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Susceptibilities of *Legionella* spp. to Newer Antimicrobials In Vitro

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The in vitro activities of 13 antimicrobial agents against 30 strains of *Legionella* spp. were determined. Rifapentine, rifampin, and clarithromycin were the most potent agents (MICs at which 90% of isolates are inhibited [MIC_{90}s], ≤0.008 μg/ml). The ketolide HMR 3647 and the fluoroquinolones levofloxacin and BAY 12-8039 (MIC_{90}s, 0.03 to 0.06 μg/ml) were more active than erythromycin A or roxithromycin. The MIC_{90}s of dalfopristin-quinupristin and linezolid were 0.5 and 8 μg/ml, respectively. Based on class characteristics and in vitro activities, several of these agents may have potential roles in the treatment of *Legionella* infections.

The array of antimicrobial agents useful for the treatment of serious infections caused by *Legionella* spp. is limited. This is in part due to the relative resistance of *Legionella* spp. to a variety of antimicrobial agents and to the fact that these organisms are obligate intracellular pathogens and, thus, to be effective, the drugs must be able to penetrate into phagocytic cells (22).

Erythromycin, rifampin, and fluoroquinolones have proven in vitro and in vivo efficacies and are used to treat clinical *Legionella* infections (23, 26). Mortality is still high in those with nosocomial pneumonia, especially immunocompromised and bacteremic patients (14), so there is a need for a wider range of suitable antibiotics to treat severe *Legionella* infections.

This study examined the in vitro activities of several newer antimicrobial agents, including a ketolide, two fluoroquinolones, two oxazolidinones, rifapentine, and dalfopristin-quinupristin, against *Legionella* spp., an initial step in assessing their potential usefulness as therapeutic agents.

(This work was presented in part at the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, Canada, 28 September to 1 October 1997 [33]).

Thirty clinical isolates of *Legionella* spp. were tested, including 21 *L. pneumophila*, 3 *L. longbeacheae*, 2 *L. bozemanii*, and 2 *L. dumoffii* isolates and one strain each of *L. micdadei* and *L. gormanii*. Strains were referred to our collection from various sources over several years and were kept frozen at −80°C.

Antimicrobial test substances and their sources are as follows. HMR 3647, erythromycin A, clarithromycin, roxithromycin, rifampin, rifapentine, and levofloxacin were gifts from Hoechst-Marion-Roussel, Romainville, France; eperezolid (U-100592) and linezolid (U-100766) were gifts from Pharmacia & Upjohn Company Laboratories, Kalamazoo, Mich.; dalfopristin-quinupristin was provided by Rhône-Poulenc Rorer Pharmaceuticals, Collegeville, Pa.; and BAY 12-8039 was a gift of Bayer Inc., West Haven, Conn. Clindamycin hydrochloride and doxycycline hydrochloride were purchased from Sigma Chemical Company, St. Louis, Mo.

Agar dilution susceptibility testing was performed on the buffered starch-yeast extract (BSYE) agar medium described by Saito et al. (32). Buffered charcoal-yeast extract medium (BCYE) has been shown to impair the activities of several antimicrobial substances (i.e., macrolides, rifampin, and fluoroquinolones) in earlier studies (3, 6, 12), so this medium was only used to subcultivate strains twice after thawing them from their −80°C storage temperature and as a growth control.

To prepare inocula, several colonies were taken from BCYE plates (Remel, Lenexa, Kans.) after 48 h of incubation and were suspended in sterile water to a turbidity corresponding to a 0.5 McFarland standard, which yielded a cell density of approximately 10^8 CFU/ml. Suspensions of bacteria were then further diluted 1:10 in sterile water for the smaller inoculum. Final inocula of 10^5 and 10^4 CFU/spot were applied to freshly made antibiotic-containing plates with a multiprong replicator device. Between each antibiotic, antibiotic-free plates were stamped to avoid carryover, and a blood agar plate was also inoculated at the end of each run to exclude contamination by other bacteria.

Plates were incubated at 35°C in ambient air and were read after 48 and 96 h. Spots yielding the growth of single colonies and those with a faint haze were considered to be negative.

