ANTIMICROBIAL SUSCEPTIBILITY OF GROUP A STREPTOCOCCI IN NEW ZEALAND IN 2001

by

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SUMMARY

Group A streptococci are universally susceptible to penicillin - the antibiotic of choice for the treatment of infections with this organism. Macrolide antibiotics are indicated for patients allergic to penicillin, when penicillin therapy fails, or in cases of multiple recurrences. While the prevalence of erythromycin resistance remains low in most parts of the world, high rates have been reported in several countries.

In March-April 2001, isolates were collected for a national survey of antimicrobial resistance among group A streptococci in New Zealand. A total of 474 isolates, from 30 hospital and community laboratories, were tested by a standard agar dilution method. The majority (94%) of isolates were reported to be community acquired, 48% were from skin/wound/abscess sites and 45% were from respiratory sites. Just over 40% were from children less than 10 years of age.

None of the 474 isolates tested were resistant to penicillin, cefotaxime, cephalothin, chloramphenicol, clindamycin, mupirocin, or trimethoprim-sulphamethoxazole. Based on the results of tests for inducible macrolide-lincosamide (ML) resistance, 3 (0.6%) of the 474 isolates could be considered to be erythromycin resistant: one with the inducible ML resistance phenotype and two with the erythromycin-resistant, clindamycin-sensitive, or so called M, phenotype. Fifty-nine (12.5%) isolates were tetracycline resistant. Isolates from patients less than 8 years of age were significantly less resistant to tetracycline than isolates from older people (p=004).

Compared with a previous survey in 1990, the erythromycin resistance was lower (0.6% vs 4.1%) and tetracycline resistance was higher (12.5% vs 6.2%) in 2001. Among the antimicrobials to which no resistance was detected in 2001, a comparison of the MIC values obtained in the two surveys indicates there has been no change, or even an increase, in susceptibility to these antimicrobials during the last 10 years. The one exception to this trend was a decrease in mupirocin susceptibility, as indicated by an increase in the upper end of the MIC range from 0.25 mg/L in 1990 to 4 mg/L in 2001.

The results of this survey of group A streptococci indicate that this organism remains extremely sensitive to the antibiotics most used for therapy, that is, penicillin and macrolides. The decrease in susceptibility to mupirocin is a concern and is likely to be the result of the high, and until recently unrestricted, use of this antibiotic in New Zealand.

RECOMMENDATIONS

- Based on the low prevalence of erythromycin resistance, and the lack of any change in penicillin MICs since 1990, we recommend that another point-prevalence survey of antimicrobial resistance among group A streptococci should not be required for at least 5-10 years.

- The ongoing monitoring of penicillin and erythromycin resistance in group A streptococci through the annual collection and collation of diagnostic laboratory data should continue.

- Erythromycin-resistant group A streptococci should continue to be included in ESR's Antibiotic-Resistant Bacteria Monitoring Scheme.

1 INTRODUCTION

The most common group A streptococcus (*Streptococcus pyogenes*) infections are upper respiratory tract infections, such as acute pharyngitis or tonsillitis, and skin infections, such as impetigo. Untreated or unsuccessful treatment of upper respiratory tract infections can lead to the serious sequelae of acute rheumatic fever, while acute glomerulonephritis can follow either respiratory or skin infections. During the last decade, there has been a resurgence of severe systemic group A streptococcal infections, including streptococcal toxic shock syndrome.[1]

Penicillin is the first-line therapy for group A streptococcal infections.[2] Although group A streptococci remain exquisitely sensitive to penicillin *in vitro*, treatment failures do occur. Erythromycin or other macrolide antibiotics are indicated for patients allergic to penicillin, when penicillin therapy fails, or in cases of multiple recurrences. While the prevalence of erythromycin resistance remains low in most parts of the world,[3,4] high rates have been reported in Japan (62% in 1974-5),[5] Australia (18% in 1987),[6] Finland (20-34% in 1990),[7] Taiwan (MIC_{50} 16 mg/L in 1992-3),[8] Spain, (17.6% in 1996),[9] and Italy (43% in 1997).[10]

In a 1990 national survey of antimicrobial resistance among group A streptococci in New Zealand, a prevalence of 3.8% erythromycin resistance was recorded.[11] Periodic monitoring of erythromycin resistance among group A streptococci has been recommended.[4] In March and April 2001, isolates were collected for a second national survey. The results of the survey are presented in this report.

