

# Low levels of fluoroquinolone resistance in *Escherichia coli*. A five-year trend in Australia measured through the use of TSN® Database Australia

John Turnidge,<sup>1</sup> Laurence R McCarthy,<sup>2</sup> Ronald N Master,<sup>3</sup> Douglas E Kepner<sup>4</sup>

## Abstract

In many countries, fluoroquinolones are among the most commonly used antibacterial drugs. Concerns about bacterial resistance to these and other frequently used drugs have been raised by the medical and scientific communities. While fluoroquinolone resistance has not yet developed among many bacteria, emergence of resistance in *Escherichia coli* would be a problem as multiple resistances to other antibiotics is now a common problem. This paper examines trends in resistance to fluoroquinolones in *Escherichia coli* through analysis of data collected from Australian institutions between 1997 and 2001. During the study period, norfloxacin and ciprofloxacin were the most frequently tested fluoroquinolones in Australian laboratories. An examination of results for strains tested simultaneously against both drugs indicated that testing against either drug accurately predicted resistance or susceptibility for the other (99.7% agreement). Over 400,000 tests were performed to determine the fluoroquinolone susceptibility of *E. coli*. Data were analysed by the test method used (Calibrated Dichotomous Sensitivity (CDS) or National Committee for Clinical Laboratory Standards (NCCLS)). The data indicate that fluoroquinolone resistance in *E. coli* has not yet emerged as a significant problem in Australia, but there are some indications of low level increases in resistance rates. Norfloxacin results are likely to be a better guide to fluoroquinolone resistance in this species using this method of surveillance. *Commun Dis Intell* 2003;27 Suppl:S89–S91.

Keywords: fluoroquinolone resistance, *Escherichia coli*, antibiotic resistance

## Introduction

The fluoroquinolones are a potent class of antimicrobial agents that have a wide range of activity against both gram-negative and gram-positive bacterial pathogens. In many countries, this has resulted in widespread use of these agents as treatment modalities for a broad range of infections. By contrast, in Australia the widespread use of quinolones has been prevented, in part through restricted access on the Pharmaceutical Benefits Scheme. The initial quinolone agents (e.g., norfloxacin and ciprofloxacin) were approved for use mainly against gram-negative pathogens including those in the family *Enterobacteriaceae* and the genus *Pseudomonas*. The more recent derivatives (e.g., moxifloxacin and gatifloxacin) retain much of the gram-negative activity, but have enhanced gram positive activity. Over the years these agents have demonstrated continued success, but there is concern about the development of resistance, especially in *E. coli* where multi-resistance to other antibiotic classes is now seen regularly.

1. Director of Microbiology and Infectious Diseases, Women's and Children's Hospital, Microbiology Department, North Adelaide, South Australia

2. President and CEO, Focus Technologies Inc, Virginia, United States of America

3. Director, TSN Operations, Focus Technologies Inc, Virginia, United States of America

4. TSN Microbiology Analyst, Focus Technologies Inc, Virginia, United States of America

Corresponding author: Associate Professor John Turnidge, Director of Microbiology and Infectious Diseases, Women's and Children's Hospital, Microbiology Department, 72 King William Road, North Adelaide, SA 5006. Telephone: +61 8 8161 6873.

Email: turnidgej@wch.sa.gov.au

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It is important to monitor the activity of fluoroquinolones using a strategy that provides an accurate and timely picture. TSN Database Australia was used as the system to monitor the activity of two fluoroquinolones; ciprofloxacin and norfloxacin, against *Escherichia coli* in Australia over the past five years.

## Methods

The Surveillance Network (TSN) Database was first initiated in 1994 by Focus Technologies, Inc. (formerly 'MRL,' Herndon, Virginia). TSN assimilates antimicrobial susceptibility testing and patient demographic data from over 100 laboratories across Australia, into a database. Laboratories are included in TSN based on factors such as hospital bed size, patient population, geographic location, and the antimicrobial susceptibility test methods used. Antimicrobial susceptibility testing of patient isolates is conducted onsite by each participating laboratory as a part of their routine diagnostic testing. TSN uses a series of quality-control filters (i.e., critical rule sets) to screen susceptibility test results for patterns suggestive of testing error and 'quarantines' such results pending laboratory confirmation. TSN Database Australia reflects current testing practices in Australian laboratories and connects a significant number of laboratories in the country in an automated surveillance effort. As of 31 March 2002 TSN Database Australia contained more than 15 million antimicrobial agent/organism susceptibility test results. These results are from approximately 2 million bacterial strains isolated from 1.2 million patients across Australia since 1995.

