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Letter to the Editor

Emerging fluoroquinolone and ketolide resistance in *Haemophilus parainfluenzae* in South Africa

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Dear Editor,

Fluoroquinolones, macrolides and ketolides remain effective antibiotics for the treatment of infections caused by *Haemophilus influenzae* and *Haemophilus parainfluenzae* (*Haemophilus* species) especially the beta lactam-resistant isolates [1,2]. Fluoroquinolone and macrolide resistance in *Haemophilus* species, although low, has been reported [2,3]. A Chinese study, conducted from 2006 to 2008, reported 9% to 24% resistance to various fluoroquinolones and 5.9% to 8.8% to a number of macrolides in *H. parainfluenzae* isolates collected from Acute Exacerbation of Chronic Obstructive Pulmonary Diseases (AECOPD) patients [4]. In comparison, a ten-year retrospective study (2004-2014) in a hospital in Germany revealed no ciprofloxacin resistance in *Haemophilus* species implicated in pneumonia but a high resistance rate to ampicillin (24.4 %), erythromycin (38.3 %), piperacillin (20.8 %), cefuroxime (8.5 %), ampicillin-sulbactam (7.3 %), piperacillin-sulbactam (4.3 %), piperacillin-tazobactam (2.5 %), cefotaxime (2.5 %), and levofloxacin (1.6 %) [3]. There is a dearth of information on the antibiotic susceptibility of *Haemophilus species* (especially *H. parainfluenzae*) in South Africa. There is very limited information from the public and private sectors, as both of these species are neither routinely cultured, nor included in the few institution-specific surveillance projects in public health institutions. Therefore, the aim of this study is to describe the resistance trends to selected antibiotics in *H. influenzae* and *H. parainfluenzae* isolates from 2012 to 2015 using retrospective susceptibility data from a private sector laboratory in South Africa.

The Study

Ethical approval was received from Biomedical Research Ethics Committee of University of KwaZulu-Natal (BE473/14). Susceptibility data of *H. influenzae* (n=14,490) and *H. parainfluenzae* (n=4803) isolates collected from January 2012 to June 2015 (42 months) were retrieved from Lancet laboratories database (Lancet Laboratories, Durban, South Africa) that serves Kwazulu-Natal (KZN) and Gauteng Provinces of South Africa. Demographic and clinical data were not available. The isolates had been routinely cultured on chocolate agar (manufactured in the private lab in Durban, South Africa), incubated at 35°C in 5-10% CO_2 for 24 hours and identified using NH API and NH Vitek cards (isolates collected from January 2012 to October 2012) and Vitek MS (isolates collected from November 2012 to April 2015) (BioMerieux, Marcy l'Etoile, France). Antibiotic susceptibility was determined by the disc diffusion method using Haemophilus Test Medium (manufactured by Lancet laboratories, Durban, South Africa), and interpreted according to the Clinical and Laboratory Standards Institute Guidelines [5] using *H. influenzae* ATCC 49247 as control organism. Chi-square test for trend was performed using GraphPad Prism version 5.01 for Windows, (GraphPad Software, San Diego USA) on retrieved data that was organized into percentage resistance per quarters of each year, for each antibiotic.

The analysis of this data revealed that the resistance of *H. parainfluenzae* to ampicillin decreased gradually (14% to 9.3%), while the resistance to fluoroquinolones, namely ciprofloxacin, moxifloxacin and levofloxacin (4.1% to 21.4%) and telithromycin (7.3% to 15.9%) increased steadily over the 42-month period (Table 1). The statistical analysis using Chi-square test for trends in resistance showed that the results are statistically significant. The observed trends are consistent with the antibiotic use in South Africa, noting that fluoroquinolone consumption is more widespread than telithromycin use [6]. Resistance rates to ciprofloxacin, moxifloxacin and levofloxacin were found to be identical at 99% and are therefore reported collectively in the fluoroquinolones category. The collected data about *H. influenzae* resistance to ampicillin/amoxicillin (10.29% to 8.52%), fluoroquinolones (0.18% to 1.01%) and telithromycin (0.59% to 2.95%) were not significant in respect to the *H. parainfluenzae* ones (Table 2).

Antibiotic usage in the private sector in South Africa is not disciplined and their prescription is at practitioners discretion [7]. Thus the antibiotic prescription practices may explain the reported antibiotic susceptibility trends. A comparison between the private and the public sector is not possible since neither antibiotic use nor resistance rates are routinely quantified in the public sector in KwaZulu-Natal through surveillance studies.