Table 1 shows the results for the 48-h incubation time for both inocula. For most agents, a twofold increase in the MIC at which 90% of the isolates were inhibited (MIC_{90}) was observed when the plates were examined after 96 h of incubation (Table 2). Such results may reflect either incomplete inhibition of growth at a particular antibiotic dilution or the loss of antimicrobial potency with prolonged incubation. Subsequent comments will be directed to results of the 48-h readings. With the larger inoculum, all strains grew on BSYE agar as well as on BCYE agar, whereas with the smaller inoculum, three to six strains yielded insufficient growth on control plates and therefore were excluded from the analysis. These findings are consistent with results from other studies, which showed that BSYE agar does not support the growth of some *Legionella* species as well as does BCYE agar (4, 15). Table 3 compares the MICs of several antimicrobial agents tested against *Legionella* spp., obtained in different studies using different media and methods.

Erythromycin, probably the most widely used drug for treatment of *Legionella* pneumonia (14, 27), inhibited all strains at ≤0.25 and ≤0.5 μg/ml with the small and the large inocula, respectively. Those data were comparable to erythromycin A MICs obtained previously in our laboratory (7).

A new ketolide designated HMR 3004 has been shown to

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TABLE 1. Comparison of in vitro activities of 13 antimicrobial agents against *Legionella* spp., determined at 48 h of incubation

Antibiotic	No. of strains tested with inoculum of 10^4[a]	MIC (μg/ml) at inoculum size shown (CFU/spot)					
		Range		MIC_{50}		MIC_{90}	
		10^4	10^5	10^4	10^5	10^4	10^5
HMR 3647	27	≤0.004–0.06	≤0.004–0.12	0.008	0.015	0.03	0.03
Erythromycin A	27	0.008–0.25	0.06–0.5	0.03	0.12	0.12	0.12
Clarithromycin	27	≤0.004	≤0.004–0.03	≤0.004	≤0.004	≤0.004	≤0.004
Roxithromycin	27	≤0.004–0.06	0.03–0.25	0.015	0.06	0.03	0.12
Levofloxacin	27	≤0.004–0.03	0.015–0.06	0.008	0.015	0.015	0.03
BAY 12-8039	27	0.015–0.06	0.03–0.12	0.03	0.03	0.06	0.06
Rifampin	27	≤0.0005–0.015	≤0.0005–0.015	≤0.0005	≤0.0005	0.002	0.008
Rifapentine	27	≤0.001–0.002	≤0.001–0.002	≤0.001	≤0.001	≤0.001	0.002
Dalfopristin-quinupristin	24	0.015–0.05	0.12–1	0.12	0.25	0.5	0.5
Doxycycline	24	0.5–2	1.0–8.0	1	4	2	8
Eperezolid	24	1.0–8	2–≥16	1	4	4	≥16
Linezolid	24	1.0–4	4.0–8	2	4	4	8
Clindamycin	27	0.008–8	1.0–16	2	8	8	8

[a] $n = 30$ strains for the larger inoculum in all cases.

reach high intracellular concentrations in phagocytes; therefore, agents of this class may be of potential therapeutic use against intracellular pathogens like *Legionella* spp. (1). The ketolide tested here, HMR 3647, inhibited 90% of all organisms at concentrations of 0.03 μg/ml and thus showed fourfold-higher activity than erythromycin A. These data complement a study by Bornstein et al. (5), who found HMR 3004 to be active against *Legionella* spp. with a range of MICs virtually identical to those obtained for HMR 3647 in our study (MIC, ≤0.03 to 0.12 μg/ml) when performed by the agar dilution technique on a different medium (buffered antibiotic medium no. 1). Clarithromycin was the most potent macrolide in our study, exhibiting an MIC_{90} of ≤0.004 μg/ml with both inocula.

Rifampin is used in combination with other drugs in severe or refractory cases of legionellosis (13). In a number of comparative studies, it was the most active drug tested (6, 10, 24). In the present study, 90% of isolates were inhibited at concentrations of 0.008 μg/ml with the larger inoculum. Rifapentine is a newly developed agent related to rifampin. The MIC_{90} of this drug was 0.002 μg/ml, fourfold lower than that of rifampin, with the large inoculum. All strains of *L. pneumophila* were inhibited at the lowest concentrations of rifampin and rifapentine tested, 0.0005 and 0.001 μg/ml, respectively. The MICs of rifampin and rifapentine for other species ranged from 0.0005 to 0.015 μg/ml and from 0.001 to 0.002 μg/ml, respectively, after 48 h of incubation.

