Update on the adverse effects of antimicrobial therapies in community practice

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Abstract

Objective To gather information about antibiotic side effects to be used as a reference and learning resource for prescribing physicians.

Quality of evidence A search of websites of various independent national agencies and recent review articles was performed. A summary table of adverse effects for each group of antimicrobials was then created, identifying allergies, short-term harms, and serious harms. The occurrence rate of each was listed when available.

Main message Antimicrobials are necessary to treat various diseases. However, they cause adverse effects, such as allergic reactions, in addition to increased bacterial resistance. There is increasing awareness of the need to detect and evaluate adverse effects associated with medicines. Recently, severe and serious harms have been described for commonly used antibiotics. Therefore, current knowledge of harms from systemic oral antibiotics that are regularly used in family medicine is summarized in this article.

Conclusion It is difficult to identify and ascribe exact probabilities of most harms. However, all common antimicrobials create harms that must be considered when choosing whether to prescribe. Many adverse effects go unrecognized by prescribers. As side effects are inevitable, antimicrobials must be prescribed for as short a course as possible, only when the probability of benefit is greater than the risk of harm.

Editor's key points

- Identifying harms for antimicrobial therapies is difficult; warnings are often written in cautious language. Common and mild side effects were identified in this article, as well as more severe effects, which are rare for drugs that are allowed to remain on the market. Allergic effects are mostly dermatologic, although other systems can be involved, especially in the more severe effects such as anaphylaxis. Persistent serious harms are specific to each group of drugs.
- All antibiotics assessed can cause gastrointestinal effects (eg, nausea, vomiting, diarrhea, abdominal pain, loss of appetite, bloating), often owing to disturbance of gut flora. Broad-spectrum antibiotics are also likely to cause secondary *Candida* species overgrowth, especially in those with diabetes. *Clostridium difficile* infections are more likely to be caused by ampicillin or amoxicillin, clindamycin, third-generation cephalosporins (such as cefotaxime and ceftazidime), and fluoroquinolones.
- While some adverse effects follow antimicrobials received in hospital, about half of adverse effects start after taking antimicrobials in community settings, often prescribed by non–family physician specialists for complex medical problems.

Antibiotics are among our most commonly used drugs. They are valuable in treating severe and potentially fatal infections. Conversely, their use can lead to increasing bacterial resistance and adverse effects. Most of the research on antibiotics focuses on their benefits, and much less has been published on their harms. Yet in prescribing any drug, clinicians must balance the potential benefit from our prescription against the harm it might cause. When there is a large potential benefit from a drug, a moderate risk of harm is acceptable. However, when the benefit is small, even a small risk can be unacceptable. For example, when chloramphenicol was available and few other drugs penetrated the blood-brain barrier, it was a useful drug for meningitis and worth the rare but serious risk of aplastic anemia. However, after the advent of safer antibiotics for meningitis, this risk became too great. The sulfonamides were "wonder drugs" when first introduced, and they were the only antibacterials available to treat many infections. They were widely used for many years, but their contribution to severe skin reactions has diminished their use.[1]

Allergic reactions are the most well-known harms, and have been the subject of recent reviews.[2,3] Medical professionals are taught to routinely inquire about allergy before prescribing or dispensing antibiotics (or other drugs). However, accuracy of allergy information is often poor, with many allergies

unrecorded. There are also frequent false-positive allergy test results.[2]

Community antibiotic resistance is in the news, with many warnings about the increasing prevalence of and potential for multidrug-resistant infections with no available antibiotic treatment options and the risk of secondary infection (most notoriously from *Clostridium difficile*).[4-11] This antibiotic resistance occurs not only at the societal level but also at individual level; those who take more antibiotics might be more likely to develop another infection and might have more resistant bacterial flora when they next need antibiotics.[8,9]

