KUCERS' THE USE OF ANTIBIOTICS

A CLINICAL REVIEW OF ANTIBACTERIAL, ANTIFUNGAL, ANTIPARASITIC AND ANTIVIRAL DRUGS

VOLUME 1

6TH EDITION

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN 978 0 340 927 670

M Lindsay Grayson MB BS MD MSC FRACP FRCP FAFPHM
Professor of Medicine and Director, Infectious Disease and Microbiology Departments, Austin Health
Department of Epidemiology and Preventive Medicine, Monash University
Department of Medicine, University of Melbourne, Melbourne, Australia

Suzanne M Crowe MBBS FRACP MD
Head, Centre for Virology, Burnet Institute for Medical Research and Public Health
Consultant Physician in Infectious Diseases and General Medicine, The Alfred Hospital
Professor of Medicine, Monash University, Victoria, Australia

James S McCarthy MD FRACP
Queensland Institute for Medical Research, University of Queensland
Department of Infectious Diseases, Royal Brisbane and Womens Hospital
Brisbane, Australia

John Mills MD FACP FRACP
Professor of Medicine, Microbiology & Epidemiology, Monash University and Consultant Physician in Infectious Diseases, The Alfred Hospital, Melbourne, Australia

Johan W Mouton MD PhD
Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, Nijmegen;
Department of Medical Microbiology, Radboud University Nijmegen Medical Center, The Netherlands

S Ragnar Norrby MD PhD FRCP
Professor Emeritus, Swedish Institute for Infectious Disease Control, Solna, Sweden

David L Paterson MBBS PhD FRACP FRCPA
Professor of Medicine, University of Queensland Centre for Clinical Research,
Consultant Physician, Infectious Diseases Unit, Royal Brisbane and Women's Hospital,
Consultant Clinical Microbiologist, Pathology, Queensland,
Brisbane, Queensland, Australia

Michael A Pfaller MD
Professor Emeritus, Departments of Pathology and Epidemiology, University of Iowa College of Medicine and College of Public Health, Iowa, USA

HODDER ARNOLD
AN HACHETTE UK COMPANY

Pages 819-824

63 Josamycin and Rosaramicin

Françoise Van Bambeke

1. DESCRIPTION

Josamycin and rosaramicin (rosamicin, rosamycin), together with spiramycin (see Chapter 182, Spiramycin), share the property of being constructed on a 16-atom macrocycle instead of a 14-atom macrocycle as most macrolides, or a 15-atom macrocycle as in azithromycin. Within this class, a series of molecules have been assessed clinically, with often only limited success. These include natural products, including spiramycin (isolated from *Streptomyces ambofaciens* (Kellow *et al.*, 1955)), josamycin (isolated from *S. narbonensis* var. *josamyceticus* (Nitta *et al.*, 1967)), rosaramicin, formerly called rosamicin (isolated from *Micromonospora rosaria* (Wagman *et al.*, 1972; Waitz *et al.*, 1972)), midecamycin (Kanazawa and Kuramata, 1976), and semisynthetic compounds such as miocamycin, derived from midecamycin (Omoto *et al.*, 1976; Kawaharajo *et al.*, 1981), and rokitamycin, derived from leucomycin A5 (Sakakibara *et al.*, 1981).

This chapter is limited to the description of josamycin (CAS number 16846-24-5; molecular formula $C_{42}H_{69}NO_{15}$; molecular weight 828.00), and rosaramicin (CAS number 35834-26-5; molecular formula $C_{31}H_{51}NO_9$; molecular weight 581.74). The chemical structures of these two agents are shown in Figure 63.1. Their spectrum of activity is similar to that of other macrolides.

2. ANTIMICROBIAL ACTIVITY

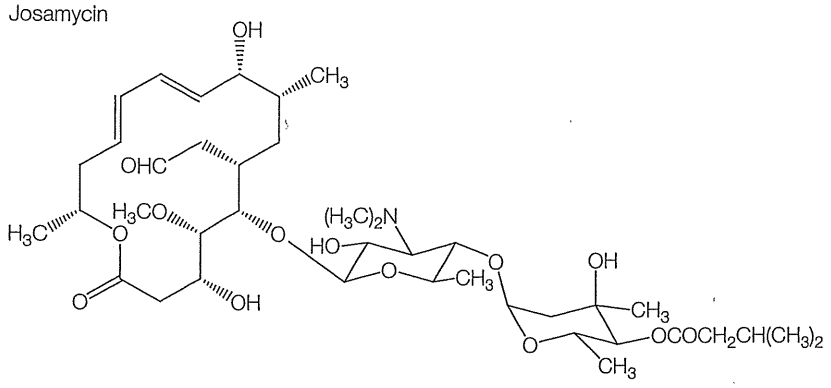
2a. Routine susceptibility

Macrolides are bacteriostatic antibiotics, characterized by a moderately broad spectrum of activity, which includes most Gram-positive but only selected Gram-negative organisms, as well as several bacteria responsible for intracellular infection, such as *Mycobacterium* spp., *Chlamydia* spp., *Chlamydophyla* spp., and or *Legionella* spp. Their activity is markedly reduced in acidic environments. Table 63.1 summarizes the susceptibilities observed for the most relevant target organisms.

