Global Resistance Patterns of Quinolones, Macrolides and β-Lactams From a Multi-center, Multi-country Study of >40,000 Isolates: The Gemifloxacin Surveillance Study

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Abstract

Background: A global *in vitro* surveillance study of 43,768 clinical isolates collected between September 1997 and April 2000 from 130 sites in 42 countries was recently completed. Global and regional resistance patterns to approximately 18,000 of these isolates have been determined for quinolones, macrolides and β-lactam antimicrobials. **Methods:** MICs were determined by broth microdilution using a standardized protocol and reporting system, following NCCLS recommended procedures, using Sensititre or MicroScan panels and ancillary products. **Results:** MIC_{90}s expressed as µg/ml and percent non-susceptible (%) results for gemifloxacin (GEM), levofloxacin (LEV), azithromycin (AZI), clarithromycin (CLA), cefuroxime (CFX) and penicillin (PEN) are listed below:

Number of isolates	GEM	LEV	AZI	CLA	CFX	PEN
North America						
S. pneumoniae (417)	0.03[a]	1 (0)	16 (26)	8 (26)	8 (31)	2 (40)
MSSA (196)	0.12[a]	0.5 (8)	>64 (22)	>16 (21)	4 (6)	>16 (88)
E. coli (358)	0.03[a]	0.5 (5)	16[a]	>16[a]	16 (25)	>16[a]
Latin America						
S. pneumoniae (181)	0.06[a]	1 (0)	16 (16)	2 (16)	4 (18)	1 (41)
MSSA (103)	1[a]	4 (12)	>64 (35)	>16 (28)	8 (9)	>16 (92)
E. coli (393)	8[a]	4 (11)	32[a]	>16[a]	>64 (30)	>16[a]
Europe						
S. pneumoniae (2019)	0.03[a]	1 (1)	>64 (29)	>16 (30)	4 (24)	2 (37)
MSSA (689)	0.06[a]	0.5 (5)	>64 (18)	>16 (16)	4 (5)	>16 (84)
E. coli (3036)	0.5[a]	0.5 (9)	8[a]	>16[a]	8 (22)	>16[a]
Asia/Pacific						
S. pneumoniae (778)	0.06[a]	1 (0)	>64 (51)	>16 (51)	8 (40)	2 (56)
MSSA (1145)	1[a]	4 (22)	>64 (66)	>16 (37)	2 (2)	>16 (92)
E. coli (1069)	32[a]	>16 (23)	64[a]	>16[a]	>64 (33)	>16[a]

MSSA, methicillin-susceptible *Staphylococcus aureus*. [a]Breakpoints have not been established by NCCLS

Conclusions: Regional variations in resistance patterns were observed in all antimicrobials tested. Greatest variations were seen with the macrolides, penicillin and cefuroxime. Quinolones exhibited the least variation among regions. The gemifloxacin MIC_{90} for *S. pneumoniae* was lower than other quinolones and all other groups tested.

Introduction

Gemifloxacin, an enhanced-affinity fluoroquinolone, has demonstrated *in vitro* activity that includes the Gram negative bacteria *Escherichia coli*, *Klebsiella pneumoniae* and *Haemophilus influenzae* as well as Gram positive bacteria such as streptococci and staphylococci.[1-4] The *in vitro* activities of gemifloxacin, other quinolones, macrolides and β-lactams were determined against 18,144 recent clinical isolates of *H. influenzae*, *Streptococcos pneumoniae*, *E. coli*, *K. pneumoniae*, *Moraxella catarrhalis* and methicillin-susceptible *Staphylococcus aureus* in 130 centers located in 42 countries throughout Europe, North America, Latin America, Asia, Africa/Middle East and the South Pacific. Regional *in vitro* activity and susceptibility differences were calculated for all organisms tested in this study.

Materials and Methods

Isolates

- Isolates were collected between September 1997 and April 2000. Most sites (n = 130) in 42 countries contributed up to 50 isolates of each aerobic Gram positive and Gram negative pathogen as well as up to 100 isolates each of *E. coli* and *K. pneumoniae*.
- Only one isolate per patient was accepted. Each isolate was identified and deemed to be a significant pathogen using local laboratory criteria.
- Isolate collection, processing, transport and antimicrobial susceptibility testing methods, as well as the construction of a centralized database to record worldwide antimicrobial susceptibility testing results, were coordinated by Laboratories International for Microbiology Studies, International Health Management Associates (IHMA) (Rolling Meadows, IL, USA).
- Available demographic information included patient age, specimen source and inpatient *versus* outpatient information.

