In the present study, the clinician decided whether the CNS isolate represented a true bacteraemic episode. This did not change treatment decisions, or disrupt patient care. There was no evidence for increased resistance trends, nor did vancomycin utilisation increase more than would be expected, since there were also more patients with central venous catheters, more foreign body-related infections, and more infections overall caused by CNS, *Enterococcus* spp. and methicillin-resistant *Staphylococcus aureus*. Increased vancomycin use cannot, therefore, result solely from the absence of routine AST of blood culture CNS isolates. Ongoing review has validated this practice and it is now laboratory policy. The laboratory is now also performing AST only upon request for CNS isolates from central venous catheters in the same patient populations.

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RESEARCH NOTE

Activity of five quinolones, three macrolides and telithromycin against 12 *Haemophilus influenzae* strains with different resistance phenotypes

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ABSTRACT

Gemifloxacin MICs for 12 *Haemophilus influenzae* strains with different resistance phenotypes were 0.001–0.015 mg/L. Gemifloxacin was bactericidal against all 12 strains after 24 h at 2 × MIC. Ciprofloxacin, levofloxacin, gatifloxacin and

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moxifloxacin had MICs of 0.008–0.03 mg/L and similar kill kinetics. Macrolides and telithromycin had unimodal MICs (1.0–8.0 mg/L), except for two strains without efflux systems (0.0125–0.5 mg/L) and two with efflux systems and ribosomal protein mutations (> 64.0 mg/L), and were bactericidal against eight to ten strains tested at 2 × MIC after 24 h.

Keywords *Haemophilus influenzae*, kill kinetics, macrolides, quinolones, resistance, telithromycin

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Haemophilus influenzae, together with *Streptococcus pneumoniae* and *Moraxella catarrhalis*, is a major cause of community-acquired respiratory infections in children and adults, including pneumonia, acute exacerbations of chronic bronchitis, sinusitis and otitis media [1–6]. In countries where the *H. influenzae* type b vaccine is used widely, such as the USA, *H. influenzae* type b has been replaced in many infections by untypeable *H. influenzae* strains [2–4,7].

The major resistance mechanism in *H. influenzae* in the USA and Europe is β-lactamase production (TEM-1, ROB-1). The incidence of β-lactamase-negative ampicillin-resistant strains in the USA is < 1%, but is higher in Japan [8] and France [9]. Of the β-lactams available for treatment of *H. influenzae* infections, cefixime and cefpodoxime are the most active from both an MIC and pharmacokinetic/pharmacodynamic viewpoint, followed by amoxycillin–clavulanate and cefuroxime. Among macrolides and azalides, azithromycin has the lowest MIC for *H. influenzae*, followed by erythromycin and clarithromycin [3,4,10]. However, the pharmacokinetic and pharmacodynamic properties of these compounds, and the results of double-tap otitis media studies, cast doubt on their clinical efficacy against *H. influenzae* [3–6]; additionally, a macrolide efflux mechanism has been described in 'baseline' *H. influenzae* strains, and added ribosomal protein mutations in macrolide-hyper-resistant strains [11–13]. Quinolone resistance in *H. influenzae* is still very rare [7,10,14].

To cast further light on the utility of quinolones vs. macrolides and ketolides for the treatment of community-acquired respiratory tract infections, macrobroth and time-kill methodology was used to examine the activities of ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, gemifloxacin, erythromycin, azithromycin, clarithromycin and telithromycin against 12 *H. influenzae* strains with different β-lactam and macrolide resistance phenotypes. Of the 12 strains tested, two each were β-lactamase-positive, β-lactamase-negative, β-lactamase-negative and ampicillin-resistant with mutations in PBP3 [8], β-lactamase positive and amoxycillin–clavulanate-resistant (PBP3 mutations plus TEM-1 production) [8], macrolide-hyper-susceptible without a carbonyl cyanide m-chlorophenylhydrazone-dependent macrolide efflux mechanism, and macrolide-hyper-resistant with an efflux mechanism plus one or more ribosomal protein mutations [11–13]. m-Chlorophenylhydrazone is a mitochondrial protonophore that uncouples oxidative phosphorylation, and thus inhibits efflux [11–13]. Strains were stored frozen in double strength skimmed milk (Difco, Detroit, MI, USA) before testing. Drugs were obtained from their respective manufacturers.