Gram-positive bacteria

These drugs are active against bacteria such as *Staphylococcus aureus* (including beta-lactamase- producing strains), coagulase-negative staphylococci, *S. pyogenes*, *S. pneumoniae*, and most strains of *Enterococcus faecalis*. Josamycin is reported to be as active as or less active than erythromycin against *S. aureus* (Shadomy *et al.*, 1976; Strausbaugh *et al.*, 1976b; Westerman *et al.*, 1976). Rosaramicin is more potent than josamycin against *S. aureus* (Shadomy *et al.*, 1976),

Josamycin



Rosaramicin

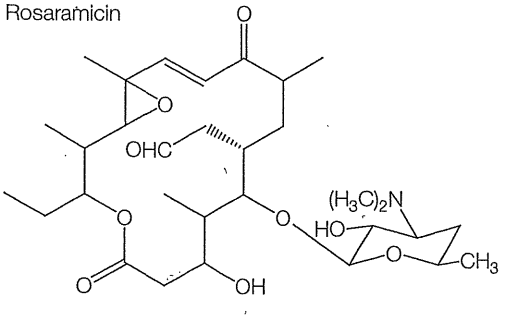


Figure 63.1 Chemical structure of josamycin and rosaramicin. Chemical stability in acid medium is due to absence of a keto group in position 9.

Table 63.1 *In vitro* activity (μg/ml) of josamycin against target bacteria.

Bacteria	Clinical isolates				Resistance issues	References
	Study period	range	MIC_{50}	MIC_{90}		
Staphylococcus aureus	<1997 (Munich Germany)	<0.06–>512	1	>512	HA-MRSA frequently multiresistant	Schmalreck *et al.*, 1997
Streptococcus pneumoniae	2002–2003	0.06–>256	≤0.06	128	High prevalence in many countries; often multiresistant strains	Mazzariol *et al.*, 2007
Streptococcus pyogenes	2000–2001 (Hungary)	0.12–256	0.25	0.5		Gattringer *et al.*, 2004
	2002–2003	≤0.06–>256	≤0.06	>256		Mazzariol *et al.*, 2007
Haemophilus influenzae	<1997 (Munich Germany)	<0.06–>64	1	>64		Schmalreck *et al.*, 1997
Neisseria gonorrhoeae	1978 (Belgium)	0.024–25	0.78	6.25		Gordts *et al.*, 1982

but less active than erythromycin against group A streptococci and *E. faecalis* (Saroglou and Bisno, 1978; Tofte *et al.*, 1984). *Corynebacterium diphtheriae* and *Bacillus anthracis* are susceptible to rosaramicin.

Of the Gram-positive anaerobes, *Peptococcus*, *Peptostreptococcus*, *Propionibacterium*, and *Eubacterium* spp. are susceptible to josamycin, but *Clostridium* spp. strains may be resistant (Long *et al.*, 1976). Rosaramicin is also active against anaerobes (Sutter and Finegold, 1976). It is much more active than erythromycin against *Peptococcus* spp., but has the same activity against the others, such as *Peptostreptococcus*, *Eubacterium*, *Propionibacterium*, *Actinomyces*, and *Lactobacillus* spp. *Clostridium tetani* and C. *perfringens* are susceptible to spiramycin and rosaramicin.

Gram-negative bacteria

Neisseria meningitidis is generally susceptible to these antibiotics, whereas resistance is reported in *N. gonorrhoeae*. Rosaramicin is more active than penicillin G, erythromycin, and tetracycline against *N. gonorrhoeae*; this activity also encompasses beta-lactamase-producing strains (Sanders and Sanders, 1977).