Fluoroquinolones have been shown to be highly effective in vitro (17), and they have also been shown to inhibit the growth of legionellae in alveolar macrophage systems and in experimental treatment models of *L. pneumophila* pneumonia in guinea pigs (9, 16, 18). Moreover, fluoroquinolones have been used clinically for treatment of *Legionella* pneumonia (35). In the present study, the MIC_{90}s for BAY 12-8039 and levofloxacin were 0.06 and 0.03 μg/ml, respectively, with the larger inoculum. The MICs for levofloxacin were two to three times higher in a study by Baltch et al. (2), but their study utilized BCYE agar, which is known to inhibit the activity of certain antimicrobial agents, especially fluoroquinolones (17). In experimental Legionnaires' disease in guinea pigs, levofloxacin appeared to be as active as ofloxacin, which was superior to ciprofloxacin and erythromycin (11, 31). Our data for BAY 12-8039 were comparable to those reported by Ruckdeschel et al. (30); in the latter study, a larger inoculum was used (10^8 CFU/spot).

The streptogramin combination dalfopristin-quinupristin inhibited 90% of all isolates at a concentration of 0.5 μg/ml. The overall MICs were two- to fourfold higher than those of erythromycin A, which is consistent with a report by Johnson et al. (24), in which they showed the same correlation between those two drugs with a larger inoculum (10^6 CFU/spot). In contrast, in a study by Dubois and Joly (10), dalfopristin-quinupristin demonstrated twofold-higher activity than erythromycin against some *Legionella* species. A possible role for this drug in the treatment of legionellosis is supported by reports which showed high intracellular accumulation and activity against intracellular staphylococci (8); however, the activity of dalfopristin-quinupristin against intracellular enterococci was modest (21).

The oxazolidinones linezolid (U-100766) and eperezolid (U-100592) are recently developed antimicrobial agents which have shown therapeutic potential based on in vitro activity against various respiratory pathogens, including multidrug-resistant pneumococci, streptococci, staphylococci, *Haemophilus* spp., and *Moraxella* spp. (25, 34, 36). At the smaller inoculum, 90% of the legionellae tested were inhibited by a 4-μg/ml concentration of each drug, a concentration equivalent to MICs

TABLE 2. Comparison of MIC_{90}s at 48 and 96 h of incubation for inocula of 10^4 and 10^5 CFU/spot

Antibiotic	MIC 90 (μg/ml) at time point and inoculum indicated			
	48 h		96 h	
	10^4	10^5	10^4	10^5
HMR 3647	0.03	0.03	0.06	0.06
Erythromycin A	0.12	0.12	0.25	0.25
Clarithromycin	≤0.004	≤0.004	≤0.004	0.015
Roxithromycin	0.03	0.12	0.06	0.12
Dalfopristin-quinupristin	0.5	0.5	0.5	1
Levofloxacin	0.015	0.03	0.03	0.03
BAY 12-8039	0.06	0.06	0.12	0.12
Rifampin	0.002	0.008	0.004	0.008
Rifapentine	≤0.001	0.002	0.002	0.004
Doxycycline	2	8	8	16
Eperezolid	4	≥16	16	≥16
Linezolid	4	8	8	16
Clindamycin	8	8	16	16

TABLE 3. Comparison of methods used and MICs of antimicrobial agents tested against *Legionella* spp. in different studies