Antimicrobial Susceptibility Testing

- MICs were determined by the NCCLS recommended broth microdilution testing method.[5] The microdilution panels used in this study were purchased from Sensititre® (Trek Diagnostics Inc., Westlake, OH, USA) and MicroScan® (Dade Behring Inc., Sacramento, CA, USA) and utilized identical antimicrobial dilution configurations. Gemifloxacin was supplied by SmithKline Beecham (Collegeville, PA, USA) and comparative antimicrobials by their respective manufacturers or the panel manufacturer. Appropriate broth media were also provided directly by the panel manufacturers.
- MICs were determined in each participating country at one or more designated laboratories.
- Gemifloxacin disk testing (5 and 10 µg disks) was conducted by most testing sites in Europe and North America.
- The antimicrobial breakpoints used for data analysis were those recommended by the NCCLS for broth dilution susceptibility testing.[6]
- Each designated testing laboratory performed quality controls on each day of testing using *E. coli* ATCC 35218 and 25922, *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49766 and 49247, and *S. aureus* ATCC 29213. Test isolate results were accepted into the final analysis only if the quality control isolate MICs were within the acceptable range defined by NCCLS guidelines.[6]

Participating Study Centers

The number of isolates and collecting sites per region are shown in Table 1.

Results

The results are shown in Tables 2–7 and Figure 1.

Table 1. Number of Sites and Isolates Per Region

	Europe	North America	Latin America	Asia	Africa/ Middle East	S. Pacific
No. of sites	61	15	19	17	11	7
Microrganism						
S. pneumoniae	2019	417	181	693	132	85
H. influenzae	1510	316	182	329	158	83
M. catarrhalis	471	231	98	107	119	56
MSSA	689	196	103	1068	207	77
E. coli	3036	358	393	894	284	175
K. pneumoniae	1575	282	290	864	298	168

MSSA, methicillin-susceptible *S. aureus*

Table 2. *In Vitro* Activity of Gemifloxacin, Other Quinolones, Macrolides and β-Lactams Against 3527 Isolates of *S. pneumoniae* from Six Global Regions

Antimicrobial	MIC (µg/ml)	Europe (n = 2019)	North America (n = 417)	Latin America (n = 181)	Asia (n = 693)	Africa/ Middle East (n = 132)	South Pacific (n = 85)
Gemifloxacin	MIC_{50}	0.015	0.015	0.03	0.03	0.03	0.03
	MIC_{90}	0.03	0.03	0.06	0.06	0.06	0.06
	% S[a]	NA[c]	NA	NA	NA	NA	NA
	% NS[b]	NA	NA	NA	NA	NA	NA
Ciprofloxacin	MIC_{50}	1	1	1	1	1	1
	MIC_{90}	2	2	2	2	1	2
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA
Levofloxacin	MIC_{50}	0.5	1	1	1	1	1
	MIC_{90}	1	1	1	1	1	2
	% S	99.5	100	100	99.9	100	100
	% NS	0.5	0	0	0.1	0	0
Azithromycin	MIC_{50}	<0.06	0.06	<0.06	4	0.12	0.06
	MIC_{90}	>64	16	16	>64	8	8
	% S	70.8	74.3	84.5	43.9	79.0	88.2
	% NS	29.2	25.7	15.5	56.1	21.0	11.8
Clarithromycin	MIC_{50}	0.03	0.03	<0.015	2	0.03	0.03
	MIC_{90}	>16	8	2	>16	2	1
	% S	70.0	73.6	84.0	44.7	82.7	88.2
	% NS	30.0	26.4	16.0	55.3	17.3	11.8
Cefuroxime	MIC_{50}	<0.06	0.06	<0.06	0.5	0.12	<0.06
	MIC_{90}	4	8	4	8	2	4
	% S	76.0	69.3	82.3	58.0	86.5	77.4
	% NS	24.0	30.7	17.7	42.0	13.5	22.6
Penicillin	MIC_{50}	0.015	0.03	0.03	0.25	0.12	0.03
	MIC_{90}	2	2	1	2	1	2
	% S	63.1	59.7	59.4	41.4	36.1	68.2
	% NS	36.9	40.3	40.6	58.6	63.9	31.8