Bordetella pertussis is susceptible to josamycin. The *in vitro* activity of rosaramicin against *Haemophilus influenzae* is greater than that of chloramphenicol, ampicillin, or erythromycin (Sanders and Sanders, 1977). Rosaramicin is also active on *Haemophilus ducreyi*, with MICs as low as 0.06 mg/l (Feltham *et al.*, 1979). *Campylobacter* spp. are readily inhibited, but some variation in sensitivity between subspecies occurs, which may assist laboratory differentiation (Ahonkhai *et al.*, 1981). For instance, C. *jejuni* was somewhat more susceptible than C. *coli* to both spiramycin and josamycin (Elharrif *et al.*, 1985). *Legionella* spp. were very susceptible to rosaramicin: the mean MIC of 33 strains was only one-fifth of the corresponding MIC of erythromycin (Edelstein *et al.*, 1982). Josamycin has therapeutic efficacy in experimental *Legionella pneumophila* pneumonia in guinea-pigs (Saito *et al.*, 1985).

Josamycin is active against *Bacteroides fragilis* (Strausbaugh *et al.*, 1976a), but *Fusobacterium* spp. often show MICs > 2 mg/l (Long *et al.*, 1976). Rosaramicin is generally more active than erythromycin against Gram-negative anaerobes such as the *Fusobacterium* and *Bacteroides* spp., with *B. fragilis* MICs < 4 mg/l (Sutter and Finegold, 1976).

Other bacteria

Mycoplasmas and *Ureaplasma urealyticum* are susceptible to both josamycin and rosaramicin (Robertson *et al.*, 1981; Chabbert, 1988). In a Greek study involving 369 women with clinical vaginitis, 79% of *U. urealyticum* stains were susceptible (Kechagia *et al.*, 2008). In a Turkish study involving 382 women with abnormal vaginal discharge, suceptibilty to josamycin was 94.1% for *M. hominis* and 98.4% for *U. urealyticum* (Karabay *et al.*, 2006). *Chlamydia trachomatis* is susceptible to rosaramicin but *Chlamydophila psittaci* is not (Orfila *et al.*, 1988). *Rickettsia rickettsii* and *R. conorii* are also susceptible to josamycin (Raoult *et al.*, 1988).

2b. Emerging resistance and cross-resistance

Resistance to macrolides has become a major issue for most of the bacteria originally described as susceptible, including *Staphylococcus* spp., *Streptococcus* spp., *Bacteroides* spp., *Enterococcus* spp., *Clostridium* spp., *Bacillus* spp., *Lactobacillus* spp., *M. pneumoniae*, *Campylobacter* spp., *Corynebacterium diphtheria*, and *Propionobacterium*, as well as many members of the Enterobacteriaceae (Leclercq and Courvalin, 1991). The main mechanisms of resistance are similar to those described for erythromycin and include target modification and antibiotic inactivation (see Chapter 59, Erythromycin). Of interest, however, 16-atom macrolides remain active against streptococci harboring the M phenotype (resistance by efflux) (Mazzariol *et al.*, 2007) and testing these agents separately is therefore necessary in these bacteria. Interestingly, 16-membered ring macrolides seem to be more effective inducers than 14-membered ring macrolides in enterococci (Min *et al.*, 2003). *Enterococcus faecium* strains with reduced susceptibility to quinopristin–dalfopristin all showed high-level resistance to josamycin (López *et al.*, 2008).

Resistance of C. *psittaci* is described, but carries a prohibitive physiological cost (Binet and Maurelli, 2007). In Russia, point mutations responsible for josamycin resistance were found in 48% of *M. hominis* strains isolated from patients with bacterial vaginosis (Karamova *et al.*, 2004).

3. MECHANISM OF DRUG ACTION

The mechanism of action is similar to erythromycin and other macrolides (see Chapter 59, Erythromycin).

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

4a. Adults

The usual dosage of josamycin is 2–3 g orally per day, given in two to four divided doses; this may be increased to 4 g daily in severe infections (Wenzel *et al.*, 1976). Rosaramicin has been administered in a dosage of 250 mg orally four times daily (Brunham *et al.*, 1982). Their bioavailability is not affected by food intake.

4b. Newborn infants and children

Dosage is 30–75 mg/kg/day orally for josamycin, given in two to four divided doses. Josamycin propionate is a tasteless derivative used as a suspension in pediatrics.

4c. Altered dosages

Impaired hepatic function

Because of extensive hepatic metabolism, dosage adjustment is suggested for josamycin in patients with hepatic insufficiency (Periti *et al.*, 1989), but no specific guidelines have been provided.

The elderly

A significant increase in the elimination half-life of josamycin has been reported in elderly subjects, so that the administration of lower doses at longer intervals has been suggested (Periti *et al.*, 1989).

5. PHARMACOKINETICS AND PHARMACODYNAMICS

The main pharmacokinetic properties of 16-atom macrolides are summarized in Table 63.2.