Medium[a]	Inoculum (CFU/spot)	Incubation time (h)	MIC_{90}, MIC_{90} range, or geometric mean MIC (μg/ml) for:					Reference
			Erythromycin	Rifampin	Ciprofloxacin	Levofloxacin	Dalfopristin-quinupristin	
BSYE	$10^4/10^5$	48	0.12	0.002/0.008	d.n.a.[d]	0.015/0.03	0.5	This study
BCYE	10^4	48	1	≤0.004	d.n.a.	0.125	d.n.a.	2[e]
BCYE	10^4	72	d.n.a.	0.03–0.125	d.n.a.	d.n.a.	d.n.a.	3[e]
LHRC-BYE	10^4	72	d.n.a.	0.00035–0.00075	d.n.a.	d.n.a.	d.n.a.	3[e]
BAM_1	6×10^5	72	0.25[b]	d.n.a.	d.n.a.	d.n.a.	d.n.a.	4
BCYE	6×10^5	72	0.12[b]	d.n.a.	d.n.a.	d.n.a.	d.n.a.	4
BYE	6×10^5	72	0.12[b]	d.n.a.	d.n.a.	d.n.a.	d.n.a.	4
BCYE	10^5	48	1	0.008	2	d.n.a.	d.n.a.	6
BSYE	10^5	48	0.5	≤0.002	0.125	d.n.a.	d.n.a.	6
BYE	10^4	48	0.25–1[c]	≤0.004–0.008[c]	0.01–0.12[c]	d.n.a.	0.12–0.5[c]	10[e]
CYE	$10^4/10^5$	72	0.25/0.5	0.125/0.125	d.n.a.	d.n.a.	d.n.a.	15[e]
BCYE	10^4	96	≥2	0.5	2	d.n.a.	d.n.a.	17
BSYE	10^4	96	0.5	≤0.015	≤0.06	d.n.a.	d.n.a.	17
BSYE	10^6	48	0.5	0.008	0.06	d.n.a.	1	24[e]
BCYE	10^4	48	1	d.n.a.	1	0.5	d.n.a.	29[e]
BSYE	10^6	48	0.06	d.n.a.	0.015	0.015	d.n.a.	29[e]

[a] Abbreviations: LHRC, lysed horse red cell; BYE, buffered yeast extract; BAM_1, buffered antibiotic medium no. 1; CYE, charcoal-yeast extract.
[b] Geometric mean MIC.
[c] MIC_{90} range.
[d] d.n.a., data not available.
[e] Data for *L. pneumophila.*

for other presumptively susceptible organisms. However, at the larger inoculum, the MIC_{90}s of the agents were 8 and ≥16 μg/ml, respectively. Unless there was evidence for intracellular accumulation in phagocytes, such in vitro data would not suggest that these specific oxazolidinones would be likely candidates for treatment of *Legionella* infections.

At the smaller and larger inocula, doxycycline inhibited 90% of strains at 2 and 8 μg/ml, respectively, after 48 h of incubation. MICs of 8 μg/ml would indicate intermediate susceptibility (7). Nevertheless, doxycycline showed activity against *L. pneumophila* in intracellular monocyte experiments when added at concentrations of 0.4 μg/ml (20). It was also shown to be therapeutically effective in a guinea pig model of experimental legionellosis (28) and showed clinical efficacy in the treatment of human legionellosis (14). It is known that tetracyclines accumulate in human neutrophils (19), and such discrepancies between in vitro activity and therapeutic results exemplify the potential pitfalls in predicting clinical effectiveness from in vitro data alone.

This study identified several new antimicrobial agents with in vitro activities against legionellae that were higher than that of the widely used agent erythromycin. To further explore the potential applicability of these in vitro findings to the clinical setting, intracellular susceptibility testing and animal model studies would be of interest.

