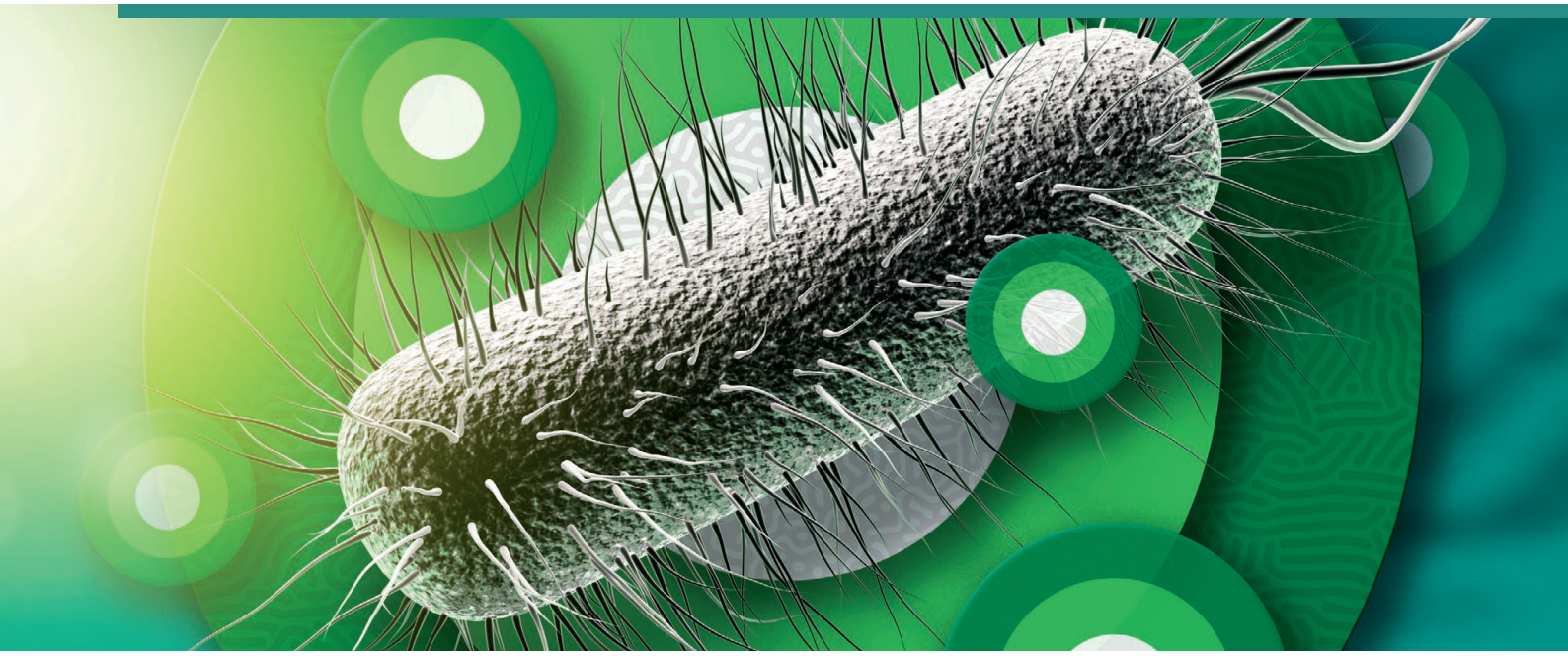


Limiting the use of quinolone antibiotics

Quinolones (e.g. ciprofloxacin, norfloxacin) are associated with increasing antimicrobial resistance and rare, but potentially harmful, adverse effects. Their use should be reserved for specific indications involving serious bacterial infections, in order to protect their effectiveness. There are few situations where quinolones are recommended first-line, such as bacterial prostatitis, epididymo-orchitis (if a urinary pathogen is suspected) and severe cases of salmonellosis. Patients prescribed quinolones should be advised about the risk of rare but serious adverse effects, including tendon rupture and aortic aneurysm.

KEY PRACTICE POINTS:

- Reserve for specific indications:
  - Limit use to serious, life-threatening or difficult-to-treat infections, when other antibiotics cannot be used due to allergy, intolerance or antimicrobial resistance
  - Dispensing data show that ciprofloxacin and norfloxacin use has been steadily decreasing since 2015; conversely, moxifloxacin use has more than doubled between 2015 and 2019
- Indications for ciprofloxacin:
  - First-line for the treatment of patients with bacterial prostatitis, epididymo-orchitis (if a urinary tract infection pathogen is suspected) and severe cases of salmonellosis
  - Gonorrhoea (if known to be susceptible) and severe cases of shigellosis (if known to be susceptible and unable to take the first-line treatment), *Campylobacter* enterocolitis (second-line) and some eye and ear infections
  - Ciprofloxacin can be considered for the treatment of patients with uncomplicated urinary tract infection that is unresponsive or resistant to a first-line treatment
  - Ciprofloxacin should not be used for pneumococcal pneumonia or travellers' diarrhoea
- Indications for other quinolones:
  - Moxifloxacin is indicated (unapproved) for *Mycoplasma genitalium* infection if first-line treatment with doxycycline followed by azithromycin has failed or there is known macrolide resistance. Moxifloxacin is also an approved treatment for multi-drug resistant tuberculosis.
  - Norfloxacin is no longer recommended for the treatment of patients with uncomplicated urinary tract infection due to the potential for resistance
- Adverse effects of quinolones:
  - These medicines are generally well tolerated, with the most common adverse effect being gastrointestinal disturbance. In rare circumstances serious adverse effects can occur, including tendon rupture, aortic aneurysm rupture or dissection, CNS excitation and seizures, and QT prolongation.
  - Older or frail people are at increased risk of experiencing adverse effects with quinolones; ciprofloxacin and norfloxacin dose adjustment is required for patients with impaired renal function