5a. Bioavailability

A peak of 0.65 mg/l is reached 1 hour after the administration of 500 mg josamycin (Periti *et al.*, 1989), the absorption is nearly complete by the oral route (Strausbaugh *et al.*, 1976a; Privitera *et al.*, 1984). The absorption of josamycin base is delayed by food.

Peak serum levels of 0.3–0.5 mg/l were obtained 1.5–2 hours after oral administration of 0.5 g of rosaramicin. Oral bioavailability was 32–39% (Lin *et al.*, 1984).

5b. Drug distribution

Josamycin penetrates well into saliva, sweat, and tears (Strausbaugh *et al.*, 1976a). The drug is concentrated up to 20-fold in phagocytic cells compared with serum (Labro and Babin-Chevaye, 1989).

Rosaramicin is concentrated in human prostatic tissue and, therefore, it has been suggested that it may be useful for the treatment of bacterial prostatitis (Baumueller *et al.*, 1977). After a single 250-mg dose was given to ten lactating mothers, only 0.0025% of the dose was recoverable from breast milk over the first 10 hours. Drug-induced toxicity in an infant via breast milk is, therefore, unlikely (Stoehr *et al.*, 1985).

5c. Clinically important pharmacokinetic and pharmacodynamic features

Cure rates for macrolides mainly depend on the AUC/MIC ratio (Andes *et al.*, 2004), based on their time-dependent effect coupled with a postantibiotic effect, both in *in vitro* and in animal models (Rolin and Bouanchaud, 1989; Novelli *et al.*, 2002). No specific studies using pharmacodynamic models have examined these molecules in details.

5d. Excretion

Josamycin is metabolized in the liver and excreted in the bile in an inactive form. Less than 20% of the drug is excreted in the urine in the active form. Rosaramicin is also eliminated in the bile (87% of the dose), as both active and metabolized drug. Unchanged rosaramicin accounts for only 7–9% of the drug excreted in urine (Lin *et al.*, 1984).

5e. Drug interactions

Drug interactions with macrolides can be a significant problem, and seriously limits their use in some at-risk patients. The main mechanism involved in these interactions is the ability of macrolides to bind to cytochrome P450 (group 3A4), thereby impairing the subsequent metabolism of other substrates of the same cytochrome (Periti *et al.*, 1992). The elimination of these co-administered drugs is therefore reduced, causing a potential risk of toxicity (Periti *et al.*, 1992; von Rosensteil and Adam, 1995). Spiramycin and josamycin have not been implicated as causing significant drug interactions by interfering with other drug hepatic metabolism (Pessayre, 1983; Descotes *et al.*, 1985; Ludden, 1985). Their use is, however, contraindicated when interaction with other drugs may have a life-threatening risk (see Table 63.3). A case of digoxin intoxication has been described due to co-administration of josamycin (Cambonie *et al.*, 2006).

Table 63.2 Pharmacokinetic parameters of josamycin and rosaramicin.

Pharmacokinetic parameter	Josamycin (0.5 g p.o.)	Rosaramicin (0.5 g p.o.)
C_{max} (mg/l)	0.65	0.5
T_{max} (h)	1	1.8
$t_{1/2}$ (h)	2	0.6
Bioavailability (%)	>90	39
Protein binding (%)	15	NA
$AUC_{0-24\,h}$ (mg·h/l)	8.5	NA

NA: data not available.
From Lin *et al.* (1984), Frydman *et al.* (1988), Periti *et al.* (1989), and Carbon and Rubinstein (1999).

Table 63.3 Drug interactions with the 16-atom macrolides, josamycin and rosaramicin.

Macrolide	Totally contra-indicated drugs	Drugs to use with caution (requiring dose reduction and/or therapeutic monitoring)
Josamycin	Astemizole Cisapride Ergotamine Terfenadine	Bbenzodiazepines Bromocriptine Carbamazepine Ciclosporin Theophylline

From Periti *et al.* (1992), Amsden (1995), and Zhanel *et al.* (2001).

6. TOXICITY

Hepatic transaminase elevation may occur with josamycin therapy (Fraschini, 1990; Straneo and Scarpazza, 1990), and was reported with rosaramicin in a small series of patients (Robson *et al.*, 1983). With josamycin, skin rashes have been reported (Privitera *et al.*, 1984). Although not reported extensively, side-effects similar to other macrolides do occur (see Chapter 59, Erythromycin, and Chapter 62, Azithromycin).

7. CLINICAL USES OF THE DRUG

Neither josamycin nor rosaramicin are not commonly used and in many regions their availability is limited. Nevertheless, they have some limited clinical utility for the following clinical conditions.