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate and % resistant categories[c]
[b]NS, non-susceptible (intermediate and resistant isolates)
[c]NA, breakpoints have not been established by NCCLS

Table 3. *In Vitro* Activity of Gemifloxacin, Other Quinolones, Macrolides and β-Lactams Against 2578 Isolates of *H. influenzae* from Six Global Regions

Antimicrobial	MIC (µg/ml)	Europe (n = 1510)	North America (n = 316)	Latin America (n = 182)	Asia (n = 329)	Africa/ Middle East (n = 158)	South Pacific (n = 83)
Gemifloxacin	MIC_{50}	0.002	0.008	0.008	0.008	0.008	0.004
	MIC_{90}	0.008	0.008	0.03	0.03	0.03	0.008
	% S[a]	NA[c]	NA	NA	NA	NA	NA
	% NS[b]	NA	NA	NA	NA	NA	NA
Ciprofloxacin	MIC_{50}	<0.015	0.015	<0.015	<0.015	<0.015	0.015
	MIC_{90}	0.015	0.015	0.12	0.03	0.03	0.015
	% S	99.9	100	99.5	99.1	98.1	100
	% NS	0.1	0	0.5	0.9	1.9	0
Levofloxacin	MIC_{50}	<0.015	<0.015	<0.015	<0.015	<0.015	0.015
	MIC_{90}	0.03	0.12	0.12	0.03	0.06	0.015
	% S	99.9	100	99.5	99.7	100	100
	% NS	0.1	0	0.5	0.3	0	0
Azithromycin	MIC_{50}	0.5	0.5	1	2	1	1
	MIC_{90}	2	2	2	4	4	2
	% S	99.4	95.5	96.7	96	97.5	100
	% NS	0.6	4.5	3.3	4	2.5	0
Clarithromycin	MIC_{50}	8	4	4	8	8	8
	MIC_{90}	8	8	16	>16	16	8
	% S	92.5	91.1	89.6	63.8	79.3	90.4
	% NS	7.5	8.9	10.4	36.2	20.7	9.6
Cefuroxime	MIC_{50}	0.5	0.5	0.5	1	1	0.5
	MIC_{90}	2	1	32	2	4	2
	% S	98.0	100	88.5	97	95.6	100
	% NS	2.0	0	11.5	3	4.4	0
Penicillin	MIC_{50}	0.5	0.5	0.5	0.5	0.5	0.5
	MIC_{90}	16	2	>16	>16	16	>16
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate and % resistant categories[c]
[b]NS, non-susceptible (intermediate and resistant isolates)
[c]NA, breakpoints have not been established by NCCLS

Table 4. *In Vitro* Activity of Gemifloxacin, Other Quinolones, Macrolides and β-Lactams Against 1082 Isolates of *M. catarrhalis* from Six Global Regions

Antimicrobial	MIC (µg/ml)	Europe (n = 471)	North America (n = 231)	Latin America (n = 98)	Asia (n = 107)	Africa/ Middle East (n = 119)	South Pacific (n = 56)
Gemifloxacin	MIC_{50}	0.008	0.008	0.015	0.03	0.03	0.008
	MIC_{90}	0.015	0.008	0.03	0.03	0.25	0.015
	% S[a]	NA[c]	NA	NA	NA	NA	NA
	% NS[b]	NA	NA	NA	NA	NA	NA
Ciprofloxacin	MIC_{50}	0.03	0.03	0.03	0.03	0.12	0.03
	MIC_{90}	0.06	0.03	0.06	0.06	1	0.03
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA
Levofloxacin	MIC_{50}	0.03	0.03	0.03	0.06	0.12	0.03
	MIC_{90}	0.06	0.06	0.06	0.06	1	0.06
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA
Azithromycin	MIC_{50}	<0.06	0.06	<0.06	0.12	1	0.06
	MIC_{90}	0.06	0.06	0.25	0.12	2	0.5
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA
Clarithromycin	MIC_{50}	0.12	0.06	0.06	0.12	0.5	0.12
	MIC_{90}	0.25	0.12	0.5	0.25	8	0.25
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA
Cefuroxime	MIC_{50}	1	1	1	2	2	1
	MIC_{90}	2	2	2	8	8	2
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA
Penicillin	MIC_{50}	8	8	8	>16	2	8
	MIC_{90}	>16	16	>16	>16	>16	16
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate and % resistant categories[c]
[b]NS, non-susceptible (intermediate and resistant isolates)
[c]NA, breakpoints have not been established by NCCLS