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REFERENCES

1. **Agouridas, C., A. Bonnefoy, K. Braham, P. Collette, M. Guitton, A. Hochet, P. Mauvais, and J. F. Chantot.** 1995. RU 004: uptake in phagocytes, intracellular bioactivity and other immunomodulatory effects, abstr. F175, p. 143. *In* Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
2. **Baltch, A. L., R. P. Smith, and W. Ritz.** 1995. Inhibitory and bactericidal activities of levofloxacin, ofloxacin, erythromycin, and rifampin used singly and in combination against *Legionella pneumophila*. Antimicrob. Agents Chemother. **39:**1661–1666.
3. **Barker, J., and I. D. Farrell.** 1986. The effect of charcoal on MICs for *Legionella*. J. Antimicrob. Chemother. **17:**127.
4. **Bornstein, N., C. Roudier, and J. Fleurette.** 1985. Determination of the activity on *Legionella* of eight macrolides and related agents by comparative testing on three media. J. Antimicrob. Chemother. **15:**17–22.
5. **Bornstein, N., H. Behr, Y. Brum, and J. Fleurette.** 1995. *In vitro* activity of RU 004 on *Legionella* species, abstr. F166, p. 142. *In* Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
6. **Chen, S. C. A., M. L. Paul, and G. L. Gilbert.** 1993. Susceptibility of *Legionella* species to antimicrobial agents. Pathology **25:**180–183.
7. **Collins, L. A., C. B. Wennersten, M. J. Ferraro, R. C. Moellering, Jr., and G. M. Eliopoulos.** 1994. Comparative activities of piperacillin and tazobactam against clinical isolates of *Legionella* spp. Antimicrob. Agents Chemother. **38:**144–146.
8. **Desnottes, J. F., and N. Diallo.** 1992. Cellular uptake and intracellular bactericidal activity of RP 59500 in murine macrophages. J. Antimicrob. Chemother. **30**(Suppl. A)**:**107–115.
9. **Dournon, E., P. Rajagopalan, J. L. Vilde, and J. J. Pocidalo.** 1986. Efficacy of pefloxacin in comparison with erythromycin in the treatment of experimental guinea pig legionellosis. J. Antimicrob. Chemother. **17**(Suppl. B)**:**41–48.
10. **Dubois, J., and J. R. Joly.** 1992. In vitro activity of RP 59500, a new synergistic antibacterial agent, against *Legionella* spp. J. Antimicrob. Chemother. **30**(Suppl. A)**:**77–81.
11. **Edelstein, P. H., M. A. C. Edelstein, K. H. Lehr, and J. Ren.** 1996. In-vitro activity of levofloxacin against clinical isolates of *Legionella* spp., its pharmacokinetics in guinea pigs, and use in experimental *Legionella pneumophila* pneumonia. J. Antimicrob. Chemother. **37:**117–126.
12. **Edelstein, P. H.** 1991. Rifampin resistance of *Legionella pneumophila* is not increased during therapy for experimental Legionnaires disease: a study of rifampin resistance using a guinea pig model of Legionnaires disease. Antimicrob. Agents Chemother. **35:**5–9.
13. **Edelstein, P. H.** 1993. Legionnaires' disease. Clin. Infect. Dis. **16:**741–749.
14. **Edelstein, P. H.** 1995. Antimicrobial chemotherapy for Legionnaires' disease: a review. Clin. Infect. Dis. **21**(Suppl. 3)**:**S265–S276.
15. **Edelstein, P. H., and R. D. Meyer.** 1980. Susceptibility of *Legionella pneumophila* to twenty antimicrobial agents. Antimicrob. Agents Chemother. **18:**403–408.
16. **Edelstein, P. H., M. A. C. Edelstein, J. Weidenfeld, and M. B. Dorr.** 1990. In vitro activity of sparfloxacin (CI-978; AT-4140) for clinical *Legionella* isolates, pharmacokinetics in guinea pigs, and use to treat guinea pigs with *L. pneumophila* pneumonia. Antimicrob. Agents Chemother. **34:**2122–2127.
17. **Eliopoulos, G. M., E. Reiszner, M. J. Ferraro, C. B. Wennersten, and R. C. Moellering, Jr.** 1988. Effect of growth medium on activity of fluoroquinolones and other antimicrobial agents against *Legionella* species. Rev. Infect. Dis. **10**(Suppl. 1)**:**S56.
18. **Fitzgeorge, R. B., D. H. Gibson, R. Jepras, and A. Baskerville.** 1985. Studies on ciprofloxacin therapy of experimental Legionnaires' disease. J. Infect. **10:**194–203.
19. **Gabler, W. L.** 1991. Fluxes and accumulation of tetracyclines by human