2 METHODS

2.1 Isolate collection

All hospital and community laboratories in New Zealand were invited to participate in the survey. Participating laboratories completed a questionnaire on the number of group A streptococci isolated per week. Based on these isolation rates, laboratories were requested to submit between 5 and 60 consecutive, non-duplicate group A streptococcal isolates. Isolates were collected between 26 March and 10 April 2001, or sooner if the target number was reached before 10 April. The data collected with each isolate included patient name or laboratory code for the isolate, patient gender, patient age, source (hospital-acquired or community-acquired), isolation site, and relevant clinical data.

2.2 Geographic distribution analysis

Based on the location of the referring laboratory, isolates were identified as originating from a health district. Health districts were aggregated as indicated in Table 1.

Table 1. Health district aggregation

Aggregated area	Health districts
Northland	Northland
Auckland	North West Auckland, Central Auckland and South Auckland
Waikato	Waikato
Bay of Plenty	Tauranga, Eastern Bay of Plenty and Rotorua
Gisborne/Hawkes Bay	Gisborne and Hawkes Bay
Taranaki	Taranaki
Wanganui/Manawatu	Wanganui and Manawatu
Wellington	Hutt and Wellington
Nelson/Marlborough	Nelson-Marlborough
Canterbury/West Coast	Canterbury and South Canterbury
Otago/Southland	Otago and Southland

2.3 Definition of community- and hospital-acquired isolates

Hospital-acquired isolates were defined as isolates from in-patients who had been admitted at least 48 hours earlier. Community-acquired isolates were defined as isolates from specimens referred from general practitioners, rest homes, hospital outpatient clinics, accident and emergency departments, or from hospital in-patients within 48 hours of admission.

2.4 Antimicrobial susceptibility tests

The susceptibility of the isolates was tested by an agar dilution method following National Committee for Clinical Laboratory Standards' (NCCLS) guidelines. The following antimicrobials were tested: cefotaxime, cephalothin, chloramphenicol, clindamycin, erythromycin, mupirocin, penicillin, tetracycline and trimethoprim-suphamethoxazole.[12,13] Mueller-Hinton agar supplemented with 5% sheep blood was used to test all antimicrobials except trimethoprim-sulphamethoxazole. Mueller-Hinton agar supplemented with 5% lysed horse blood was used for trimethoprim-sulphamethoxazole. An inoculum of 10^4 cfu/spot was applied to plates using a multipoint inoculator. The plates were incubated at 35°C for 16-20 hours in 5% CO_2. Minimum inhibitory concentration (MIC) endpoints were read as recommended by NCCLS and interpreted according to NCCLS recommendations, except for mupirocin. Mupirocin MICs were interpreted using the standards proposed for staphylococci.[14]

The following controls were used:

- *Streptococcus pneumoniae* NZRM Acc 3399 (ATCC 49619), sensitive control
- *Streptococcus pneumoniae* NZRM Acc 2764 (CDC 78-008109), resistant control
- *Enterococcus faecalis* NZRM Acc 2244 (ATCC 29212)

2.5 Determination of inducible macrolide-lincosamide resistance

Isolates which were resistant (MIC ≥1 mg/L) or intermediate (MIC 0.5 mg/L) to erythromycin were tested for inducible macrolide-lincosamide (ML) resistance by a double-disc diffusion induction test.[15] Clindamycin discs were used to represent lincosamides. Disc tests were set up following NCCLS guidelines, and erythromycin 15 μg (inducer) and clindamycin 2 μg discs were placed 20 mm apart. An isolate was considered to have inducible ML resistance if the clindamycin zone was blunted proximal to the erythromycin disc.

2.6 Data analysis

The results were analysed using Microsoft Excel and SAS.

3 RESULTS

3.1 Survey sample

A total of 474 group A streptococci from 30 hospital and community laboratories were included in the survey. The participating laboratories, an estimate of the number of group A streptococci isolated in each participating laboratory per week, and the number of isolates from each laboratory included in the survey, are listed in Appendix 1. The distribution of the isolates among the health district aggregates is shown in Table 2.