October, 2023 update: The recommended pharmacological treatment for acute and chronic bacterial prostatitis has been updated. For further information on the diagnosis and management of prostatitis, see **bpac.org.nz/2023/prostatitis.aspx**

Quinolones: an overview

Quinolones are a class of broad-spectrum antibiotics that inhibit bacterial DNA synthesis. The addition of a fluorine atom to a quinolone forms a subset of medicines referred to as fluoroquinolones, which have enhanced antimicrobial activity. Fluoroquinolones available in New Zealand include:[1]

- Ciprofloxacin (tablets, eye drops, ear drops* and solution for IV infusion)
- Norfloxacin (tablets)
- Moxifloxacin (tablets and solution for IV infusion)
- Levofloxacin (tablets [section 29, unapproved medicine])

* Formulated with hydrocortisone; indicated for the treatment of otitis externa if *Pseudomonas* is suspected

N.B. Prescribing restrictions, endorsements and Special Authority criteria apply, see Table 1 for details.

Quinolones are most active against Gram-negative bacteria

Quinolones are very active against aerobic Gram-negative bacilli and cocci, including *Enterobacteriaceae, Pseudomonas aeruginosa, Haemophilus influenzae, Moraxella catarrhalis* (*Branhamella catarrhalis*) and *Neisseria gonorrhoeae*. They are generally less active against Gram-positive organisms such as staphylococci and much less active against streptococci such as *Streptococcus pneumoniae*.[2] Quinolones are generally not effective against anaerobic organisms.

Moxifloxacin is a later generation quinolone and has greater activity against Gram-positive organisms and atypical organisms than ciprofloxacin or norfloxacin, and is also active against anaerobes.[2] Many treatment resistant *Streptococcus pneumoniae* isolates are susceptible to moxifloxacin, although it is not funded for this indication. Moxifloxacin should not be considered effective against *Pseudomonas aeruginosa*. While it is not first-line, it does have activity against susceptible methicillin-resistant *Staphylococcus aureus*.[3]

There are few indications for use in primary care

A restrictive approach to the use of quinolones is recommended as community prescribing of quinolones significantly contributes to antimicrobial resistance (see: "Quinolone resistance is increasing"). Ideally, quinolones should be reserved for serious, life-threatening or difficult-to-treat infections, when other antibiotics cannot be used due to allergy or intolerance, or when the pathogen is resistant to alternative antimicrobial agents (see Table 1).

For further information on prescribing quinolones for individual conditions as per Table 1, including dosing and regimen recommendations, see: **https://bpac.org.nz/antibiotics/guide.aspx**

Clinical scenarios where ciprofloxacin is not recommended

Ciprofloxacin should not be used for:

- Pneumococcal pneumonia – it does not cover *Streptococcus pneumoniae* adequately
- Repeat courses for chronic prostatitis if bacterial involvement not confirmed – chronic prostate pain is frequently not due to infection
- Travellers' diarrhoea – antibiotic treatment is not typically required as the infection is usually self-limiting and may be caused by bacteria, viruses or protozoa. Patients with severe or persistent symptoms should be discussed with an Infectious Diseases Physician or Clinical Microbiologist to decide on an appropriate treatment regimen, depending on the causative pathogen. Azithromycin is often a recommended choice.
- Diverticulitis – anecdotally, patients are often treated with ciprofloxacin, however, the recommended first-line regimen is trimethoprim + sulfamethoxazole and metronidazole; amoxicillin clavulanate is an alternative.[4]

Ciprofloxacin is generally not recommended for pyelonephritis, although it is used occasionally. Trimethoprim + sulfamethoxazole is first-line; amoxicillin clavulanate and cefalexin are alternatives.[4]

N.B. Norfloxacin should not be used for pyelonephritis as it has poor tissue penetration and is no longer recommended for uncomplicated urinary tract infection. Some DHBs have excluded norfloxacin from their formularies as it is no longer considered appropriate due to resistance and safety concerns.