blood cells. Res. Commun. Chem. Pathol. Pharmacol. **72:**39–51.
20. **Havlichek, D., L. Saravolatz, and D. Pohlod.** 1987. Effect of quinolones and other antimicrobial agents on cell-associated *Legionella pneumophila*. Antimicrob. Agents Chemother. **31:**1529–1534.
21. **Herrera-Insúa, I., K. Jacques-Palaz, B. E. Murray, and R. M. Rakita.** 1996. Intracellular activities of RP 59500 (quinupristin/dalfopristin) and sparfloxacin against *Enterococcus faecium*. Antimicrob. Agents Chemother. **40:**886–890.
22. **Horwitz, M. A., and S. C. Silverstein.** 1982. Legionnaire's disease bacterium (*Legionella pneumophila*) multiplies intracellulary in human monocytes. J. Clin. Invest. **66:**441–450.
23. **Horwitz, M. A., and S. C. Silverstein.** 1983. Intracellular multiplication of Legionnaires' disease bacteria (*Legionella pneumophila*) in human monocytes is reversely inhibited by erythromycin and rifampin. J. Clin. Invest. **71:**15–28.
24. **Johnson, D. M., M. E. Erwin, M. S. Barret, B. Brings Gooding, and R. N. Jones.** 1992. Antimicrobial activity of ten macrolide, lincosamine and streptogramin drugs tested against *Legionella* species. Eur. J. Clin. Microbiol. Infect. Dis. **11:**751–755.
25. **Mason, E. O., Jr., L. B. Lamberth, and S. L. Kaplan.** 1996. In vitro activities of oxazolidinones U-100592 and U-100766 against penicillin-resistant and cephalosporin-resistant strains of *Streptococcus pneumoniae*. Antimicrob. Agents Chemother. **40:**1039–1040.
26. **Meyer, R. D.** 1991. Role of quinolones in the treatment of legionellosis. J. Antimicrob. Chemother. **28:**623–625.
27. **Nguyen, M. H., J. E. Stout, and V. L. Yu.** 1991. Legionellosis. Infect. Dis. Clin. N. Am. **5:**561–584.
28. **Nowicki, M., J. C. Paucod, N. Bornstein, H. Meugnier, J. Freney, P. Isoard, and J. Fleurette.** 1987. Traitement par la doxycycline de la légionellose experimentale du cobaye infecté par aérosole. Pathol. Biol. **35:**865–869.
29. **Pendland, S. L., S. J. Martin, C. Chen, P. C. Schreckenberger, and L. H. Danziger.** 1997. Comparison of charcoal- and starch-based media for testing susceptibilities of *Legionella* species to macrolides, azalides, and fluoroquinolones. J. Clin. Microbiol. **35:**3004–3006.
30. **Ruckdeschel, G., and S. Lob.** 1996. In vitro activity of a new 8-methoxyquinolone, BAY 12-8039, against *Legionella* spp. in comparison to ciprofloxacin (CIP), erythromycin (ERY) and rifampin (RIF), abstr. F7, p. 101. *In* Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
31. **Saito, A., H. Koga, H. Shigeno, K. Watanabe, K. Mori, S. Kohno, Y. Shigeno, Y. Suzuyama, K. Yamaguchi, M. Hirota, et al.** 1986. The antimicrobial activity of ciprofloxacin against *Legionella* species and the treatment of experimental *Legionella* pneumonia in guinea pigs. J. Antimicrob. Chemother. **10:**251–260.
32. **Saito, A., K. Sawatari, Y. Fukuda, M. Nagasawa, H. Koga, A. Tomonaga, H. Nakazato, K. Fujita, Y. Shigeno, Y. Suzuyama, K. Yamaguchi, K. Izumikawa, and K. Hara.** 1985. Susceptibility of *Legionella pneumophila* to ofloxacin in vitro and in experimental *Legionella* pneumonia in guinea pigs. Antimicrob. Agents Chemother. **28:**15–20.
33. **Schülin, T., C. B. Wennersten, M. J. Ferraro, R. C. Moellering, Jr., and G. M. Eliopoulos.** 1997. Susceptibility of *Legionella* spp. to ketolide HMR 3647 and other newer antimicrobials, abstr. F-250, p. 188. *In* Abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
34. **Spangler, S. K., M. R. Jacobs, and P. C. Appelbaum.** 1996. Activities of RPR 106972 (a new oral streptogramin), cefditoren (a new oral cephalosporin), two new oxazolidinones (U-100592 and U-100766), and other oral and parental agents against 203 penicillin-susceptible and -resistant pneumococci. Antimicrob. Agents Chemother. **40:**481–484.
35. **Stout, J. E., and V. L. Yu.** 1997. Legionellosis. N. Engl. J. Med. **337:**682–687.
36. **Zurenko, G. E., B. H. Yagi, R. D. Schaadt, J. W. Allison, S. E. Glickman, D. K. Hutchinson, M. R. Barbachyn, and S. J. Brickner.** 1996. In vitro activity of U-100592 and U-100766, novel oxazolidinone antibacterial agents. Antimicrob. Agents Chemother. **40:**839–845.