Table 2. Geographic distribution of group A streptococci included in the survey

Health district aggregate	Number of isolates
Northland	6
Auckland	195
Waikato	73
Bay of Plenty	44
Gisborne/Hawkes Bay	10
Taranaki	13
Wanganui/Manawatu	14
Wellington	64
Nelson/Marlborough	2
Canterbury/West Coast	30
Otago/Southland	23

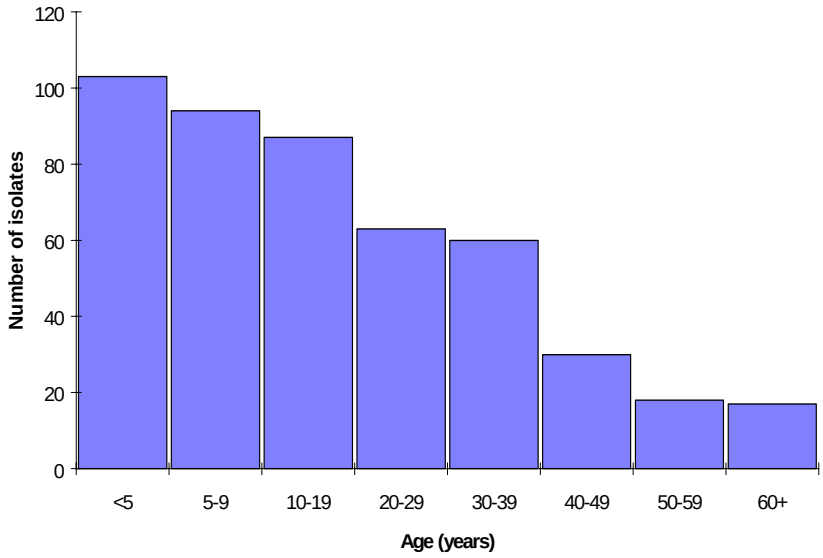
The source of the group A streptococci included in the survey was reported for 470 (99.2%) isolates, of which 443 (94.3%) were reported to be community-acquired and 27 (5.7%) were hospital-acquired. The site of isolation of 466 (98.3%) of the isolates included in the survey was reported. The majority (92.6%) were from skin lesions, wounds, abscesses or respiratory sites (Table 3).

Table 3. Site of isolation of group A streptococci included in the survey

Isolation site	Number	Percent
Skin lesions, wounds, abscesses	227	47.9
Respiratory (throat, nose, sputum)	212	44.7
Urogenital	11	2.3
Ear	9	1.9
Invasive (blood, aspirate)	7	1.5
Unknown	8	1.7

The distribution of the isolates by age groups is shown in Figure 1.

Figure 1. Ages of patients from whom group A streptococci were isolated



3.2 Antimicrobial susceptibility

The MIC range, MIC_{50}, MIC_{90} and resistance to each antimicrobial tested is shown in Table 4. The full MIC distribution for each antimicrobial is presented in Appendix 2. The prevalence of resistance to all antimicrobials except tetracycline was less than 0.5%, with no resistance to penicillin, cefotaxime, cephalothin, chloramphenicol, clindamycin, mupirocin, or trimethoprim-sulphamethoxazole. No isolate was resistant to more than one of the antimicrobials tested.

Two isolates were resistant to erythromycin (MIC ≥1 mg/L) and one isolate had intermediate resistance (MIC 0.5 mg/L). The erythromycin-intermediate isolate had inducible ML resistance, as demonstrated by blunting of the clindamycin inhibition zone in the double-disc diffusion induction test. Neither of the erythromycin-resistant isolates had inducible ML resistance, as demonstrated by the retention of full clindamycin sensitivity proximal to erythromycin in the disc diffusion test. Therefore, overall 0.6% (3) of the 474 isolates surveyed were considered to be erythromycin resistant: one with inducible ML resistance and two with the erythromycin-resistant, clindamycin-sensitive phenotype.