Key considerations when prescribing quinolones

Quinolones are generally well tolerated, with the most common adverse effects resulting from gastrointestinal disturbance, as with most antibiotics. Less frequently, people using quinolones may experience central nervous system effects (e.g. headache, insomnia, dizziness, anxiety, restlessness, tremor), crystalluria*, rash or photosensitivity.[18]

In rare circumstances, serious adverse effects can occur, including tendinitis and tendon rupture, progression or rupture of an aortic aneurysm or aortic dissection, QT prolongation, retinal detachment, CNS excitation and seizures (see: "Tendinitis and tendon ruptures are a rare adverse effect" and "Caution is required when prescribing quinolones in some patients").[2,19] The risk of serious adverse effects seems to be greater with later generation quinolones (i.e. moxifloxacin) than with earlier generations (i.e. ciprofloxacin and norfloxacin).[18]

* The formation of crystals in the urine due to poor hydration and urine alkalinity; the condition is usually benign, but there have been reported cases of renal failure associated with crystal precipitation [20, 21]

Table 1. Indications for quinolones in primary care. N.B. There are no indications for norfloxacin in primary care.[1, 4–8]

Ciprofloxacin	Moxifloxacin
■ **Epididymo-orchitis** – first-line if a UTI pathogen is suspected ■ **Prostatitis** – first-line for acute and chronic bacterial prostatitis ■ **Otitis externa with secondary infection** – only if *Pseudomonas* is suspected* ■ **Chronic suppurative otitis media** [unapproved indication]† ■ **Bacterial keratitis** or **severe bacterial conjunctivitis** resistant to chloramphenicol† ■ **Gonorrhoea** – only if isolate is known to be susceptible and an alternative to first-line treatment is required ■ **Chronic relapsing UTI in adults** – fourth-line if treatment with nitrofurantoin, trimethoprim or cefalexin has failed or the organism is not sensitive‡ ■ ***Salmonella* enterocolitis** – first-line for severe infection, those who are immunocompromised or have prosthetic vascular grafts ■ ***Salmonella typhi*** and ***S. paratyphi*** – if isolate is known to be susceptible ■ ***Campylobacter* enterocolitis** – second-line after erythromycin for severe or prolonged infection, or those at high risk of complications ■ **Shigellosis** – only if severe and isolate is known to be sensitive ■ **Other indications** include invasive *Pseudomonas* infections, *Legionella* pneumonia, bone and joint infections and prophylaxis of meningococcal disease, when no alternative is available	■ ***Mycoplasma genitalium* urethritis**** [unapproved indication] – first-line is doxycycline (to reduce bacterial load) followed by either azithromycin or moxifloxacin (if macrolide resistant or treatment with azithromycin has failed). Neither azithromycin nor moxifloxacin are recommended first-line.

* Ear drops formulated with hydrocortisone (not funded)

† Eye drops are subsidised by endorsement when prescribed for the treatment of bacterial keratitis or severe bacterial conjunctivitis resistant to chloramphenicol; or for the second-line treatment of chronic suppurative otitis media (unapproved indication).

** Moxifloxacin can be prescribed fully funded with Special Authority approval for the treatment of *M. genitalium* infection (unapproved indication). Applications are to be made by a sexual health specialist or on their recommendation. N.B. A similar regimen is likely to be appropriate for persistent cervicitis or severe pelvic inflammatory disease caused by *M. genitalium* infection.

‡ Consider the underlying cause of relapsing UTI, e.g. a prostatic abscess or renal tract abnormality

For further information on *Mycoplasma genitalium*, see: **https://bpac.org.nz/2019/mycoplasma-genitalium.aspx**

Patients should be advised about the risks so that they can prevent or minimise the impact of any adverse effects if they occur.

Advise patients to:

- Increase fluid intake to reduce the risk of crystalluria
- Apply sunscreen or cover exposed areas of skin when outdoors to avoid a photosensitivity reaction
- Stop taking the quinolone and consult with a health professional if tendon pain or swelling occurs, or symptoms of neuropathy, e.g. pain, burning, tingling, numbness or weakness
- Report any neurological symptoms, e.g. confusion, anxiety, restlessness, to a health professional

N.B. Prescribers should report adverse reactions to the Centre for Adverse Reactions Monitoring (CARM). Reports can be made through your Adverse Reaction Reporting tool in your patient management system or via a variety of other methods. For further information, see: **https://nzphvc.otago.ac.nz/reporting/**

Patient information leaflets are available from the New Zealand Formulary: **https://www.nzf.org.nz/nzf_70421**

Caution is required when prescribing quinolones in some patients

Many of the adverse effects associated with quinolones occur more frequently in people with pre-existing risk factors, or in certain at-risk groups, including older people and those with epilepsy.