Table 5. *In Vitro* Activity of Gemifloxacin, Other Quinolones, Macrolides and β-Lactams Against 2340 Isolates of Methicillin-susceptible *S. aureus* from Six Global Regions

Antimicrobial	MIC (µg/ml)	Europe (n = 689)	North America (n = 196)	Latin America (n = 103)	Asia (n = 1068)	Africa/ Middle East (n = 207)	South Pacific (n = 77)
Gemifloxacin	MIC_{50}	0.015	0.015	0.03	0.03	0.03	0.03
	MIC_{90}	0.06	0.12	1	1	4	0.03
	% S[a]	NA[c]	NA	NA	NA	NA	NA
	% NS[b]	NA	NA	NA	NA	NA	NA
Ciprofloxacin	MIC_{50}	0.25	0.25	0.5	0.25	0.25	0.25
	MIC_{90}	1	1	2	8	8	0.5
	% S	90.3	90.8	87.5	76.1	85.5	96.1
	% NS	9.7	9.2	12.5	23.9	14.5	3.9
Levofloxacin	MIC_{50}	0.12	0.12	0.25	0.25	0.25	0.12
	MIC_{90}	0.5	0.5	4	4	4	0.25
	% S	95.1	92.4	88.5	76.3	89.4	97.4
	% NS	4.9	7.6	11.5	23.7	10.6	2.6
Azithromycin	MIC_{50}	0.5	0.5	2	4	1	1
	MIC_{90}	>64	>64	>64	>64	>64	>64
	% S	81.6	78.1	65.4	30.4	67.6	88.3
	% NS	18.4	21.9	34.6	69.6	32.4	11.7
Clarithromycin	MIC_{50}	0.25	0.25	0.25	0.5	0.25	0.25
	MIC_{90}	>16	>16	>16	>16	>16	>16
	% S	84.0	78.6	72.1	61.6	70.1	88.3
	% NS	16.0	21.4	27.9	38.4	29.9	11.7
Cefuroxime	MIC_{50}	2	2	2	1	1	1
	MIC_{90}	4	4	8	2	>64	2
	% S	95.5	93.9	91.4	98.5	75.9	95.4
	% NS	4.5	6.1	8.6	1.5	24.1	4.6
Penicillin	MIC_{50}	8	2	8	>16	16	4
	MIC_{90}	>16	>16	>16	>16	>16	>16
	% S	16.1	11.8	7.7	7.4	5.8	11.7
	% NS	83.9	88.2	92.3	92.6	94.2	88.3

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate and % resistant categories[c]
[b]NS, non-susceptible (intermediate and resistant isolates)
[c]NA, breakpoints have not been established by NCCLS

Table 6. *In Vitro* Activity of Gemifloxacin, Other Quinolones, Macrolides and β-Lactams Against 5140 Isolates of *E. coli* from Six Global Regions