Table 4. MIC range, MIC_{50}, MIC_{90} and resistance among group A streptococci, 2001

Antimicrobial agent (resistance breakpoint mg/L)	MIC (mg/L)			Percent (number) resistance
	range	MIC_{50}	MIC_{90}	
Cefotaxime (MIC ≥1)	0.008-0.03	0.016	0.016	0 (0)
Cephalothin (MIC ≥1)	0.06-0.25	0.12	0.25	0 (0)
Chloramphenicol (MIC ≥16)	1-4	2	4	0 (0)
Clindamycin (MIC ≥1)	0.03-0.12	0.06	0.06	0 (0)
Erythromycin (MIC ≥1)	0.06-8.0	0.06	0.06	0.4 (2)[1]
Mupirocin (MIC ≥8)	0.03-4	0.12	0.25	0 (0)
Penicillin (MIC ≥0.25)	0.004-0.03	0.016	0.016	0 (0)
Tetracycline (MIC ≥8)	0.06-64	0.25	16	12.5 (59)
Trimethoprim-sulphamethoxazole (MIC ≥4)[2]	0.03-0.5	0.06	0.12	0 (0)

Notes: 1 Based on the results of tests for inducible macrolide-lincosamide resistance, 0.6% (3) of the 474 isolates were considered to be erythromycin resistant.

2 The MICs for trimethoprim-sulphamethaxazole refer to the trimethoprim content in a ratio of 1 part trimethoprim to 19 parts sulphamethoxazole.

Fifty-nine (12.5%) isolates were resistant to tetracycline. There was no association between tetracycline resistance and the geographic source of the isolate, the site of isolation, or the place of acquisition (hospital vs community). There was a significant difference (p=004) in resistance among isolates from patients less than 8 years of age (5.8%) and older patients 15.1%).

3.3 Comparison with previous survey in 1990

The MIC range, MIC_{90} and resistance to the antimicrobials which were commonly tested in both 1990 and 2001 are shown in Table 5. The full MIC distribution for each antimicrobial tested in 1990 is presented in Appendix 3. The test methods used in the two surveys were very similar. Compared with the 1990 survey, resistance to erythromycin was lower in the 2001 survey and tetracycline resistance was higher (Table 5). The MIC_{90} estimates for most antimicrobials were similar in the two surveys or lower in 2001. The two exceptions to this trend were tetracycline and mupirocin. The tetracycline MIC_{90} was markedly higher in 2001 (0.5 vs 16 mg/L) while the mupirocin MIC_{90} was one doubling dilution higher (0.12 vs 0.25 mg/L). Concomitantly, the upper end of the range of mupirocin MICs was higher in 2001 (Table 5 and Appendices 2 and 3).

Table 5. Comparison of MIC ranges, MIC_{90} and resistance among group A streptococci in 1990 and 2001

Antimicrobial agent	1990 n=434			2001 n=474		
	MIC range (mg/L)	**MIC_{90} (mg/L)**	**Percent resistance[1]**	**MIC range (mg/L)**	**MIC_{90} (mg/L)**	**Percent resistance**
Cefotaxime	0.004-0.25	0.03	0	0.008-0.03	0.016	0
Cephalothin	0.06-0.25	0.25	0	0.06-0.25	0.25	0
Chloramphenicol	2-16	4	0.5	1-4	4	0
Clindamycin	0.06-0.5	0.12	0	0.03-0.12	0.06	0
Erythromycin	0.06-16	0.25	4.1	0.06-8.0	0.06	0.4
Mupirocin	0.03-0.5	0.12	0	0.03-4	0.25	0
Penicillin	0.008-0.03	0.016	0	0.004-0.03	0.016	0
Tetracycline	0.12-32	0.5	6.2	0.06-64	16	12.5
Trimethoprim-sulphamethoxazole[2]	0.03-0.5	0.25	0	0.03-0.5	0.12	0

Notes: 1 These estimates of resistance have been calculated using the current interpretive standards, which differ from those recommended and used in 1990. Therefore, these estimates differ from those in the published report on the 1990 survey.[11]

2 The MICs for trimethoprim-sulphamethaxazole refer to the trimethoprim content in a ratio of 1 part trimethoprim to 19 parts sulphamethoxazole.