Older people

Quinolones should be used at the lowest effective dose in older people for as short a duration as clinically possible, to reduce the development of resistance and adverse effects. Renal function declines consistently with age and ciprofloxacin and norfloxacin doses need to be reduced accordingly to avoid adverse effects. For example, an appropriate oral dose for ciprofloxacin in renal impairment is 250–500 mg, twice daily, if eGFR is 30–60 mL/minute/1.73 m^2 or once daily, if eGFR < 30 mL/minute/1.73 m^2.[1]

Many antibiotic classes are associated with adverse CNS effects; these appear to be more common with quinolones than other systemic antimicrobials and are of particular concern in older people.[24] Some adverse CNS effects in older people may be attributed to ageing, acute illness, other conditions or other medicines so it is important to consider quinolone use when CNS symptoms are reported.

Tendinitis and tendon ruptures are a rare adverse effect

A number of toxicological studies have confirmed that quinolones damage the collagen within tendons, which on rare occasions can result in tendinitis and tendon rupture, particularly affecting the Achilles tendon with bilateral involvement possible. This can occur even after a single dose of quinolone and the risk can persist for months.[22] Tendon rupture has been reported within 48 hours of starting treatment, however, cases have also been reported several months after stopping treatment.[22]

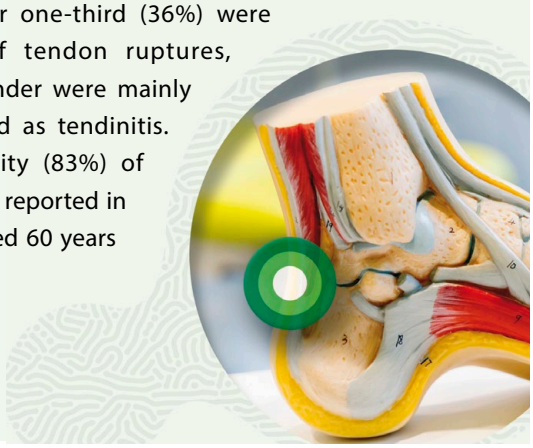
Risk factors for tendon disorders associated with the use of quinolones include:[1, 19, 23]

- Age over 60 years
- Concomitant oral corticosteroid treatment
- Chronic kidney disease
- Previous kidney, heart or lung transplant
- Prior history of tendon damage

Although this adverse effect is rare (estimated incidence rate 0.14% to 0.40%),[22] it is important to remember that:[1]

- Quinolones are contraindicated in patients with a history of tendon disorders related to previous quinolone use
- If tendinitis is suspected, the quinolone should be discontinued immediately

Between 2007 and 2012, CARM received 53 reports of tendon disorders associated with quinolone use.[14] Over one-third (36%) were reports of tendon ruptures, the remainder were mainly categorised as tendinitis. The majority (83%) of cases were reported in people aged 60 years and over.



People with epilepsy or a history of CNS disorders

Quinolones should be used with caution in people at increased risk of seizures, those with CNS disorders or in patients concurrently using medicines which may lower the seizure threshold, e.g. bupropion, due to the potential for adverse CNS effects.[25] The risk of seizures, although very rare, may be increased with concomitant NSAID treatment.[25]

People at risk of aortic aneurysm or dissection

A similar mechanism relating to collagen degradation with quinolone treatment that leads to tendon rupture (see: "Tendinitis and tendon ruptures are a rare adverse effect") may occur in the wall of the aorta, contributing to an approximately two-fold increase in the risk of progression or rupture of an aortic aneurysm or aortic dissection within 60 days following treatment.[15, 26] This is a rare effect and as of March 2019, no cases were reported in New Zealand.[15]

Risk factors include:[15, 19, 27]

- Family history of aneurysm
- Pre-existing aortic aneurysm or dissection
- Certain pre-disposing conditions, e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu's arteritis, giant cell arteritis, Behçet's disease
- Atherosclerosis
- Hypertension
- Age > 65 years

Quinolones should only be prescribed to people with these risk factors if there are no suitable alternatives and the benefits of treatment outweigh the potential harms. Patients should be advised to seek urgent medical advice if they develop sudden-onset, severe chest, abdominal or lower back pain during or following treatment.[19]

Medicine interactions

Quinolones can interact with a number of other medicines, such as those that reduce seizure threshold, prolong the QT interval, warfarin and medicines metabolised by common pathways in the liver. For further details on medicines that interact with quinolones, refer to the NZF Stockley's interactions checker: **https://www.nzf.org.nz**

Quinolones should be used cautiously in patients taking warfarin as these medicines may interact to increase the international normalised ratio (INR) and cause severe bleeding. If a quinolone is the most appropriate treatment option, monitor the INR three days after initiating antibiotic treatment.[1]

Other at-risk groups

Caution is also required with quinolone use in people with:[1]