Other harms or adverse effects from antibiotics are being identified with increasing frequency. Adverse effects can be common or rare, can range in severity, and might be dose or duration dependent or entirely idiosyncratic. Unfortunately, direct harms of antibiotics are seldom identified by either the patient or the prescriber, partly because many common side effects are masked by the effects of the illness or infection itself (eg, nausea, vomiting) and patients might not report them. Some adverse events occur after treatment is complete, so if patients are not followed longitudinally, the physician who initiated antibiotic therapy might be unaware of them. Because many adverse events can occur at relatively low rates (and are only identified in large trials or with postmarket long-term follow-up), it can be challenging to recognize them or attribute them directly to a drug. Recently, severe harms were reported for quinolones, antibiotics that have been commonly used in practice for many years.[12]

Accurate knowledge of harms from antibiotics is necessary to inform our approach to management of infections, especially in the community setting. Awareness of the variable nature and frequency of harms for each agent or class of antimicrobial therapies is challenging for physicians.[13-15] Yet, information on adverse effects is often abbreviated or simplified in drug reference materials. Understanding potential benefits of antibiotics and assessing them against potential harms is a key step in clinical approaches to infection management.

Objective

To assist physicians in community practice settings, we summarized information about antibiotic side effects to create a reference and learning resource for prescribing. We conducted a review and gathered reports of adverse effects of commonly used antimicrobial therapies beyond allergic reactions and resistance. We focused on harms that might change prescribing choices in community practice, but did not collect evidence about drug interactions or overdoses.

We focused our search on systemic oral antibiotics and antifungals that are regularly used in community care: β-lactams (penicillins and cephalosporins), fosfomycin, lincosamides, linezolid, macrolides, methenamine, metronidazole, nitrofurantoin, quinolones, sulfonamides, tetracyclines, vancomycin, and azole antifungals.

Quality of evidence

We searched the websites of important independent national agencies that use similar methods in pharmacovigilance and judgments about drug safety[16]: the Health Products and Food Branch of Health Canada, the US Food and Drug Administration (FDA), the UK Medicines and Healthcare products Regulatory Agency, the European Medicines Agency, the Australian Therapeutic Goods Administration, and New Zealand's Medsafe.[17-21] We researched each antimicrobial listed in **Table 1** on these websites and reported on allergic reactions, frequent self-limiting and usually transient side effects, and serious harms.[2,3,10,12,22-63] *Serious harms* are defined as occurrences that might result in death, cause serious disfigurement, greatly affect the quality of life of an individual, or cause substantial loss or impairment of mobility.[16] Serious harms include boxed warnings (also known as *black-box warnings*) issued by the FDA to alert prescribers to a serious side effect or to restrict use of the medicine. We found little conflict among these websites on reported adverse effects; generally, the FDA provided the most detail. (However, warnings about moxifloxacin are discordant.)

The process of identifying adverse reactions to drugs by these agencies starts with identification of a possible hazard (a signal) that is then evaluated and investigated further. To identify a signal, national agencies largely rely on reporting of adverse reactions to medicines. Signals are also identified by monitoring information on adverse effects from multiple other sources (eg, observational and controlled trial data). Signals are then triaged for further investigation by assessing their strength of evidence, biological plausibility, seriousness, and frequency of effect. Further investigation on chosen signals is then done through laboratory mechanistic studies and epidemiologic approaches.[16]

As some adverse effects might not be reported from these agencies, we also performed a literature search to provide a comprehensive view of adverse effects for each antimicrobial medication. The MEDLINE, PubMed, and Google Scholar databases were searched using the following subject headings: adverse effects, prevalence, and specific antimicrobial names and synonyms. We recorded rates of adverse events, when available, in the form in which they were given (eg, percentage of patients, number needed to harm, relative risk). Where these were not available, we used the descriptors of the Council for International Organizations of Medical Sciences working group (**Table 2**).[22]

Table 1. Adverse effects of antibiotics: *Items in bold text are included in FDA boxed warnings; risk is indicated using CIOMS categories (**Table 2**)[22] where rates of adverse events were not available.*