For analysis of trends, all strains of *E. coli* tested were included. Significance of trends in rates of resistance was analysed using the Chi-square test for linear trend.

Isolates tested concurrently against ciprofloxacin and norfloxacin were also analysed to examine the degree of concordance.

## Results

Data from TSN Database Australia demonstrated continued excellent activity of both ciprofloxacin and norfloxacin against *E. coli*, with a small but steady decrease in susceptibility over five years, as shown in Table 1. Both drugs showed increasing trends to resistance, and both trends were significant at  $p < 0.0001$ ; but more than 97 per cent of isolates were susceptible. This was true for isolates tested by both CDS and NCCLS methods. The ciprofloxacin rate of resistance changed from 1.7 per cent in 1997 to 4.7 per cent in 2001, and the norfloxacin resistance rate increased from 0.3 per cent in 1997 to 1.1 per cent in 2001.

There appear to be differences in the resistance rates between ciprofloxacin and norfloxacin tested by either CDS or NCCLS test methods. These differences are likely to be due to selective testing of ciprofloxacin, in strains demonstrating intermediate or resistant result to norfloxacin. There are large differences in the number of tests with norfloxacin being tested significantly more frequently than ciprofloxacin. For the CDS test method in 2001 there were 1,654 ciprofloxacin results versus 67,320 norfloxacin results. For the NCCLS test methods in 2001 there were 13,643 ciprofloxacin results versus 69,535 results for norfloxacin. Norfloxacin is the fluoroquinolone most frequently routinely tested in Australia and as such is the better indicator of resistance trends using this method of surveillance. We do not believe that the ciprofloxacin results from the TSN Database Australia provide an accurate guide to true rates of fluoroquinolone resistance in *E. coli* at this time.

The activities of the two fluoroquinolones were compared using 3 by 3 analyses for data from both 2000 and 2001. Of the 11,225 strains of *E. coli* examined in 2000 for this study, 99.7 per cent were concordant (data not shown), and for the 13,445 strains examined in 2001, the same percentage were concordant (Table 2). The rates of concordance were high and no differences were observed between the CDS and NCCLS methodologies.

**Table 1. Ciprofloxacin and norfloxacin against *E. coli*, number and per cent susceptible, intermediate and resistant**

Year	Drug	S		I		R	
		n	%	n	%	n	%
1997	Ciprofloxacin	4,987	99.5	0	0	25	0.5
	Norfloxacin	45,307	99.7	0	0	121	0.3
1998	Ciprofloxacin	6,480	99.2	0	0	53	0.8
	Norfloxacin	61,834	99.6	0	0	234	0.4
1999	Ciprofloxacin	11,054	98.7	3	0	145	1.3
	Norfloxacin	84,044	99.5	16	0	380	0.5
2000	Ciprofloxacin	15,697	98.4	2	0	260	1.6
	Norfloxacin	126,325	99.3	20	0	851	0.7
2001	Ciprofloxacin	18,240	97.8	1	0	409	2.2
	Norfloxacin	138,202	99.0	34	0	1,306	0.9

**Table 2. *E. coli*, ciprofloxacin versus norfloxacin, 2001**

			Norfloxacin		
			S %	I %	R %
Ciprofloxacin	S	% n	97.11 (13,057)	0.00 (0)	0.19 (25)
	I	% n	0.02 (3)	0.00 (0)	0.01 (1)
	R	% n	0.13 (17)	0.01 (1)	2.54 (341)

S Susceptible.

I Intermediate.

R Resistant

## Discussion

This study demonstrates several interesting findings. Firstly, both ciprofloxacin and norfloxacin remain highly active against *E. coli* in Australia. Secondly, a direct comparison of ciprofloxacin and norfloxacin tested concurrently demonstrates a high degree of concordance between the two when tested against Australian isolates of *E. coli*. Testing either drug predicted resistance or susceptibility for the other drug. Thirdly, while fluoroquinolone resistance in Australia has not yet emerged as a significant problem, there are indications of increasing resistance rates at low levels. The overall rate of resistance to norfloxacin increased from 0.3 per cent in 1997 to 0.9 per cent in 2001. This trend of increasing resistance rates suggests the need for continued surveillance.

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