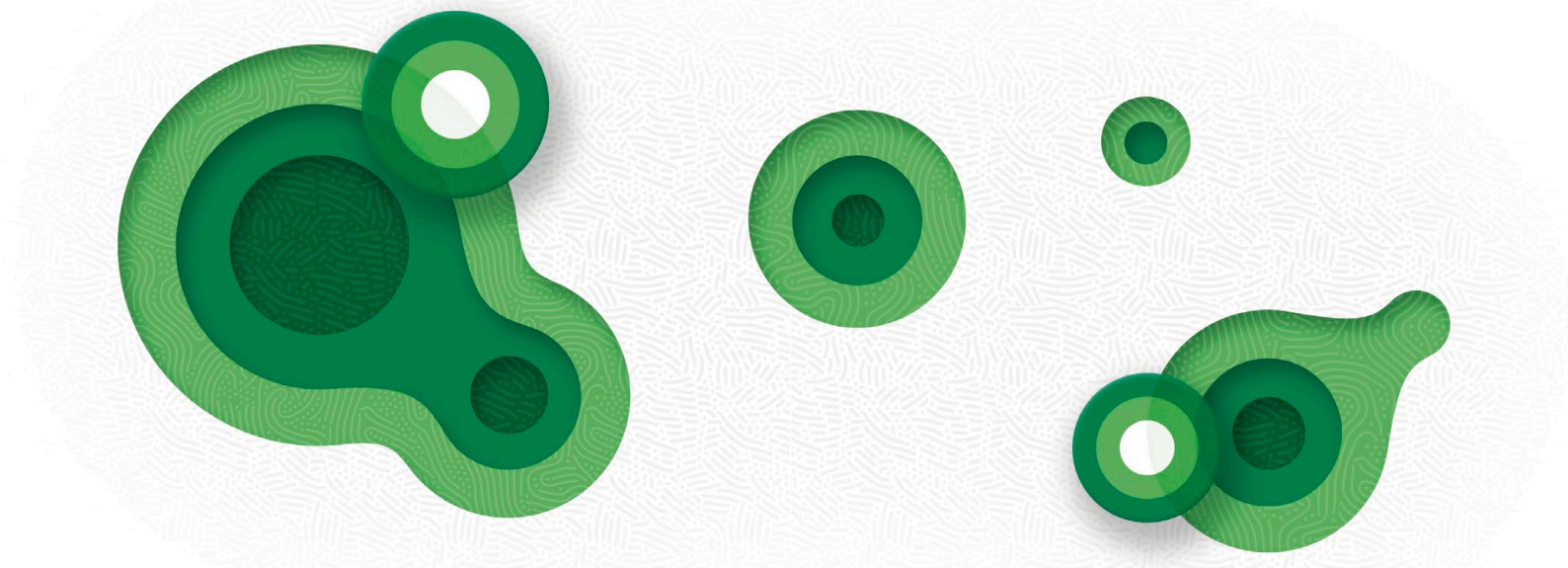
- Diabetes – glucose levels may be increased or decreased
- Myasthenia gravis – symptoms may be exacerbated
- G6PD deficiency – increased risk of haemolytic anaemia

Quinolones are generally not used in children

Quinolones are not recommended for use in people aged under 18 years as they have been associated with arthropathy and damage to immature cartilage of weight-bearing joints in animal studies.[1] There are some specific circumstances, such as pseudomonal infections associated with cystic fibrosis, where the short-term use of ciprofloxacin may be justified in children.[28]

Quinolones should be avoided in pregnancy and while breastfeeding

All quinolones should be avoided in pregnancy as they have been shown to cause arthropathy in animal studies.[1] There are limited data available on the safety of quinolone use while breastfeeding. The manufacturers recommend avoiding use as small amounts are detected in the breast milk.[1]



Quinolone resistance is increasing

Antimicrobial resistance to quinolones is prevalent globally, and includes both Gram-negative and Gram-positive strains. In New Zealand, resistance has been shown in:

- *Haemophilus influenzae* – susceptibility testing of 83 isolates by the Institute of Environmental Science and Research (ESR) in 2017 found 2.4% were resistant to ciprofloxacin[9]
- *Neisseria gonorrhoeae* – susceptibility testing of 425 isolates by the ESR in 2015 found 32% were resistant to ciprofloxacin[10]
- *Mycoplasma genitalium* – studies conducted in 2017 and 2020 reported 19–27% of 115 and 81 *M. genitalium* isolates, respectively, had mutations associated with increased resistance to quinolones[11,12]
- *Shigella* – a 2018 study reported 23% of 263 *Shigella* isolates were resistant to ciprofloxacin and norfloxacin[13]

Ciprofloxacin and norfloxacin use in New Zealand is decreasing

Dispensing data from the last five years show that ciprofloxacin and norfloxacin use has been steadily decreasing (Figures 1 A and B). Increased awareness of the harms of quinolone treatment, as well as education on rational use, may help to explain this prescribing trend. There have also been changes to funding endorsement for norfloxacin. Medsafe has published two Prescriber Updates on quinolones since 2012, highlighting the risks of tendon rupture and aortic aneurysm or dissection.[14,15] In 2016, the United States Food and Drug Association revised the warnings for quinolones due to the potential for disabling and potentially permanent adverse effects.[16] In 2018, several news media articles on the use and safety of quinolones were published in New Zealand.