Antimicrobial	MIC (µg/ml)	Europe (n = 3036)	North America (n = 358)	Latin America (n = 393)	Asia (n = 894)	Africa/ Middle East (n = 284)	South Pacific (n = 175)
Gemifloxacin	MIC_{50}	0.008	0.008	0.03	0.06	0.03	0.015
	MIC_{90}	0.5	0.03	8	32	16	0.03
	% S[a]	NA[c]	NA	NA	NA	NA	NA
	% NS[b]	NA	NA	NA	NA	NA	NA
Ciprofloxacin	MIC_{50}	<0.015	0.015	<0.015	0.03	<0.015	0.015
	MIC_{90}	1	0.5	8	>16	8	0.015
	% S	90.5	94.9	86.0	72.4	81.0	98.3
	% NS	9.5	5.1	14.0	27.6	19.0	1.7
Levofloxacin	MIC_{50}	0.03	0.03	0.03	0.06	0.03	0.03
	MIC_{90}	0.5	0.5	4	>16	8	0.03
	% S	91.7	95.5	88.8	73.2	81.3	98.9
	% NS	8.3	4.5	11.2	26.8	18.7	1.1
Azithromycin	MIC_{50}	4	2	4	8	4	4
	MIC_{90}	8	16	32	64	64	16
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA
Clarithromycin	MIC_{50}	>16	>16	>16	>16	>16	>16
	MIC_{90}	>16	>16	>16	>16	>16	>16
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA
Cefuroxime	MIC_{50}	4	4	4	4	2	2
	MIC_{90}	8	16	>64	>64	8	4
	% S	77.8	75.1	69.7	62.6	77.8	91.3
	% NS	22.2	24.9	30.3	37.2	22.2	8.7
Penicillin	MIC_{50}	>16	>16	16	>16	>16	>16
	MIC_{90}	>16	>16	>16	>16	>16	>16
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA

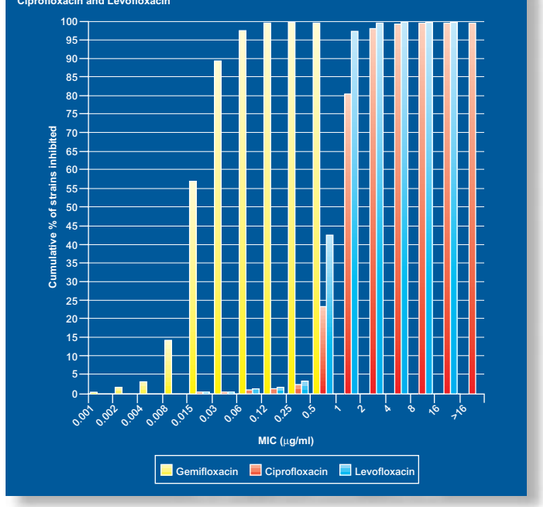
[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate and % resistant categories[c]
[b]NS, non-susceptible (intermediate and resistant isolates)
[c]NA, breakpoints have not been established by NCCLS

Table 7. *In Vitro* Activity of Gemifloxacin, Other Quinolones, Macrolides and β-Lactams Against 3477 Isolates of *K. pneumoniae* from Six Global Regions

Antimicrobial	MIC (µg/ml)	Europe (n = 1575)	North America (n = 282)	Latin America (n = 290)	Asia (n = 864)	Africa/ Middle East (n = 298)	South Pacific (n = 168)
Gemifloxacin	MIC_{50}	0.03	0.03	0.06	0.25	0.06	0.03
	MIC_{90}	1	0.25	2	2	1	0.12
	% S[a]	NA[c]	NA	NA	NA	NA	NA
	% NS[b]	NA	NA	NA	NA	NA	NA
Ciprofloxacin	MIC_{50}	0.03	0.03	0.03	0.12	0.03	0.03
	MIC_{90}	2	0.5	1	2	1	0.12
	% S	88.7	95.0	92.1	88.9	91.6	97.0
	% NS	11.3	5.0	7.9	11.1	8.4	3.0
Levofloxacin	MIC_{50}	0.06	0.06	0.06	0.12	0.06	0.06
	MIC_{90}	2	0.5	1	4	2	0.25
	% S	90.8	96.5	93.8	88.1	90.3	97.0
	% NS	9.2	3.9	6.2	11.9	9.7	3.0
Azithromycin	MIC_{50}	8	8	8	32	8	8
	MIC_{90}	16	16	32	64	16	16
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA
Clarithromycin	MIC_{50}	>16	>16	>16	>16	>16	>16
	MIC_{90}	>16	>16	>16	>16	>16	>16
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA
Cefuroxime	MIC_{50}	4	2	8	4	2	2
	MIC_{90}	64	8	>64	>64	64	8
	% S	71.3	75.2	44.5	59.0	73.5	89.6
	% NS	28.7	24.8	55.5	41.0	26.5	10.4
Penicillin	MIC_{50}	>16	>16	>16	>16	>16	>16
	MIC_{90}	>16	>16	>16	>16	>16	>16
	% S	NA	NA	NA	NA	NA	NA
	% NS	NA	NA	NA	NA	NA	NA