4 DISCUSSION

The results of this survey of antimicrobial resistance among a sample of 474 group A streptococci isolated in New Zealand early in 2001 are reassuring. As expected, all isolates included in the survey tested as susceptible to penicillin. Moreover, comparison of the MIC ranges and MIC_{90} values obtained in 2001 with those obtained in the only previous national survey of antimicrobial resistance among group A streptococci in 1990 (Appendices 2 and 3 and Table 5) shows that there has been no reduction in susceptibility (ie, no increase in MIC values) to penicillin. Penicillin tolerance was not examined in this survey. In the 1990 survey, estimates of penicillin tolerance ranged from 28 to 8.8%, depending on whether MICs were estimated after 24 or 48 hours incubation.[11]

Erythromycin resistance was infrequent, with only two (0.4%) isolates categorised as resistant and one as intermediate resistant. Three resistance phenotypes, which can be distinguished on the basis of clindamycin susceptibility, have been described among erythromycin-resistant group A streptococci:[16,17,18,19]

1 Constitutive macrolide, lincosamide and streptogramin B resistance (cMLS): characterised by high-level erythromycin resistance (MIC >64 mg/L) and constitutive clindamycin resistance.
2 Inducible macrolide, lincosamide and streptogramin B resistance (iMLS): characterised by low-level erythromycin resistance (MIC 1-16 mg/L) and inducible clindamycin resistance.
3 Macrolide resistance only (M phenotype): characterised by low-level erythromycin resistance and persistent susceptibility to clindamycin despite induction.

Strains with the cMLS or iMLS phenotype have genes belonging to the *ermB(AM)* or *ermA(TR)* classes which encode an alteration to the MLS_B target site on the 23S rRNA. Strains with the M resistance phenotype possess the *mefA* gene which encodes an efflux (pump) protein that affects macrolides, but not lincosamides or streptogramin B. No form of macrolide inactivation has yet been described for streptococci. Irrespective of the phenotype, all erythromycin-resistant group A streptococci are also resistant to the other 14- and the 15-membered macrolides, such as roxithromycin, clarithromycin and azithromycin, but not the 16-membered macrolides.

The two erythromycin-resistant isolates detected in this survey appear to have the M phenotype. They had relatively low erythromycin MICs (2 and 8 mg/L) and were persistently clindamycin sensitive. The one erythromycin intermediate-resistant isolate appears to have the iMLS phenotype, as it displayed inducible clindamycin resistance.

While increases in erythromycin resistance among group A streptococci have been reported from several countries during the last 2-3 decades, resistance appears to have decreased in New Zealand from 4.1% in 1990 to 0.6% in 2001. Data on erythromycin resistance among group A streptococci has also been collected annually from diagnostic laboratories since 1998. These data, based on an average annual sample size of 10 000 isolates, also indicate a low prevalence of erythromycin resistance: 1.5% in 2000, 1.3% in 1999 and 0.9% in 1998.[20,21,22]

The experience in several countries which have had a high prevalence of erythromycin resistance in group A streptococci suggests that acquisition of resistance is linked to the amount of antibiotic used. This association between resistance and antibiotic consumption has been demonstrated in Japan,[23] Finland,[24] and Italy.[25] The decrease in erythromycin resistance in New Zealand since 1990 may indicate prudent use of macrolides, at least in the community setting where the majority of the isolates included in this survey originated.

The prevalence of tetracycline resistance has doubled from 6.2% in 1990 to 12.5% in 2001. While tetracycline is not indicated for group A streptococcal infections,[2] its use for other infections may be contributing to the maintenance of tetracycline resistance in group A streptococci. Isolates from patients less than 8 years of age, who are unlikely to have been prescribed tetracycline, were significantly less resistant to tetracycline than isolates from people aged 8 years or more. This finding also suggests that children more commonly acquire their group A streptococcal infections from their peers than from older people.

No resistance was detected to any of the other antimicrobials tested, that is, cefotaxime, cephalothin, chloramphenicol, mupirocin, and trimethoprim-sulphamethoxazole (co-trimoxazole). As for penicillin, when compared with the results obtained in the 1990 survey, there was either no change or an increase in susceptibility to cefotaxime, cephalothin, chloramphenicol and co-trimoxazole (Appendices 2 and 3 and Table 5). However, there appears to have been a reduction in susceptibility to mupirocin, with an increase in the MIC_{90} value from 0.12 mg/L in 1990 to 0.25 mg/L in 2001 (Table 5), and an extension of the upper MIC range from 0.5 mg/L to 4 mg/L (Appendices 2 and 3). This finding is consistent with the high levels of mupirocin use in New Zealand and the high prevalence (21.5%) of mupirocin resistance among *Staphylococcus aureus* in New Zealand.[22]