DRUGS	ALLERGIC REACTIONS	SELF-LIMITING AND USUALLY TRANSIENT REACTIONS	SERIOUS HARMS
β-lactams			
Penicillins			
• Penicillin V potassium	• Skin rash or hives • Itching[2] • Uncommon: true anaphylaxis hypersensitivity (0.01%)[23] • Common: allergy (9%)[3]	• Uncommon: gastrointestinal effects—vomiting • Nausea, diarrhea, bloating, indigestion, abdominal pain, and loss of appetite (0.1% to 1% of patients)[23]	• Fatal anaphylaxis (0.0015% to 0.002%)[3] • Very rare: drug-induced anemia, renal inflammation, and serum sickness[2,23] • *Clostridium difficile* infection[24]
• Amoxicillin	• Rash (5% to 10%)[3] • **Anaphylaxis** • Common: allergy[3]	• Common: gastrointestinal effects[25] • Diarrhea (about 2%)[25] • Candidiasis (OR = 7.77, NNH = 27)[25,26] • Diaper rash (50%)[27,28] • Skin rash in patients with mononucleosis[29,30]	• **Anaphylaxis**[30] • ***C difficile* infection**[30,31] • Hematuria[25]
• Amoxicillin plus clavulanate	Same as for amoxicillin, plus the following: • Rash • Hives[2]	Same as for amoxicillin, plus the following: • Common: gastrointestinal effects • Headache[32] • Diarrhea (OR = 3.30, NNH = 10)[25,33] • Candidiasis (OR = 7.77, NNH = 20)[25,26]	Same as for amoxicillin, plus the following: • Rare: drug-induced mixed hepatitis[32] • ***C difficile* infection** (RR = 15.50)[10,31]
• Cloxacillin	• Very rare: rash • Very rare: hives • Very rare: anaphylaxis[2]	• Gastrointestinal effects[34]	• Neutropenia with eosinophilia[34]
Cephalosporins			
• Cephalexin (first generation), cefuroxime (second generation), and cefixime (third generation)[35,36]	• Common: dermatologic effects (rash, 1% to 2%)[2] • Common: allergy (1.3%)[2]	• Common: gastrointestinal effects seen in more cases with third generation vs first generation (2.5% for first; 4.5% to 15% for third) • Common: headaches, neurologic symptoms (dizziness, paresthesias) (1% to 2%) • Prolonged prothrombin time (4%)	• Serum sickness–like syndrome (0.024% to 0.2%)[2] • Thrombophlebitis (1% to 2%) • Uncommon: hematologic toxicities (< 1%) • *C difficile* infection (third generation; RR = 15.33)[10]
Non–β-lactams			
Fosfomycin[37,38]	• Rash (1.4%) • Rare: angioedema	• Diarrhea (10.4%) • Nausea (5.2%) • Headache (10.3%) • Vaginitis (7.6%) • Rhinitis (4.5%) • Back pain (3.0%) • Dysmenorrhea (2.6%) • Menstrual disorder (< 1%) • Pharyngitis (2.5%) • Dizziness (2.3%) • Abdominal pain (2.2%) • Pain (2.2%) • Dyspepsia (1.8%)	• Lymphadenopathy (< 1%), aplastic anemia, asthma (exacerbation), cholestatic jaundice, hepatic necrosis, and toxic megacolon[38]
Lincosamides			
• Clindamycin	• Very rare: allergy[2]	• Very common: gastrointestinal effects—diarrhea most common (12% to 14%)[39] • Dermatologic effects (red skin, rash)	• ***C difficile* reaction** (RR = 29.97)[10,39]