In most DHBs, ciprofloxacin and norfloxacin dispensing decreased by 25–50% between 2015 and 2019 (Figure 2).[17] The only DHB without a decrease in ciprofloxacin and norfloxacin

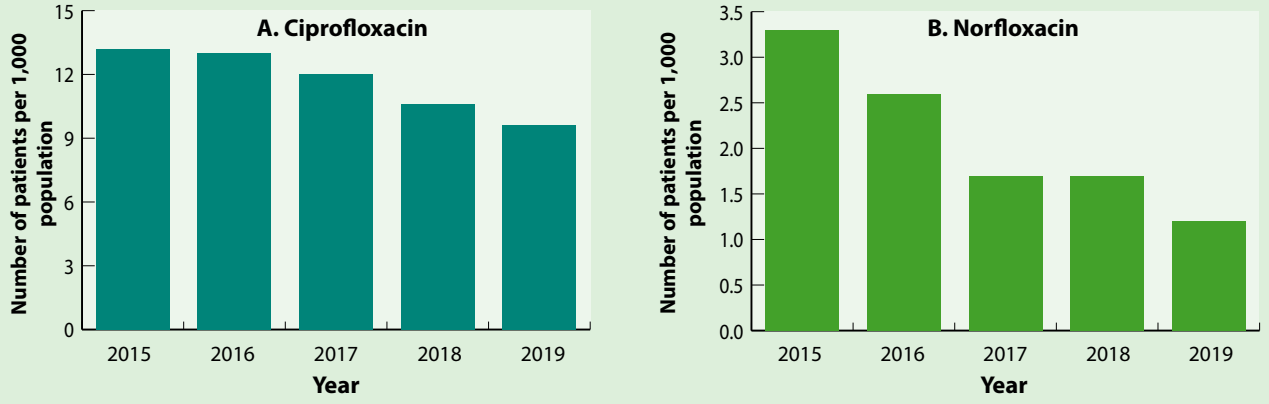


Figure 1 A and B. Number of patients (per 1,000 enrolled patients) dispensed ciprofloxacin (A) or norfloxacin (B), 2015–2019. Note the different scale on the Y axes.

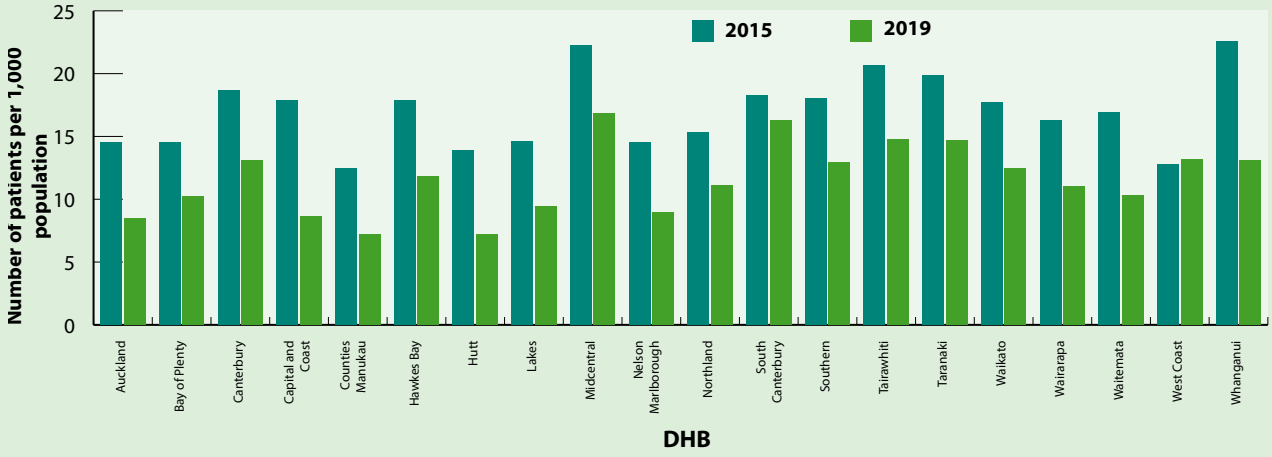


Figure 2. Number of patients (per 1,000 enrolled patients) who were dispensed ciprofloxacin or norfloxacin in 2015 and 2019, by DHB.

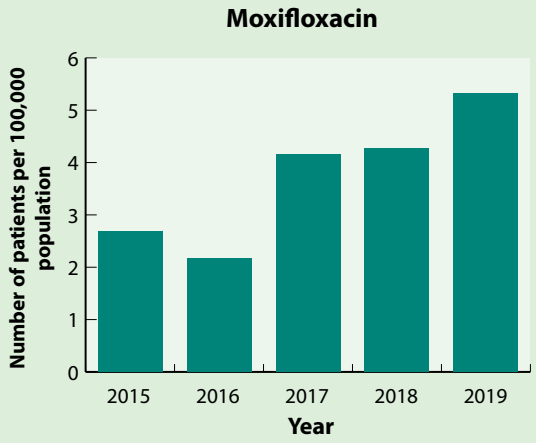
dispensing was West Coast. In 2019, ciprofloxacin and norfloxacin use was highest in Midcentral DHB (17 people per 1,000 population) and lowest in Hutt and Counties Manukau DHBs (7 people per 1,000 population).