7a. Respiratory tract infections

Macrolides were long considered as an alternative to beta-lactams for the treatment of respiratory tract infections, but increasing rates of resistance among common respiratory pathogens have reduced their utility in many regions (Brunton and Iannini, 2005; Lode, 2007). The published experience with josamycin and rosaramicin is limited.

Josamycin 500 mg three times a day was less effective than brodimoprim in the treatment of otitis media (de Campora *et al.*, 1993). In a study comparing 5 days' treatment of josamycin with penicillin G for 10 days for the treatment of acute group A beta-hemolytic streptococcal tonsillitis, the two regimens resulted in equal clinical outcome (Portier *et al.*, 2001).

Josamycin has reportedly proved effective for the treatment of respiratory tract infections occurring in pediatric practice (Privitera *et al.*, 1984).

Josamycin has been reported as being as effective as clarithromycin for the treatment of bacterial pneumonia and acute exacerbations of chronic bronchitis (Fraschini, 1990; Straneo and Scarpazza, 1990), and a 5-day treatment with josamycin was satisfactory for nonsevere community-acquired pneumonia (Mensa *et al.*, 1993). In one controlled study, josamycin and erythromycin, both given in an oral dose of 2.0 g daily in four divided doses, were equally effective in adults with mycoplasma pneumonia (Wenzel *et al.*, 1976). However, josamycin was less efficient than ciprofloxacin in the treatment of recurrent exacerbated bronchitis (Canton *et al.*, 1989).

7b. Sexually transmitted diseases

Rosaramicin (1 g daily for 7 days) was as effective as erythromycin stearate (2 g daily for 7 days) or as tetracycline (2 g daily for 7 days) in women with *C. trachomatis* cervicitis (Brunham *et al.*, 1982; Robson *et al.*, 1983). Nongonococcal urethritis in men was treated in two controlled trials with either rosaramicin or tetracycline, each given in a dosage of 1 g per day for 7 days, with equivalent success (Juvakoski *et al.*, 1981; Darne *et al.*, 1982). A comparative study of erythromycin base 500 mg and rosaramicin 250 mg, each four times daily for 10 days, in the treatment of genital ulcers due to *Haemophilus ducreyi* in Kenyan men resulted in similar healing times (5 days to 2 weeks), with no treatment failures in either group (Plummer *et al.*, 1983).

7c. Other uses

A 5-day josamycin regimen was as effective as 1-day doxycycline treatment for Mediterranean spotted fever, the tick-borne rickettsiosis caused by *Rickettsia conorii* (Bella *et al.*, 1990). Josamycin has also been investigated as a component of quadruple therapy for *H. pylori* with good success rates (Liu *et al.*, 2000). Josamycin and erythromycin were equally effective in reducing the carrier rates of *S. aureus* (Wilson *et al.*, 1977).

References

Ahonkhai VI, Cherubin CE, Sierra MF *et al.* (1981). *In vitro* susceptibility of *Campylobacter fetus* subsp. *jejuni* to N-formimidoyl thienamycin, rosaramicin, cefoperazone, and other antimicrobial agents. *Antimicrob Agents Chemother* 20: 850.

Amsden GW (1995). Macrolides versus azalides: a drug interaction update. *Ann Pharmacother* 29: 906.

Andes D, Anon J, Jacobs MR, Craig WA (2004). Application of pharmacokinetics and pharmacodynamics to antimicrobial therapy of respiratory tract infections. *Clin Lab Med* 24: 477.

Baumueller A, Hoyme U, Madsen PO (1977). Rosamicin – a new drug for the treatment of bacterial prostatitis. *Antimicrob Agents Chemother* 12: 240.

Bella F, Font B, Uriz S *et al.* (1990). Randomized trial of doxycycline versus josamycin for Mediterranean spotted fever. *Antimicrob Agents Chemother* 34: 937.

Binet R, Maurelli AT (2007). Frequency of development and associated physiological cost of azithromycin resistance in *Chlamydia psittaci* 6BC and *C. trachomatis* L2. *Antimicrob Agents Chemother* 51: 4267.

Brunham RC, Kuo CC, Stevens CE, Holmes KK (1982). Therapy of cervical chlamydial infection. *Ann Intern Med* 97: 216.

Brunton S, Iannini P (2005). Macrolide-resistant *Streptococcus pneumoniae*: Clinical implications for the empiric treatment of community-acquired respiratory tract infections. *MedGenMed* 7: 63.