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DRUGS	ALLERGIC REACTIONS	SELF-LIMITING AND USUALLY TRANSIENT REACTIONS	SERIOUS HARMS
Linezolid[40]	• Common: rash (2%) and hives • Very rare: allergic reactions	• Nausea (6.2%), constipation (2.2%), vomiting, diarrhea (8.3%) • Fever (1.6%) • Dizziness (2.0%)	• **Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia; some irreversible.** Monitor CBC weekly during treatment) • ***C difficile* infection** • Peripheral and optic neuropathy (some irreversible) • Hypertension, convulsions, lactic acidosis • Serotonin syndrome (weak MAO inhibitor) when taking MAO inhibitors or serotonergic drugs, especially SSRIs or SNRIs, but also other drugs
Macrolides			• ***C difficile* infection** (RR = 5.8)[10]
• Erythromycin, clarithromycin, and azithromycin	• Rare: skin allergic reaction[41,42]	• Gastrointestinal effects: stomach pain (NNT = 17), diarrhea (NNT = 19), nausea (NNT = 19), and vomiting (NNT = 45)[41]	• **Irregular heart rhythms (irreversible; especially with underlying QT prolongation)**[42] • Hearing loss (irreversible)[41] • Rare: cardiovascular deaths (azithromycin)[43] • Drug-induced mixed hepatitis (idiosyncratic)[32] • *C difficile* infection: erythromycin (RR = 10.03), clarithromycin (RR = 7.49), and azithromycin (RR = 2.88)
Methenamine[44]	• Rash and hives (2% to 5%)	• Gastrointestinal effects (3.5%) • Urologic effects with large doses (eg, dysuria, changes in frequency, hematuria, albuminuria)	• NA
Metronidazole[45]	• Dermatologic effects (3%)	• Gastrointestinal effects: mostly nausea (12%) • Metallic taste • Secondary *Candida* species infection	• **Carcinogenic in rats and mice** • Seizures (with prolonged use; reversible) • Peripheral neuropathy (with prolonged use; irreversible) • Pancytopenia (reversible with discontinuation) • Reproductive system effects (dyspareunia, pelvic pressure, proctitis, vaginal dryness, decreased libido; reversible) • Urologic effects (eg, dysuria, polyuria, incontinence, darkened urine [1 in 100 000]; reversible) • Others: arthralgias, nasal congestion (reversible)
Nitrofurantoin	• Dermatologic effects such as rash and DRESS[2]	• Gastrointestinal effects such as vomiting, diarrhea, and stomach pain[46] • Nausea (8%), headache (6%), and flatulence (1.5%)[46]	• **Pulmonary toxicity: chronic pulmonary reactions; diffuse interstitial pneumonitis, pulmonary fibrosis, or both (irreversible)**[46] • Drug-induced liver injury[32] • Aplastic anemia[46] • Peripheral neuropathy (irreversible)[46] • Hemolytic anemia[46]