Moxifloxacin use is increasing, but total numbers are still small

Moxifloxacin is funded with Special Authority approval for active tuberculosis, *Mycoplasma genitalium* infection and penetrating eye injury. The majority of moxifloxacin prescribing for these indications will occur in secondary care; only applications for *M. genitalium* can be made by a primary care clinician, but this must be on the recommendation of a sexual health physician. Moxifloxacin use more than doubled between 2015 and 2019, however, the total number of patients dispensed moxifloxacin is still very low (i.e. 251 people in total were dispensed moxifloxacin in 2019) (Figure 3). Moxifloxacin dispensing increased in most DHBs between 2015 and 2019 (Figure 4). The highest dispensing rate in 2019 was in Taranaki DHB (17 people per 100,000 population). Possible reasons for this increase include:

- Treatment of infections caused by multi-resistant *S. pneumoniae*
- Increased awareness and laboratory detection of *M. genitalium* infection as a cause of urethritis, cervicitis and pelvic inflammatory disease
- An outbreak of tuberculosis where first-line treatments were inappropriate due to resistance or intolerance

Figure 3. Patients dispensed moxifloxacin (per 100,000 enrolled patients), 2015–2019. Note the scale on the Y axis has been adjusted to represent the comparatively small population of patients dispensed moxifloxacin.



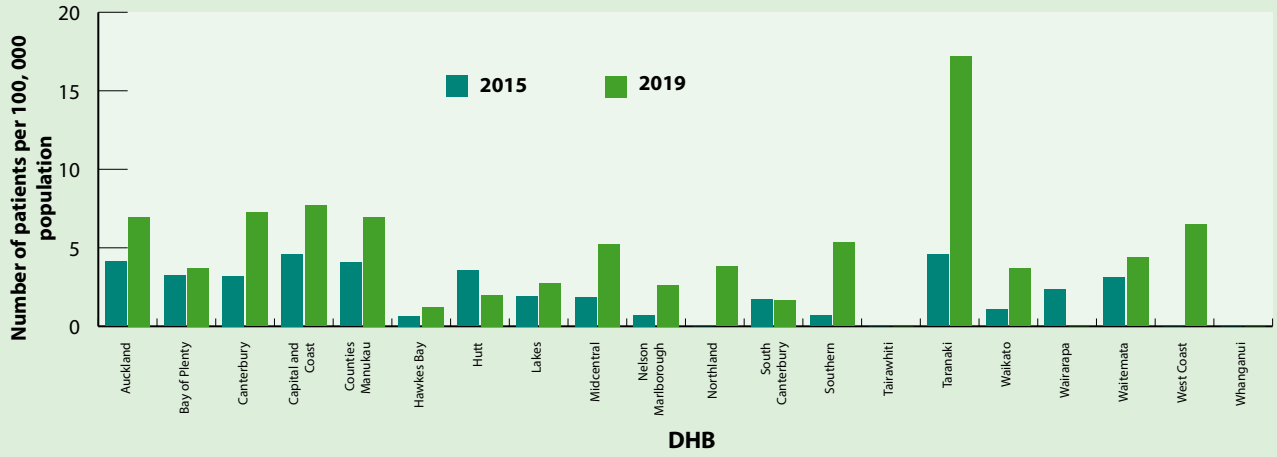


Figure 4. Number of patients (per 100,000 enrolled patients) who were dispensed moxifloxacin in 2015 and 2019, by DHB.

Acknowledgement: Thank you to **Dr Arlo Upton**, Clinical Microbiologist, Southern Community Laboratories for expert review of this article.

N.B. Expert reviewers do not write the articles and are not responsible for the final content. bpac^{nz} retains editorial oversight of all content.