Time-kill studies were performed as described previously [10,15–17]. Glass tubes containing 5 mL of freshly made *Haemophilus* test medium containing doubling antibiotic concentrations were inoculated with *c.* 5×10^5 to 5×10^6 CFU/mL and incubated at 35°C in a shaking water bath. Viability counts of antibiotic-containing suspensions were performed at 0, 3, 6, 12 and 24 h by plating ten-fold dilutions of 0.1-mL aliquots from each tube in sterile *Haemophilus* test medium on to chocolate agar plates (BBL Microbiology Systems, Cockeysville, MD, USA). Recovery plates were incubated for up to 48 h. Colony counts were performed on plates yielding 30–300 colonies [10,15–17]. The lower limit of sensitivity of colony counts was 300 CFU/mL. Results were analysed by determining the number of strains that yielded a $\Delta \log_{10}$ CFU/mL of −1, −2 and −3 dilutions at each of the time-points, compared with counts at 0 h. Antibacterial agents were considered bactericidal at the lowest concentration that reduced the original inoculum by $\geq 3 \times \log_{10}$ CFU/mL (99.9%) at each of the time-points, and were considered bacteriostatic if the inoculum was reduced by $< 3 \times$ CFU/mL [10,15–17]. MICs were determined by the macrobroth method [18]. Erythromycin, azithromycin, clarithromycin and telithromycin kill kinetics were not determined for the two strains with efflux systems plus ribosomal protein mutations.

Table 1. MICs (mg/L) of 12 strains of *Haemophilus influenzae*

	Phenotype											
Drug	1 β-lac$^+$, MBL	2 β-lac$^+$, MBL	3 β-lac$^-$, MBL	4 β-lac$^-$, MBL	5 BLNAR, MBL	6 BLNAR MBL	7 BLPACR, MBL	8 BLPACR, MBL	9 MHS	10 MHS	11 MHR	12 MHR
Ciprofloxacin	0.015	0.015	0.008	0.015	0.015	0.015	0.008	0.015	0.008	0.008	0.008	0.008
Levofloxacin	0.03	0.03	0.008	0.03	0.015	0.03	0.015	0.03	0.015	0.008	0.015	0.015
Gatifloxacin	0.015	0.03	0.015	0.03	0.015	0.015	0.015	0.015	0.004	0.008	0.008	0.008
Moxifloxacin	0.03	0.015	0.015	0.06	0.015	0.03	0.03	0.015	0.008	0.008	0.008	0.015
Gemifloxacin	0.015	0.015	0.004	0.008	0.002	0.002	0.004	0.008	0.004	0.001	0.002	0.002
Erythromycin	8.0	8.0	4.0	8.0	4.0	4.0	4.0	4.0	0.5	0.25	> 64	> 64
Azithromycin	2.0	2.0	1.0	2.0	2.0	1.0	1.0	1.0	0.12	0.25	> 64	> 64
Clarithromycin	8.0	8.0	8.0	8.0	8.0	4.0	4.0	8.0	0.25	0.25	> 64	> 64
Telithromycin	2.0	2.0	1.0	1.0	2.0	4.0	1.0	2.0	0.12	0.12	> 64	> 64

β-lac$^+$, β-lactamase-positive; β-lac$^-$, β-lactamase-negative; BLNAR, β-lactamase-negative, ampicillin-resistant; BLPACR, β-lactamase-positive, amoxycillin–clavulanate-resistant; MHS, macrolide-hyper-susceptible; MHR, macrolide-hyper-resistant; MBL, strains with 'baseline' macrolide MICs and efflux mechanisms.

