restricted its *Enterococcus* spp. surveillance

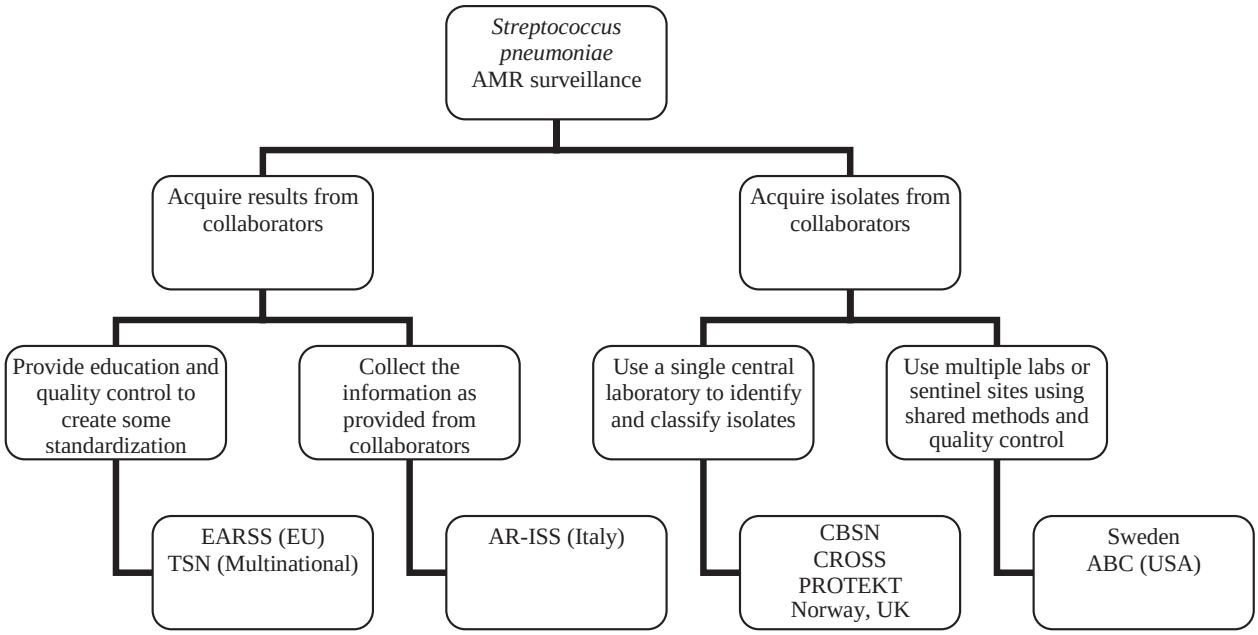

FIG. 1. Overview of general methodological approach of various international programs for tracking antimicrobial resistance patterns for *S. pneumoniae*, with some example programs.

to retail chicken meat samples. Other similar programs included the National Antimicrobial Resistance Monitoring Program (NARMS, United States), DANMAP (Denmark), Norm/NormVet (Norway), and S-VARM (Sweden).

A potential advantage of programs like CIPARS, NARMS, and DANMAP is that they seek data both on clinical outcomes and potential risk factors such as food contamination or drug use. However, these data were usually population based and not well suited to analyses that can adjust for individual characteristics or examine dose–response relationships between increasing exposure and resistance.[10] For example, a WHO analysis of tuberculosis programs failed to find a relationship between national data on measures of coverage, functionality, or effectiveness of their programs with resistance rates reported at an aggregated level, even though there is evidence to indicate that such factors affect emergence of resistance at an individual patient level.[32] Associations between antibiotic prescribing and resistance can be found by looking at individual level data but not be apparent at the aggregate level analysis.[3]

Countries varied with respect to how broadly or adequately national laboratories sampled their populations at risk for enteric infections. In Canada, smaller provinces provided all human *Salmonella* isolates whereas larger provinces provided samples from the first 15 days of a month plus all *S. newport* and *S. typhi* isolates. Norway subjected all *Salmonella* serotypes to some amount of testing, but the proportion of isolates tested varied with serotypes. In Denmark, random samples of all isolates sent to a central laboratory were tested for resistance. NARMS employed a sentinel program for human salmonellosis involving health departments and public health agencies in a number of locations (28 in 2002). NARMS participants selected every tenth non-typhi *Salmonella* and every *S. typhi* and submitted them to a central laboratory for sensitivity testing.

The proportion of specific isolates tested for drug susceptibility varied with host and *Salmonella* species/serotype. Varying the proportion of the isolates sampled created a possible selection bias that could call into question claims of absence of resistant clones or estimates of the prevalence of resistance in different serotypes, as resistance patterns tended to cluster by serotype. For example, increasing recognition of outbreaks of *S. enterica* serotype *typhimurium* definitive phage type 104 by DANMAP meant that a pentaresistant phage type accounted for a disproportionally high percentage of *S. typhimurium* isolates, potentially skewing aggregate data on *Salmonella* resistance.[21]

The way countries collected animal clinical *Salmonella* isolates varied considerably. CIPARS relied on passively acquired isolates from provincial diagnostic laboratories, receiving over 70% of their data in 1 year from one province (Ontario). DANMAP used "pseudorandom" selection of isolates from clinical and subclinical cases sent to three national centers, including the national reference center. NormVet tested all animal clinical isolates, but, in 1 year, only received five isolates in total due to an ongoing national control program. In Sweden, all *Salmonella* isolates from warm-blooded animals were reportable (unlike in Canada) and testing of at least one isolate per incident was mandatory. Teale *et al*.[29] concluded that multinational comparison of abattoir data for enteric AMR cannot proceed without harmonized international standards and methods due to variation in the methods used to isolate, culture, and classify animal pathogens.