This article is available online at:
www.bpac.org.nz/2021/quinolone.aspx

References

1. New Zealand Formulary (NZF). NZF v101. Available from: www.nzf.org.nz (Accessed Oct, 2020).
2. Pham TDM, Ziora ZM, Blaskovich MAT. Quinolone antibiotics. Med chem comm 2019;10:1719–39. doi:10.1039/c9md00120d
3. Lemaire S, Kosowska-Shick K, Appelbaum PC, et al. Activity of moxifloxacin against intracellular community-acquired methicillin-resistant Staphylococcus aureus: comparison with clindamycin, linezolid and co-trimoxazole and attempt at defining an intracellular susceptibility breakpoint. J Antimicrob Chemother 2011;66:596–607. doi:10.1093/jac/dkq478
4. bpacnz. Antibiotics: choices for common infections. 2017. Available from: https://bpac.org.nz/antibiotics/guide.aspx (Accessed Nov, 2020)
5. National Institute for Health and Care Excellence. Prostatitis (acute): antimicrobial prescribing. 2018. Available from: https://www.nice.org.uk/guidance/ng110/chapter/Recommendations#choice-of-antibiotic (Accessed Oct, 2020).
6. Rees J, Abrahams M, Doble A, et al. Diagnosis and treatment of chronic bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: a consensus guideline. BJU Int 2015;116:509–25. doi:10.1111/bju.13101
7. Williams PCM, Berkley JA. Guidelines for the treatment of dysentery (shigellosis): a systematic review of the evidence. Paediatrics and International Child Health 2018;38:S50–65. doi:10.1080/20469047.2017.1409454
8. Australasian Sexual Health Alliance. Australian STI management guidelines for use in primary care: Mycoplasma genitalium. 2018. Available from: http://www.sti.guidelines.org.au/sexually-transmissible-infections/mycoplasma-genitalium#management (Accessed Nov, 2020).
9. Institute of Environmental Science and Research. Antimicrobial susceptibility of invasive Haemophilus influenzae, 2017. 2017. Available from: https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/HIN/HIN_2017.pdf (Accessed Oct, 2020).
10. Institute of Environmental Science and Research. Antimicrobial resistance and molecular epidemiology of Neisseria gonorrhoeae in New Zealand, 2014-15. 2015. Available from: https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/Gono/NgonosurveyfinalreportZ015.pdf (Accessed Oct, 2020).
11. Anderson T, Coughlan E, Werno A. Mycoplasma genitalium macrolide and fluoroquinolone resistance detection and clinical implications in a selected cohort in New Zealand. J Clin Microbiol 2017;55:3242–8. doi:10.1128/JCM.01087-17
12. Vesty A, McAuliffe G, Roberts S, et al. Mycoplasma genitalium antimicrobial resistance in community and sexual health clinic patients, Auckland, New Zealand. Emerg Infect Dis 2020;26:332–5. doi:10.3201/eid2602.190533
13. Heffernan H, Woodhouse R, Hewison C, et al. Antimicrobial resistance among Shigella in New Zealand. N Z Med J 2018;131:56–62.
14. Medsafe. Quinolones - A tendoncy to rupture. 2012. Available from: https://www.medsafe.govt.nz/profs/PUArticles/QuinolonesSept2012.htm (Accessed Nov, 2020).
15. Medsafe. Aortic aneurysm/dissection – The Achilles heels of fluoroquinolones. 2019. Available from: https://www.medsafe.govt.nz/profs/PUArticles/December2019/Aortic-aneurysm-dissection-fluoroquinolones.htm (Accessed Oct, 2020).
16. Food and Drug Administration. FDA Drug safety communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. 2018. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-updates-warnings-oral-and-injectable-fluoroquinolone-antibiotics (Accessed Oct, 2020).
17. Ministry of Health. Pharmaceutical Claims Collection. 2020.
18. Scavone C, Mascolo A, Ruggiero R, et al. Quinolones-induced musculoskeletal, neurological, and psychiatric ADRs: a pharmacovigilance study based on data from the Italian Spontaneous Reporting System. Front Pharmacol 2020;11:428. doi:10.3389/fphar.2020.00428
19. Wade S, Williams M. Antibiotic side-effects: from the anticipated to the bizarre. Prescriber 2019;30:16–21. doi:10.1002/psb.1801
20. Khan M, Ortega LM, Bagwan N, et al. Crystal-induced acute kidney injury due to ciprofloxacin. J Nephropathol 2015;4:29–31. doi:10.12860/jnp.2015.06
21. Stratta P, Lazzarich E, Canavese C, et al. Ciprofloxacin crystal nephropathy. American Journal of Kidney Diseases 2007;50:330–5. doi:10.1053/j.ajkd.2007.05.014
22. Godoy-Santos AL, Bruschini H, Cury J, et al. Fluoroquinolones and the risk of Achilles tendon disorders: update on a neglected complication. Urology 2018;113:20–5. doi:10.1016/j.urology.2017.10.017
23. Morales DR, Slattery J, Pacurariu A, et al. Relative and absolute risk of tendon rupture with fluoroquinolone and concomitant fluoroquinolone/corticosteroid therapy: population-based cested case–control study. Clin Drug Investig 2019;39:205–13. doi:10.1007/s40261-018-0729-y
24. Zareifopoulos N, Panayiotakopoulos G. Neuropsychiatric effects of antimicrobial agents. Clin Drug Investig 2017;37:423–37. doi:10.1007/s40261-017-0498-z
25. New Zealand Formulary. Stockley's interactions checker. 2020. Available from: https://www.nzf.org.nz/ (Accessed Nov, 2020).
26. Rawla P, El Helou ML, Vellipuram AR. Fluoroquinolones and the risk of aortic aneurysm or aortic dissection: a systematic review and meta-analysis. CHAMC 2019;17:3–10. doi:10.2174/1871525717666190402121958
27. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open 2015;5:e010077–e010077. doi:10.1136/bmjopen-2015-010077
28. New Zealand Formulary for Children. NZFC v101. 2020. Available from: www.nzfchildren.org.nz/ (Accessed Mar, 2020).