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DRUGS	ALLERGIC REACTIONS	SELF-LIMITING AND USUALLY TRANSIENT REACTIONS	SERIOUS HARMS
Quinolones			
• Norfloxacin, ciprofloxacin, levofloxacin, and moxifloxacin	• Rare: allergic reactions[3] • Flushing, itching, and angioedema[2]	• Gastrointestinal effects[47] • Headaches[12,47] • Arthralgias and myalgias[47] • Neuropathies (numbness, tingling)[47] • Confusion[47]	• **Tendonitis and Achilles tendon rupture,** especially in those >60 y or with current corticosteroid use[12,47,48] • **Increased risk of abdominal aorta rupture**[12,49] • **Persistent peripheral neuropathy (irreversible)**[12,47] • Dysglycemia, hypoglycemic coma[47] • Neurologic or psychiatric disturbances[50] • Exacerbation of myasthenia gravis • *C difficile* infection[10]: levofloxacin (RR = 1.93), ciprofloxacin (RR = 8.03), and moxifloxacin (RR = 1.2) • Rare: retinal detachment (4 per 10 000)[51] • Drug-induced mixed hepatitis[52] • Moxifloxacin: fulminant hepatitis and toxic epidermal necrolysis[52]
Sulfonamides and related drugs			
• Single-entity trimethoprim	• Higher rate of allergic reaction effects with trimethoprim-sulfamethoxazole vs single-entity trimethoprim (3.9% to 5% vs <2%)[53,54]	• Nausea[54]	• NA
• Trimethoprim-sulfamethoxazole	• Uncommon: severe allergic reactions that can lead to death[53]	• Gastrointestinal effects (3%) • Hyperkalemia (about 3%)[55]	• **Hypersensitivity reactions (0.09%): includes anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness–like syndrome, lupuslike syndrome, pneumonitis, hepatitis, interstitial nephritis, vasculitis, and pancytopenia**[55] • Rare: drug-induced mixed hepatitis[32] • *C difficile* infection (RR = 3.32)[10,55]
Tetracyclines			• **Might cause permanent discoloration of the teeth during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 y)**[56] • **Can cause fetal harm when administered to a pregnant woman**[56] • ***C difficile*-associated diarrhea**[56]
• Doxycycline	• Rash (1%)[57] • Hives[57] • Cutaneous adverse reactions[58]	• Gastrointestinal effects (up to 20%)[57] • Phototoxicity (3% for 100 mg/d, 20% for 150 mg/d, 42% for 200 mg/d, 7.5% overall incidence)[58] • Abnormal weight gain (23% in Q fever endocarditis)[58] • Esophagitis[59] • Esophageal ulceration[59]	• Hypersensitivity reaction[57] • Serum sickness–like reaction[57] • *C difficile* infection (RR = 7.23)[10]

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DRUGS	ALLERGIC REACTIONS	SELF-LIMITING AND USUALLY TRANSIENT REACTIONS	SERIOUS HARMS
• Minocycline	• Rash[2] • Hives[2]	• Gastrointestinal effects (25%)[59] • Neurologic effects (vertigo, ataxia, dizziness, weakness)[57]	• Hypersensitivity reaction[57] • Serum sickness–like reaction[57] • Drug-induced lupus[57] • Pneumonitis[57] • Skin hyperpigmentation (irreversible)[58]
• Tetracycline	• Rash[2] • Hives[2]	• Gastrointestinal effects[59]	• Hypersensitivity reaction[57] • Serum sickness–like reaction[57] • *C difficile* (RR = 14.04)[10]
Vancomycin[60]	• Rash	• Nausea (17%), abdominal pain (15%), vomiting (9%), diarrhea (9%), flatulence (8%) • Fatigue (5%) • Back pain (6%) • Headache (7%)	• **Nephrotoxicity: reports of renal failure (5%), especially in those >65 y (some irreversible)** • Hypokalemia (13%) • Peripheral edema (6%)
Azoles			
• Fluconazole[61]	• NA	• Gastrointestinal effects (up to 7%) • Neurologic effects (up to 3%; eg, dizziness, headache, dysgeusia)	• **Severe or fatal hepatic injury (sometimes irreversible)** • Anaphylaxis • Others: asthenia, seizures, metabolic disturbances (lipid levels), myalgia, insomnia, severe skin rashes, alopecia (more frequent in persons with HIV infection)
• Itraconazole[62]	• Dermatologic effects (up to 3%)	• Gastrointestinal effects (up to 11%) • Systemic effects (up to 9%; eg, fatigue, fever, malaise) • Neurologic effects (up to 10%; eg, dizziness, headache, somnolence, abnormal dreams) • Decreased libido, impotence (1%) • Cardiac or renal effects (up to 2%; eg, hypertension, hypokalemia) • Elevated liver enzyme levels (4%) • Nasal, sinus, and respiratory symptoms (up to 9%)	• **Hepatotoxicity: fatal liver failure** • Hypersensitivity reactions • Transient or permanent hearing loss (irreversible) • Others: cytopenias, neuropathies, visual disturbances, dysgeusia, pulmonary edema, severe skin rashes (eg, Stevens-Johnson syndrome, vasculitis), edema
• Ketoconazole[63]	• Rash	• Nausea and vomiting (3%), pruritus (1.7%), abdominal pain (1.3%)	• **Hepatotoxicity 3.6% (95% CI 3.2 to 4.2)**