Antibiotic use reporting

With respect to drug use monitoring, countries varied in: (1) the route by which drugs were made available; (2) the source(s) of data collected to reflect use (pharmacies, hospitals, wholesalers, feed mills); (3) requirements to report prescriptions to a central authority; (4) the drugs available for use; and (5) the ability to convert sales or dispensing data into drug-use measurements. Norway and Sweden used wholesale sales or kilograms of active ingredient sold to reflect consumption, whereas Canada and Denmark attempted to calculate DDD per unit population. CIPARS recognized limits in its human drug use data in that the available sources could not account for variation in how pharmacists entered data or in differences in dispensing form. CIPARS also recognized limits in linking data on mass-dispensed drugs or DDD with specific therapeutic uses. CIPARS could not report on veterinary use of drugs because there was no national requirement or voluntary program to record drug use comprehensively in animals in Canada. Some antimicrobials were available for use without veterinary prescription, and veterinarians were not required to report their drug sales or prescriptions to a central program in Canada. This is in contrast to a number of European countries where all animal antimicrobial use is done under prescriptions and must be reported. Current drug use data did not account for individual compliance with prescriptions, with off-label drug use, or with unusual uses or uses that do not require a prescription (such as some animal sales or topical applications for people). The lack of data on the number of animals treated prevented interpretation of differences in amounts sold or prescribed. Links between drug use and AMR patterns were typically indirect and often speculative. Frequently, comparisons between drug use and AMR inadequately accounted for intra-annual and spatial variations.

DISCUSSION

The numerous obstacles and biases we found led us to conclude that a multinational report card to compare Canada's performance in AMR surveillance or control cannot be justified as a reliable evaluation tool. A common feature of health system report cards is an element of evaluating performance against expectations. Given that the performance expectations of different countries reflected their epidemiological condition, we failed to find a common standard against which different nations could be compared. National interest in a disease played a crucial role in motivating evaluation of the effect and epidemiology of a specific AMR issue because it affected: (1) resources to control diseases of concern and hence their prevalence and distribution; (2) requirements to report and submit isolates for testing; (3) access to antimicrobials; and (4) requirements to report drug use. Defining and assessing the quality of Canada's AMR programs in the context of other countries with different histories, legislation, and problems may be a very tenuous foundation upon which to create a report card.

Canada did not have a single comprehensive program for collecting and integrating data on AMR, drug use, and infection control, resulting in a patchwork of programs with varying methodologies (many with unexamined potential for sig-

nificant selection and sampling bias), interpretation, sustainability, funding, and objectives that are not effectively knit together. Canadian programs that were national in scope in 2005 did not provide data that are truly representative of national patterns. Few Canadian programs have existed long enough to differentiate sustained trends from interannual variation within the normally expected limits. Similar uncertainty can be attributed to many if not all national-level programs in other countries due to the lack of research on how different surveillance and sampling strategies affect the representative nature of the data.

Most of the obstacles to multinational comparisons we found were associated with differences in the populations that were surveyed or kept under surveillance. Selection biases influencing the spectrum of patients sampled can result in misclassification of patients with respect to their AMR status.[9] For example, laboratories sampling a lower proportion of all isolates have had increasing proportions of isolates classified as being resistant due to a selection bias.[11] We found evidence to suggest there are important correlations between certain population features and AMR patterns. Failing to account for this in multinational comparisons dooms a report card to ambiguity. There was sufficient variation between countries in legislation, disease status, resources, microbiological methods, and epidemiological methods to prevent accounting for the proportion of differences reported between countries that may be due to program structure or methods rather than due to the underlying epidemiological conditions.

A primary obstacle to gauging Canada's ability to prevent, contain, or manage AMR was the lack of a defined Canadian target for performance. Most Canadian reports were largely descriptive in nature, reporting rates or numbers of AMR cases or drug use. We found few critical discussions of what rates were acceptable or how Canada was doing in terms of achieving those targeted rates. Although we might turn to other countries with similar resources to help generate our own national targets, comparing our current performance at a single point in time against another country's point estimate of performance seems a less reasonable management tool than to see how well we are progressing toward our own goals; especially when we are unable to confidently attribute causal explanations for why differences between countries exist.

There is evidence from Europe that education on methods, central coordination of multiple nations' efforts, and external quality control can significantly increase intra- and intercountry comparability.[2] This is consistent with calls for increasing international harmonization of methodologies used in AMR surveillance. Although harmonization and standardization are laudable goals, we anticipate most countries will lack the resources or will to modify their existing programs solely for the purpose of increasing international comparability, especially when intracountry comparability is still suffering. There existed a tension between the desire to create standardized surveillance programs that allowed for international comparison with those that can provide tailored local data, trading off standard methods and centralized laboratories with the flexibility required to address local issues. Simply reporting national averages for drug use or AMR can mask important risk data and may fail to describe accurately how well a country is progressing toward its AMR goals. Significant political, economic, and scientific resources will be needed before we can reliably compare multiple countries for AMR, drug use, and/or infection control outcomes.

We acknowledge that our review has limitations and was not a complete enumeration or description of AMR or drug use surveillance programs existing in all counties around the world because we focused our efforts on jurisdictions that were similar to Canada. However, on the basis of our review, it is unlikely that we will soon see an acceptable and meaningful single indicator of performance that can be applied across countries, not only because the nature of the problems (and hence indices of success) will be country specific, but also because the varying determinants influencing AMR make identification of the most informative indicator difficult and contentious. We could not specify an objective, evidence-based measure of performance that can be used to judge one country as being better than another. Our inability to find the required information from specific programs on design, implementation, and dissemination of results, despite hundreds of person-hours of effort, suggest that any attempt to develop a timely third-party multinational report card may be beyond what can reasonably be expected.

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