Table 2. Number of *Haemophilus influenzae* strains yielding the indicated reduction in $\log_{10}$ CFU/mL following incubation

	3 h			6 h			12 h			24 h		
Drug	90% killing	99% killing	99.9% killing	90% killing	99% killing	99.9% killing	90% killing	99% killing	99.9% killing	90% killing	99% killing	99.9% killing
Ciprofloxacin												
4 × MIC	12	5	0	12	8	3	12	12	9	12	12	12
2 × MIC	12	2	0	12	5	1	12	12	9	12	12	12
MIC	4	1	0	12	1	1	12	12	4	12	11	11
Levofloxacin												
4 × MIC	12	7	1	12	10	4	12	12	10	12	12	12
2 × MIC	11	4	0	12	9	2	12	12	9	12	12	12
MIC	9	0	0	11	4	0	11	10	5	10	10	9
Gatifloxacin												
4 × MIC	12	9	2	12	12	5	12	12	12	12	12	12
2 × MIC	11	4	1	12	10	2	12	12	8	12	12	12
MIC	8	1	0	11	4	1	12	12	5	10	10	9
Moxifloxacin												
4 × MIC	12	8	4	12	11	7	12	12	11	12	12	12
2 × MIC	11	4	2	12	10	3	12	12	10	12	12	12
MIC	6	3	1	9	5	2	12	10	5	11	11	10
Gemifloxacin												
4 × MIC	12	2	0	12	8	2	12	12	10	12	12	12
2 × MIC	9	2	0	12	4	2	12	10	7	12	12	12
MIC	4	1	0	11	4	1	11	9	4	11	10	9
Erythromycin[a]												
4 × MIC	8	3	0	9	8	3	10	10	9	10	10	10
2 × MIC	5	0	0	9	5	2	10	8	6	10	9	8
MIC	3	0	0	7	2	0	8	6	5	9	8	7
Azithromycin[a]												
4 × MIC	9	5	1	10	9	5	10	10	10	10	10	10
2 × MIC	9	3	1	9	8	4	10	9	9	10	10	10
MIC	5	1	0	6	4	2	9	8	5	10	10	7
Clarithromycin[a]												
4 × MIC	7	2	0	9	7	2	10	10	8	10	10	10
2 × MIC	3	2	0	7	5	1	10	8	5	10	10	10
MIC	1	0	0	7	3	1	7	5	4	9	7	5
Telithromycin[a]												
4 × MIC	7	2	0	9	7	3	10	9	8	10	10	10
2 × MIC	5	1	0	9	5	0	10	9	6	10	10	10
MIC	3	0	0	6	3	0	10	6	3	9	9	8

[a]Only ten of 12 strains tested.

MICs for the strains tested are listed in Table 1, and results of the time-kill experiments are shown in Table 2. All quinolones were active against all 12 strains tested. Gemifloxacin MICs were 0.001–0.015 mg/L, while ciprofloxacin, levofloxacin, gatifloxacin and moxifloxacin MICs were 0.008–0.03 mg/L. Macrolides and telithromycin gave unimodal MICs (1.0–8.0 mg/L), except for two strains without efflux systems (0.0125–0.5 mg/L) and two strains with efflux systems and ribosomal protein mutations (> 64.0 mg/L).

All quinolones showed similar kill kinetics, with bactericidal activity after 12 h at 2 × MIC for seven to ten strains, and at 2 × MIC after 24 h for all 12 strains. In comparison, erythromycin, azithromycin and clarithromycin were bactericidal against eight to ten strains (excluding the two strains with ribosomal protein mutations) at

2 × MIC after 24 h, with bactericidal activity against five to nine strains at 2 × MIC after 12 h. Telithromycin was bactericidal against all ten strains tested at 2 × MIC after 24 h, and against six strains at 2 × MIC after 12 h.