CBC—complete blood count, CIOMS—Council for International Organizations of Medical Sciences, DRESS—drug rash with eosinophilia and systemic symptoms, FDA—Food and Drug Administration, MAO—monoamine oxidase, NA—not applicable, NNH—number needed to harm, NNT—number needed to treat, OR—odds ratio, RR—relative risk, SNRI—serotonin-norepinephrine reuptake inhibitor, SSRI—selective serotonin reuptake inhibitor.

Main message

The task of identifying harms is difficult and the results unsatisfactory. The official websites are difficult to use, and warnings are often written in cautious language that makes full understanding difficult. We identified common and mild side effects, as well as more severe effects, which are rare for drugs that are allowed to remain on the market. Allergic effects are mostly dermatologic, although other systems can be involved, especially in the more severe effects such as anaphylaxis.[2] Persistent serious harms are specific to each group of drugs.[1,3]

All antibiotics assessed can cause gastrointestinal effects (eg, nausea, vomiting, diarrhea, abdominal pain, loss of appetite, bloating), often owing to disturbance of gut flora. Broad-spectrum antibiotics are also likely to cause secondary *Candida* species overgrowth, especially in those with diabetes. *Clostridium difficile* infections are mostly caused by ampicillin or amoxicillin, clindamycin, third-generation cephalosporins (such as cefotaxime and ceftazidime), and fluoroquinolones.[31] While some adverse effects start while patients are receiving antimicrobials in hospital, about half of adverse effects start after taking antimicrobials prescribed in community settings, sometimes by non–family physician specialists for complex medical problems.[64,65] Teng et al used the FDA adverse reporting system to calculate the relative risk for *C difficile* infections.[10] Their results are similar to previous estimates, except that quinolones previously demonstrated higher risks.[10] Amoxicillin produces a widespread maculopapular rash in patients with abnormal monocytes (eg,

Table 2. Frequency descriptors for events

CIOMS DESCRIPTOR	FREQUENCY
Very common	> 1 in 10
Common	1 in 10 to 1 in 100
Uncommon	1 in 100 to 1 in 1000
Rare	1 in 1000 to 1 in 10 000
Very rare	< 1 in 10 000

CIOMS—Council for International Organizations of Medical Sciences. Data from CIOMS Working Group IV.[22]

many patients with infectious mononucleosis, certain leukemias, or HIV infection).[29] The European Medicines Agency website gives specific warnings about moxifloxacin causing fulminant hepatitis.[19] This warning is also required in Canada but not in the United States.

Quinolones have a very broad spectrum of action, infections are increasingly resistant to them, and there is evidence of both general effects such as *C difficile* infection and specific harms. Therefore, physicians should consider using alternative medications for mild to moderate infections. Moxifloxacin is not more effective than other quinolones but has more serious toxic effects. Combination drugs have risks of adverse effects from both components, so they should only be used when that spectrum of coverage is needed. Sulfamethoxazole-trimethoprim is valuable for treating serious staphylococcal infections, *Pneumocystis jiroveci* pneumonia (formerly known as Pneumocystis carinii *pneumonia* or *PCP)*, and other atypical infections. Many Canadian physicians seem unaware that in many countries trimethoprim alone is the standard therapy for most urinary tract infections (including epididymo-orchitis and prostatitis) and the difference in effectiveness is not perceptible.[54] Linezolid is seldom initiated in community practice, but more awareness is needed of its high rates of side effects and interactions when patients are discharged while taking this drug, usually as step-down therapy for methicillin-resistant *Staphylococcus aureus* infections. The effectiveness of doxycycline and minocycline is similar, but the latter has higher rates of side effects[57,58] and some that are unique, especially if used for long periods. It is difficult to understand why some still prescribe minocycline.[66] Macrolides, specifically azithromycin, have been associated with cardiovascular death, especially among older patients, but recent systematic reviews and meta-analyses[67] and analysis of US administrative data[68] suggest the apparent association with myocardial infarction or cardiovascular death is likely because of bias.