Cambonie G, Sabatier E, Guillaumont S *et al.* (2006). [Digoxin-Josamycin: a dangerous drug interaction in children]. *Arch Pediatr* 13: 1118.

Canton P, Hoen B, Richet H *et al.* (1989). Comparative efficacy of ciprofloxacin versus josamycin in the treatment of acute, recurrent, or exacerbated bronchitis. *Am J Med* 87: 121S.

Carbon C, Rubinstein E (1999). Macrolides, lincosamides and streptogramins. In *Infectious diseases* (Armstrong D, Cohen J, eds), pp. 7.6.1. London Mosby.

Chabbert YA (1988). Early studies on *in-vitro* and experimental activity of spiramycin: A review. *J Antimicrob Chemother* 22 (Suppl B): 1.

Darne JF, Ridgway GL, Oriel JD (1982). Rosaramicin and tetracycline in the treatment of non-gonococcal urethritis. A comparison of clinical and microbiological results. *Br J Vener Dis* 58: 117.

De Campora E, Radici M, Camaioni A (1993). Efficacy and tolerability of brodimoprim in otitis. *J Chemother* 5: 529.

Descotes J, Andre P, Evreux JC (1985). Pharmacokinetic drug interactions with macrolide antibiotics. *J Antimicrob Chemother* 15: 659.

Edelstein PH, Pasiecznik KA, Yasui VK, Meyer RD (1982). Susceptibility of *Legionella* spp. to mycinamicin I and II and other macrolide antibiotics: Effects of media composition and origin of organisms. *Antimicrob Agents Chemother* 22: 90.

Elharrif Z, Megraud F, Marchand AM (1985). Susceptibility of *Campylobacter jejuni* and *Campylobacter coli* to macrolides and related compounds. *Antimicrob Agents Chemother* 28: 695.

Feltham S, Ronald AR, Albritton WL (1979). A comparison of the *in vitro* activity of rosamicin, erythromycin, clindamycin, metronidazole and

ornidazole against *Haemophilus ducreyi*, including beta-lactamase producing strains. *J Antimicrob Chemother* 5: 731.

Fraschini F (1990). Clinical efficacy and tolerance of two new macrolides, clarithromycin and josamycin, in the treatment of patients with acute exacerbations of chronic bronchitis. *J Int Med Res* 18: 171.

Frydman AM, Le Roux Y, Desnottes JF *et al.* (1988). Pharmacokinetics of spiramycin in man. *J Antimicrob Chemother* 22: 93.

Gattringer R, Sauermann R, Lagler H *et al.* (2004). Antimicrobial susceptibility and macrolide resistance genes in *Streptococcus pyogenes* collected in Austria and Hungary. *Int J Antimicrob Agents* 24: 290.

Gordts B, Vanhoof R, Hubrechts JM *et al.* (1982). *In-vitro* activity of 21 antimicrobial agents against *Neisseria gonorrhoeae* in Brussels. *Br J Vener Dis* 58: 23.

Juvakoski T, Allgulander C, Lassus A (1981). Rosaramicin and tetracycline treatment in *Chlamydia trachomatis*-positive and -negative nongonococcal urethritis. *Sex Transm Dis* 8: 12.

Kanazawa Y, Kuramata T (1976). [Evaluation of midecamycin sensitivity disc (author's transl)]. *Jpn J Antibiot* 29: 178.

Karabay O *et al.* (2006). Prevalence and antibiotic susceptibility of genital *Mycoplasma hominis* and *Ureaplasma urealyticum* in a university hospital in Turkey. *Clin Exp Obstet Gynecol* 33: 36.

Karamova AE, Polyakov AV, Komarova NV (2004). Detection of mutant *Mycoplasma hominis* strains resistant to 16-membered macrolide antibiotic josamycin in clinical samples. *Bull Exp Biol Med* 137: 483.

Kawaharajo K, Sekizawa Y, Inoue M (1981). *In vitro* and *in vivo* antibacterial activity of 9,3″-Di-o-acetyl midecamycin (Mom), a new macrolide antibiotic. *J Antibiot (Tokyo)* 34: 436.

Kechagia N, Bersimis S, Chatzipanagiotou S (2008). Incidence and antimicrobial susceptibilities of genital mycoplasmas in outpatient women with clinical vaginitis in Athens, Greece. *Antimicrob Chemother* 62: 122.

Kellow WH, Lepper M, Plauts Se *al.*1955). Spiramycin in the treatment of infection. *Antibiot Annu* 3: 658.

Labro MT, Babin-Chevaye C (1989). Synergistic interaction of josamycin with human neutrophils bactericidal function *in vitro*. *J Antimicrob Chemother* 24: 731.