An earlier study revealed an increase in the consumption of fluoroquinolones and macrolides in South Africa in the past decade [6]. Fluoroquinolones, macrolides and ketolides (telithromycin) are widely used for the treatment of various infections in South Africa including those of respiratory, gastrointestinal and urinary tract ones [8,9]. Moreover, it should be mentioned that moxifloxacin is part of the drug regimen to treat drug resistant tuberculosis (National Tuberculosis Management Guidelines 2014) [10]. The consumption of ampicillin in the private sector is minimal, as preference is given to other antibiotic classes (anecdotal evidence from prescribers and pharmacists in the private sector) which may explain the decrease in resistance to this antibiotic.

A 5-year surveillance study that involved all 50 states in the United States (TRUST, 2001 to 2005) reported *H. influenzae* 70% of susceptibility to ampicillin and almost no resistance to respiratory fluoroquinolones (99% susceptibility) [11]. In agreement with this, the SENTRY Antimicrobial Surveillance Program report for Brazil (1998 to 2004) shown *H. influenzae* resistance to ampicillin and fluoroquinolones to be 14% and 1% respectively [12]. The 99% susceptibility of *H. influenzae* to fluoroquinolones found in the present study is

Table 1. Percentage resistance of *H. parainfluenzae* isolates collected over a 42-month period in the private sector of KwaZulu-Natal and Gauteng provinces.

Year	2012	2013	2014	2015	[a]P values
Antibiotic		**Resistance Percentages**			
[b]Ampicillin	14	12.6	10.9	9.3	<0.0002[#]
[c]Fluoroquinolones	4.1	9.3	18	21.4	<0.0002[#]
Telithromycin	8.4	7.3	9.1	15.4	<0.0001[#]
Total No. Isolates	1048	1275	1664	816	

[a]P values for the trends based on Chi-square test for trend determined using Graphpad prism 5 (version 5.01 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com), [b]Ampicillin and Amoxicillin, [c]Moxifloxacin, Ciprofloxacin, and Levofloxacin, [#] statistically significant.

Table 2. Percentage resistance of *H. influenzae* isolates collected over a 42-month period in the private sector of KwaZulu-Natal and Gauteng provinces.

Year	2012	2013	2014	2015	[a]P values
Antibiotic		**Resistance Percentage**			
[b]Ampicillin	10.29	10.77	9.72	8.52	<0.0613[*]
[c]Fluoroquinolones	0.18	0.62	1.47	1.01	<0.0001[#]
Telithromycin	0.59	1.4	1.65	2.95	<0.0001[#]
Total No. Isolates	3390	4253	4958	1889	

[a]P values for the trend based on Chi-square test for trend determined using Graphpad prism 5 (version 5.01 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com), [b]Ampicillin and Amoxicillin, [c]Moxifloxacin, Ciprofloxacin, and Levofloxacin, [*] not statistically significant, [#] statistically significant.

consistent with the United States and Brazilian findings. However, the isolates from the private sector of South Africa show a higher resistance rate to ampicillin, currently 8.52% (Table 2).

The resistance trend of *H. parainfluenzae* detected in our study is comparable to the Chinese study results reported in 2013, which revealed up to 24% resistance to various fluoroquinolones [4]. In divergence with the present study results, the German study, mentioned earlier [3], documented 24% resistance of *Haemophilus* species to ampicillin and 1.6% resistance to levofloxacin and no resistance to ciprofloxacin, contrasting with the 9.3% (ampicillin) and 21.4% (ciprofloxacin, moxifloxacin and levofloxacin) resistance rate found in the present study. There is an urgent need to investigate the increasing fluoroquinolone resistance observed in *H. parainfluenzae* but not in *H influenzae.*

Fluoroquinolone resistance in *Haemophilus parainfluenzae* is mediated mainly by mutations in the chromosomal Topoisomerase II and Topoisomerase IV genes but can also be acquired via mobile genetic elements such as plasmids which allow dissemination between bacterial species [13]. The aforementioned phenomena can compromise the effectiveness of these drug classes in the treatment of infections. This is of a major concern in Kwazulu-Natal Province, which has the highest prevalence of HIV/AIDS patients with tuberculosis comorbidity in South Africa [14] as fluoroquinolones remain one of the backbones for the treatment of multidrug resistance tuberculosis (MDR TB).

Conclusions

There is an emerging fluoroquinolone resistance mainly in *Haemophilus parainfluenzae* isolates from the private sector that requires urgent investigation as this ability could be transferred to more clinically relevant bacterial species such as *H. influenzae* and *Mycobacterium tuberculosis,* in which fluoroquinolones remain the backbone for treatment. Ketolide (telithromycin) resistance in these microbes is also emerging and needs to be monitored carefully in order to enhance antibiotic stewardship in Kwazulu-Natal and Gauteng provinces of South Africa.

Limitations to Study

The isolates could not be analyzed by source or syndrome, nor we are certain that duplicates have been omitted, as this information was not available.

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