Based on the low prevalence of erythromycin resistance and the lack of any change in penicillin susceptibility found in this survey, we recommend that another point-prevalence survey of antimicrobial resistance among group A streptococci should not be required for at least 5-10 years. However, the ongoing monitoring of penicillin and erythromycin resistance through the annual collection and collation of diagnostic laboratory data should continue. In addition, erythromycin-resistant group A streptococci should continue to be included in ESR's Antibiotic-Resistant Bacteria Monitoring Scheme,[26] which requests any laboratory isolating

an erythromycin-resistant group A streptococcus to refer the isolate to ESR. This Scheme also requests laboratories to refer unusual and emerging resistances, so it should detect any group A streptococci that show a change in penicillin susceptibility.

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APPENDIX 1. Laboratories contributing isolates for group A streptococci survey, 2001

Laboratory	Estimated number of group A streptococci isolated per week	Number of isolates included in the survey
Northland Hospital, Whangarei	5	6
North Shore Hospital, Auckland	ne[1]	5
Diagnostic Medical Laboratory, Auckland	180	149
Auckland and Starship Children's Hospital, Auckland	15	16
Middlemore Hospital, Auckland	25	25
Medlab, Hamilton	55	27
Waikato Pathology, Hamilton	40	39
Waikato Hospital, Hamilton	4	5
Thames Hospital, Thames	2	2
Medlab Bay of Plenty, Tauranga	20	19
Whakatane Hospital, Whakatane	5	5
Rotorua Diagnostic, Rotorua	14	15
Rotorua Hospital, Rotorua	4	5
Gisborne Hospital, Gisborne	2	3
Hawkes Bay Hospital, Hastings	1	7
Medlab, New Plymouth	11	10
Taranaki Hospital, New Plymouth	5	3
Diagnostic Laboratory, Wanganui	5	1
Medlab Central, Palmerston North	25	13
Valley Diagnostic Laboratories, Lower Hutt	18	15
Hutt Hospital, Lower Hutt	4	4
Medlab, Wellington	37	35
Wellington Hospital, Wellington	11	10
Nelson Hospital, Nelson	4	2
Medlab South, Christchurch	20	20
Canterbury Health Laboratories, Christchurch	4	5
Medlab, Timaru	ne	5
Southern Community Laboratories, Dunedin	18	18
Dunedin Hospital, Dunedin	ne	4
Medlab Kew, Invercargill	3	1

Note: 1 no estimate

APPENDIX 2. MIC distribution among group A streptococci, 2001

Antimicrobial agent	Number of isolates with a MIC (mg/L) of:														
	0.004	**0.008**	**0.016**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Cefotaxime		14	438	22											
Cephalothin					12	284	178								
Chloramphenicol									21	309	144				
Clindamycin				146	327	1									
Erythromycin					471			1		1		1			
Mupirocin				11	91	280	57	28	1	5	1				
Penicillin	5	142	326	1											
Tetracycline					7	111	246	46	4		1	3	12	28	16
Trimethoprim-sulphamethoxazole[1]				34	245	162	32	1							

Note 1 The MICs for trimethoprim-sulphamethaxazole refer to the trimethoprim content in a ratio of 1 part trimethoprim to 19 parts sulphamethoxazole.

APPENDIX 3. MIC distribution among group A streptococci, 1990

Antimicrobial agent	Number of isolates with a MIC (mg/L) of:														
	0.004	**0.008**	**0.016**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Cefotaxime	2	5	375	51			1								
Cephalothin					4	216	214								
Chloramphenicol										38	394		2		
Clindamycin					25	365	42	2							
Erythromycin					16	363	35	2			1	2	15		
Mupirocin				13	344	58	16	3							
Penicillin		16	416	2											
Tetracycline						15	303	87			2	12	9	6	
Trimethoprim							1	100	284	47	2				
Trimethoprim-sulphamethoxazole[1]				34	156	139	101	4							

Note 1 The MICs for trimethoprim-sulphamethaxazole refer to the trimethoprim content in a ratio of 1 part trimethoprim to 19 parts sulphamethoxazole.