Leclercq R, Courvalin P (1991). Bacterial resistance to macrolide, lincosamide, and streptogramin antibiotics by target modification. *Antimicrob Agents Chemother* 35: 1267.

Lin CC, Chung M, Gural R *et al.* (1984). Pharmacokinetics and metabolism of rosaramicin in humans. *Antimicrob Agents Chemother* 26: 522.

Liu WZ, Xiao SD, Hu PJ *et al.* (2000). A new quadruple therapy for *Helicobacter pylori* using tripotassium dicitrato bismuthate, furazolidone, josamycin and famotidine. *Aliment Pharmacol Ther.* 14: 1519.

Lode HM (2007). Managing community-acquired pneumonia: a European perspective. *Respir Med* 101: 1864.

Long SS, Mueller S, Swenson RM (1976). *In vitro* susceptibilities of anaerobic bacteria to josamycin. *Antimicrob Agents Chemother* 9: 859.

López F, Culebras E, Betriv C *et al.* (2010) Antimicrobial susceptibility and macrolide resistance genes in *Enterococcus faecium* with reduced susceptibility to quinupristin-dalfopristin: level of quinupristin-dalfopristin resistance is not dependent on erm(B) attenuator region sequence. *Diagn Microbiol infect Dis* 66: 73.

Ludden TM (1985). Pharmacokinetic interactions of the macrolide antibiotics. *Clin Pharmacokinet* 10: 63.

Mazzariol A, Koncan R, Vitali LA, Cornaglia G (2007). Activities of 16-membered ring macrolides and telithromycin against different genotypes of erythromycin-susceptible and erythromycin-resistant *Streptococcus pyogenes* and *Streptococcus pneumoniae*. *J Antimicrob Chemother* 59: 1171.

Mensa J, Trilla A, Moreno A *et al.* (1993). Five-day treatment of non-severe, community-acquired pneumonia with josamycin. *J Antimicrob Chemother* 31: 749.

Min YH, Jeong JH, Choi YJ *et al.* (2003). Heterogeneity of macrolide-lincosamide-streptogramin B resistance phenotypes in enterococci. *Antimicrob Agents Chemother* 47: 3415.

Nitta K, Yano K, Miyamoto F *et al.* (1967). A new antibiotic, josamycin. II. Biological studies. *J Antibiot (Tokyo)* 20: 181.

Novelli A, Fallani S, Cassetta MI *et al.* (2002). *In vivo* pharmacodynamic evaluation of clarithromycin in comparison to erythromycin. *J Chemother* 14: 584.

Omoto S, Iwamatsu K, Inouye S, Niida T (1976). Modifications of a macrolide antibiotic midecamycin (SF-837). I. Synthesis and structure of 9,3″-diacetylmidecamycin. *J Antibiot (Tokyo)* 29: 536.

Orfila J, Haider F, Thomas D (1988). Activity of spiramycin against chlamydia, *in vitro* and *in vivo*. *J Antimicrob Chemother* 22 (Suppl B): 73.

Periti P, Mazzei T, Mini E, Novelli A (1989). Clinical pharmacokinetic properties of the macrolide antibiotics. Effects of age and various pathophysiological states (Part II). *Clin Pharmacokinet* 16: 261.

Periti P, Mazzei T, Mini E, Novelli A (1992). Pharmacokinetic drug interactions of macrolides. *Clin Pharmacokinet* 23: 106.

Pessayre D (1983). Effects of macrolide antibiotics on drug metabolism in rats and in humans. *Int J Clin Pharmacol Res* 3: 449.

Plummer FA, D'Costa LJ, Nsanze H *et al.* (1983). Antimicrobial therapy of chancroid: effectiveness of erythromycin. *J Infect Dis* 148: 726.

Portier H, Bourrillon A, Lucht F *et al.* (2001). [Treatment of acute group A beta-hemolytic streptococcal tonsillitis in children with a 5-day course of josamycin]. *Arch Pediatr* 8: 700.

Privitera G, Bonino S, Del Mastro S (1984). Clinical multicentre trial with josamycin propionate in paediatric patients. *Int J Clin Pharmacol Res* 4: 201.

Raoult D, Roussellier P, Tamalet J (1988). *In vitro* evaluation of josamycin, spiramycin, and erythromycin against *Rickettsia rickettsii* and *R. conorii*. *Antimicrob Agents Chemother* 32: 255.

Robertson JA, Coppola JE, Heisler OR (1981). Standardized method for determining antimicrobial susceptibility of strains of *Ureaplasma urealyticum* and their response to tetracycline, erythromycin, and rosaramicin. *Antimicrob Agents Chemother* 20: 53.