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate and % resistant) categories[c]
[b]NS, non-susceptible (intermediate and resistant isolates)
[c]NA, breakpoints have not been established by NCCLS

Figure 1. Cumulative Percentage of 3527 *S. pneumoniae* Strains Inhibited by Gemifloxacin, Ciprofloxacin and Levofloxacin



Conclusions

- Gemifloxacin demonstrated the lowest MIC_{90} against *S. pneumoniae* when compared with all other antimicrobials tested.
- Macrolides exhibited the greatest variation in MIC_{90}s for *S. pneumoniae* when compared among all regions.
- MIC_{90}s for gemifloxacin, ciprofloxacin, levofloxacin and cefuroxime against Gram negative enterics were highest in Asia, Africa/Middle East and Latin America, respectively, and lowest in North America, South Pacific and Europe, respectively.
- Regional variations in MIC_{90}s were observed for all antimicrobials tested.
- Gemifloxacin MIC_{90}s for *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* were lower than most comparative agents regardless of regional differences.

Acknowledgments

A. Georgopoulos; A.G.M. Buiting; A. Perez Miravette; A. Gibb; A. Elbashier; A. King; A.M. Sherretta; A. Victor; A. Jansz; A. Morris; A. Ljungh; A. Al-Ajeel; B. Sixl; B.G.A. Hendriks; B.P. Overbeek; B. Toye; B. Allen; B. Sarachian; B. Weidemann; C. Roggeveen; C.L. Jansen; C.P. Timmerman; C. Mendes; C.M. Zocolli; C. Berhin; C. Restieri; C. Franklin; C. Nonhoff; D. Gregson; D. Stamboulian; D. Hoban; D. Church; D. Gomez Barreto; D. Andreazzi; D. Doukakis; D. Low; D. Thessaloniki; E. Stobberingh; E. Aguirre Langle; E. Sada Diaz; E. Randall; E.J. Baron; E. Mamizuka; E. Bouza Santiago; E. Grund; F. Rossi; F. Jehl; F. Allerberger; G. Petrikos; G. Weers Pothof; G.-C. Schito; S. Giuliana Lusco; G. Leven; H. Naaktgeboren; H. Miornar; H. Seifert; H. Giamarellou; H. Hudler; H. Lopez; I. Ahmed; J.H. Oudbier; J. Bille; J. Mokhbat; J.-H. Song; J. Hutchinson; J. Verhaegen; J. Moller; J. Fasogali; J. Harkness; J. Gomez Campdera; J. Santos; J. Sifuentes; J. Feichtinger; J. Carlos Tinoco; K. Kriti; K. El-Haj; K. Weiss; K. Kluqman; K. Forward; K. Machka; L.J.M. Sabbe; L.E. Espinosa; M. Lontie; M. Kuhn; M.V. Vye; M. Mueller; M. Marin; M. Seewald; M. Konkoly Thege; M. Jones; M. Vaara; M. Gallina; M. Weber; M. Delvallez; M. Chomarat; N. George; N. Rehman; N. Chan; O. Menekse; P. Kibsey; P. Patras; R. Vanhoof; R.J.A. Diepersloot; R.Garcia; R.R. Reinert; R. Thomson; R. Wilson; R.M. Hinojosa; R. Morales; R. Ikram; R. Hafiz; S. Thessaloniki; S. Chugtai; S. Al Aithan; T.A.M. Trienekens; T.D. Chugh; T. Youssef; T. Riley; V. Schaefer; W. Hryniewicz.; W. Dibb; W. Brown; Y.J. Debets Ossenkopp; Y. Abu; Z. Memish; Al-Bashir; R. Leclercq; A.O. Osaba; K. Pelz; A. Famiglietti; E. Romo; E. Kalomenopulos; E. Panagiotaki; F. Goldstein; G. Alvarez; J. Sampaio; L. Casimir; P.G.H. Peerbooms; R. Hemmer; R.W. Vreede; T. Schulin; D. Sofianou.

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