The results demonstrate excellent activity, as well as kill kinetics, for all quinolones tested against all 12 *H. influenzae* strains tested, irrespective of their β-lactam or macrolide resistance phenotype. Erythromycin, azithromycin, clarithromycin and telithromycin had unimodal MIC distributions and good kill kinetics. The results reflect those reported in previous studies of *H. influenzae* strains with 'baseline' macrolide susceptibility [10,15–17,19–21]. The differences of opinion as to the clinical efficacy of this group of drugs against *H. influenzae* have been mentioned above. In addition, the propensity of fully penicillin-resistant (MIC > 2.0 mg/L) pneumococcal strains to be resistant to erythromycin, azithromycin and clarithromycin [4] is another reason why this group of drugs may not be ideal first-choice drugs for empirical therapy of community-acquired respiratory tract infections in areas of the world where drug-resistant pneumococci are common. Typically, 75% of fully penicillin-resistant strains are also resistant to macrolides [4]. Telithromycin, which has been licensed for use in the USA, has lower MICs and better pharmacokinetics and pharmacodynamics against macrolide-resistant pneumococci [15,17], but definitive pharmacokinetic/pharmacodynamic properties and clinical efficacy against *H. influenzae* have not yet been established satisfactorily (W. A. Craig, personal communication). Efflux mechanisms for telithromycin, similar to those described previously [12,13] for erythromycin, azithromycin and clarithromycin, have recently been identified in our laboratory (T. Bogdanovich *et al.*, unpublished results).

Broad-spectrum quinolones, such as gemifloxacin, levofloxacin, gatifloxacin and moxifloxacin, provide a more rational alternative, especially for 5-day treatment of acute exacerbations of chronic bronchitis in the elderly [22], in which *H. influenzae* is the major pathogen [2,22]. Gemifloxacin has the added advantages of being very potent against pneumococci, including many quinolone-resistant strains, and of targeting both pneumococcal DNA gyrase and topoisomerase IV, resulting, theoretically, in a lower likelihood of selecting resistant mutants [22].

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RESEARCH NOTE

Analysis of the mechanisms of resistance to several antimicrobial agents in *Shigella* spp. causing travellers' diarrhoea

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ABSTRACT

Eighty isolates of *Shigella* spp. (37 *Shigella flexneri* and 43 *Shigella sonnei*) from patients with travellers' diarrhoea were studied. Susceptibility tests revealed high levels of resistance, especially to ampicillin (65%), tetracycline (78%) and trimethoprim (75%), and particularly among the *S. flexneri* isolates. Dihydrofolate reductase 1 genes (*dfrA1*) were prevalent among the trimethoprim-resistant isolates, while *oxa* genes predominated among the ampicillin-resistant isolates. Chloramphenicol resistance was associated with production of chloramphenicol acetyltransferase, while nalidixic acid-resistant isolates had a single mutation in the *gyrA* gene. The results indicate a continuing need for resistance surveillance and rational use of antimicrobial agents.

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The increase in intercontinental travel to exotic destinations has resulted in infection by *Shigella* spp. becoming an important cause of travellers' diarrhoea (TD). Although the incidence of TD caused by *Shigella* spp. is much lower than that of TD caused by the main aetiological agent (i.e., enterotoxigenic *Escherichia coli*), *Shigella* causes a more severe disease with greater morbidity. Furthermore, *Shigella* spp. have been progressively acquiring resistance to most of the antibiotics used for the treatment of infections, partly because of their ability to acquire resistance genes located on plasmids or transposons [1]. However, other socioeconomic and behavioural factors have also contributed to this increase in resistance [2]. Increased international travel means that the appearance of multiresistant pathogenic strains anywhere in the world can rapidly become a public health problem in other countries. Thus, the treatment decision for shigellosis in developed countries is now commonly influenced by the patient's travel history [3]. The present report describes the susceptibility patterns and mechanisms of resistance in *Shigella* spp. with various geographical origins, isolated from patients with TD.

Shigella isolates were obtained between 1995 and 2000 from the stool samples of patients presenting with TD at the Hospital Clinic, Barcelona, Spain. Isolates were identified to the genus and species level by conventional biochemical methods [4] and agglutination with specific