Robson HG, Shah PP, Lalonde RG *et al.* (1983). Comparison of rosaramicin and erythromycin stearate for treatment of cervical infection with *Chlamydia trachomatis*. *Sex Transm Dis* 10: 130.

Rolin O, Bouanchaud DH (1989). [Comparison of the *in vitro* post-antibiotic effect of C14 macrolides (erythromycin and roxithromycin) and C16 macrolides (josamycin and spiramycin) against *Staphylococcus aureus*]. *Pathol Biol (Paris)* 37: 375.

Saito A, Sawatari K, Fukuda Y *et al.* (1985). Susceptibility of *Legionella pneumophila* to ofloxacin *in vitro* and in experimental *Legionella pneumonia* in guinea pigs. *Antimicrob Agents Chemother* 28: 15.

Sakakibara H, Okekawa O, Fujiwara T *et al.* (1981). Acyl derivatives of 16-membered macrolides. I. Synthesis and biological properties of 3″-O-propionylleucomycin A5 (TMS-19-Q). *J Antibiot (Tokyo)* 34: 1001.

Sanders CC, Sanders Jr WE (1977). *In vitro* activity of rosamicin against *Neisseria* and *Haemophilus*, including penicillinase-producing strains. *Antimicrob Agents Chemother* 12: 293.

Saroglou G, Bisno AL (1978). Susceptibility of skin and throat strains of group A streptococci to rosamicin and erythromycin. *Antimicrob Agents Chemother* 13: 701.

Schmalreck AF, Kottmann I, Reiser A *et al.* (1997). Susceptibility testing of macrolide and lincosamide antibiotics according to DIN guidelines. Deutsches Institut fur Normung. *J Antimicrob Chemother* 40: 179.

Shadomy S, Tipple M, Paxton L (1976). Josamycin and rosamicin: *in vitro* comparisons with erythromycin and clindamycin. *Antimicrob Agents Chemother* 10: 773.

Stoehr GP, Juhl RP, Veals J *et al.* (1985). The excretion of rosaramicin in breast milk. *J Clin Pharmacol* 25: 89.

Straneo G, Scarpazza G (1990). Efficacy and safety of clarithromycin versus josamycin in the treatment of hospitalized patients with bacterial pneumonia. *J Int Med Res* 18: 164.

Strausbaugh LJ, Bolton WK, Dilworth JA *et al.* (1976a). Comparative pharmacology of josamycin and erythromycin stearate. *Antimicrob Agents Chemother* 10: 450.

Strausbaugh LJ, Dilworth JA, Gwaltney Jr JM, Sande MA (1976b). *In vitro* susceptibility studies with josamycin and erythromycin. *Antimicrob Agents Chemother* 9: 546.

Sutter VL, Finegold SM (1976). Rosamicin: *in vitro* activity against anaerobes and comparison with erythromycin. *Antimicrob Agents Chemother* 9: 350.

Tofte RW, Solliday JA, Crossley KB (1984). Susceptibilities of enterococci to twelve antibiotics. *Antimicrob Agents Chemother* 25: 532.

von Rosensteil NA and Adam D (1995). Macrolide antibacterials. Drug interactions of clinical significance. *Drug Saf* 13: 105.

Wagman GH, Waitz JA, Marquez J *et al.* (1972). A new Micromonospora-produced macrolide antibiotic, rosamicin. *J Antibiot (Tokyo)* 25: 641.

Waitz JA, Drube CG, Moss Jr EL, Weinstein MJ (1972). Biological studies with rosamicin, a new Micromonospora-produced macrolide antibiotic. *J Antibiot (Tokyo)* 25: 647.

Wenzel RP, Hendley JO, Dodd WK, Gwaltney JM (1976). Comparison of josamycin and erythromycin in the therapy of *Mycoplasma pneumoniae* pneumonia. *Antimicrob Agents Chemother* 10: 899.

Westerman EL, Williams Jr TW, Moreland N (1976). *In vitro* activity of josamycin against aerobic gram-positive cocci and anaerobes. *Antimicrob Agents Chemother* 9: 988.

Wilson SZ, Martin RR, Putman M (1977). *In vivo* effects of josamycin, erythromycin, and placebo therapy on nasal carriage of *Staphylococcus aureus*. *Antimicrob Agents Chemother* 11: 407.

Zhanel GG, Dueck M, Hoban DJ *et al.* (2001). Review of macrolides and ketolides: focus on respiratory tract infections. *Drugs* 61: 443.