Limitations

Reporting of side effects is sporadic and few clinicians recognize and report them, as the mechanisms to do so are not widely advertised and front of mind and might not be readily available when needed. Postmarketing active surveillance systems are critical to obtain longitudinal data relating to antimicrobial prescription patterns, use, and attributable adverse effects.[16] Family physicians can contribute to surveillance of antimicrobial-related (and other) adverse drug effects by reporting any reactions to Health Canada (**https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html**).

Although it is well known that nearly all drugs, and certainly antimicrobials, have associated adverse effects, there is a dearth of literature with accurate event rates to use in clinical practice. Randomized controlled trials with a placebo group represent the ideal format to study adverse effects, but antibiotic trials have a fixed (usually short) duration and seldom capture events arising from repeated or prolonged use. Adverse effects from clinical trials are based on standard dosing in specific populations and in ideal settings, but the rates of adverse effects might vary greatly in real-world settings. Studies reporting adverse events beyond the initial clinical trials are often limited to case reports or series and cohort studies, which suffer from many biases in reporting.[16] The rates of adverse events were noted for some agents at a population level but were not uniformly available and estimates vary. In recent years, the availability of very large databases of medical records enabled better measurement of harms, with a denominator for the frequency of prescription; this should increasingly enable calculation of event rates.[16]

We used the primary national surveillance databases and reviews for our reporting and thus might have missed other databases or studies, especially for rare events. We identified adverse events that were directly attributed to antibiotics. However, in any individual many factors must be considered, including confounding by indication. That is, patients who are more ill and have more comorbidities are more likely to seek help from health care providers, more likely to be treated, and will be at a greater risk of adverse effects (direct and indirectly attributable to antimicrobials).[16] Moreover, because these patients have often taken many drugs, clearly identifying the effects of any one drug is difficult.[16]

Adverse effects are likely to be underestimated globally given how difficult it is to recognize and attribute causation, and given the limited reporting to surveillance systems.[16] This means there is often several years' delay before the evidence is strong enough for official identification. Agencies such as Health Canada and the FDA add adverse effects to a drug label when they are serious and clinically significant, but rates are difficult to estimate.[16,69] Thus, the descriptions are as accurate as can reasonably be achieved.

Conclusion

Antimicrobials are and will continue to be among the most commonly prescribed therapies in medical practice. While many antibiotics are seldom used in the

community because of their common harms and consequent difficulty in using them (eg, aminoglycosides), the antimicrobials used commonly in community practice also cause adverse effects. Gastrointestinal and dermatologic events are the most frequent, but many antimicrobials have other severe and serious adverse effects. As in any other part of our practice, physicians must optimize approaches to maximize benefit and minimize patient harms.

The expression that "less is more" applies to the use of antibiotics, both in terms of whether to prescribe them and, once prescribed, how long the course should be. As the greatest risk factor for adverse effects is simply the use of the drug, we should prescribe them as infrequently as possible—only when needed and only for short courses. Short-course antibiotics have shown equivalent effectiveness to longer courses for many conditions but reduce the probability of side effects.[70-72] Several guides now recommend short-course antibiotic therapy,[73,74] yet this approach is used less often than warranted.

The summary table is designed to assist prescribers' awareness of the harms they might cause. Continuing work on education, active surveillance, and dissemination of information relating to antimicrobial-associated adverse effects is needed to optimize patient care and outcomes.

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Contributors

Ms Mohsen led obtaining and organizing the data, and writing the first draft. **Dr Dickinson** had the original idea, led the effort, and wrote much of the paper. **Dr Somayaji** revised the article and added an infectious disease perspective.

Competing interests

None declared

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