Persistently High Macrolide Resistance Rates of *Streptococcus pneumoniae* in Asia – Results of the TEST study (2004 – 2009)

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S. Bouchillon[1], S. Hawser[2], M. Hackel[1], R. Badal[1], B. Johnson[1], J. Johnson[1], D. Hoban[1], M. Dowzicky[3]
[1]International Health Management Associates, Inc., Schaumburg, IL, USA
[2]IHMA Europe Sàrl, Epalinges, Switzerland
[3]Pfizer, Inc., Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL
60173
Tel: 847.303.5003
www.ihmainc.com

Revised Abstract

Background: The global macrolide resistance (MR) rate for *Streptococcus pneumoniae* (*Spn*) has consistently remained between 25% and 35% for the last several years. MR in *Spn* varies among regions and countries and is known to increase with macrolide use and decrease with macrolide conservation and interventions. The highest MR rates have been noted in several Asian countries, prominently Taiwan. The Tigecycline Evaluation and Surveillance Trial (TEST) study has been monitoring resistance rates in selected drugs and species since 2004. This study reports the persistently high *Spn* MR rates in several Asian countries from 2004 to 2009. **Methods**: 452 *Spn* were evaluated from 8 Asian countries. Clinical isolates were identified to the species level at each participating site and confirmed by a central laboratory. MICs were determined by the local laboratory using supplied broth microdilution panels and interpreted according to CLSI or FDA guidelines. **Results**: MR rates were 98% in Taiwan followed closely by rates of 84%, 79%, 75%, and 62% in South Korea, Hong Kong, China, and Thailand, respectively. MR rates ranging from 44% to 39% were observed in Singapore and Pakistan. India had the lowest MR rate at 9.4%. Correspondingly high overall non-susceptible rates were seen for clindamycin (51%), penicillin (60%), and meropenem (65%). None of the isolates were resistant to linezolid. Overall susceptibility of tigecycline was 93%, 97% for levofloxacin, and 98% for vancomycin. **Conclusion**: High MR rates persist against *Spn* in many Asian countries with 98% resistance in Taiwan and significant MR rates in South Korea, Hong Kong, China, and Thailand. Multidrug resistance was observed for erythromycin, clindamycin, meropenem and penicillin. ≥94% MR *Spn* was susceptible against linezolid, vancomycin, levofloxacin, and tigecycline.

Introduction

Streptococcus pneumoniae (SPN) is a frequent cause of respiratory tract infections. Emergence and spread of resistance to commonly used antibiotics has complicated treatment. Increasing rates of macrolide resistance in SPN have been reported world-wide [1, 2]. Macrolide resistance rates have been reported in individual Asian countries exceeding 80% since 1999 [3-6]. There are dire implications associated with macrolide-resistance in *S. pneumoniae* including, but not limited to, clonal spreading, multi-drug resistance, and non-vaccine serotypes.

The current study investigated the *in vitro* activity of macrolides (erythromycin) and comparators in 8 Asian countries from 2004 through 2009 against clinical isolates of *S. pneumoniae* as part of the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.).

Materials & Methods

- **Clinical isolates:** Isolates were identified to the species level and tested at each participating laboratory. All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age, or gender. All sites identified each study isolate utilizing local laboratory criteria. All isolates were from the period 2004 - 2009 and originated from Africa, Asia, Europe, Latin America, Middle East, North America and the South Pacific.
- **Susceptibility testing**: Minimum inhibitory concentrations (MICs) were determined using custom plates manufactured by MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) or Trek (TREK Diagnostic Systems, Cleveland, OH, USA), following manufacturer and Clinical and Laboratory Standards Institute (CLSI) instructions for broth microdilution testing (7). Susceptibility was determined using clinical breakpoints published by the CLSI (linezolid and comparators) and the US Food and Drug Administration package insert (tigecycline), where applicable (8, 9).
- **Quality controls** (QC) were performed by each testing *site on* each day of *testing* using *S. aureus* ATCC 29213; *E. faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2010) guidelines (8).

References

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Acknowledgements

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Results

Figure 1. Distribution *Streptococcus pneumoniae* isolates (n=452) collected in Asia from 2004 – 2009 categorized by country.

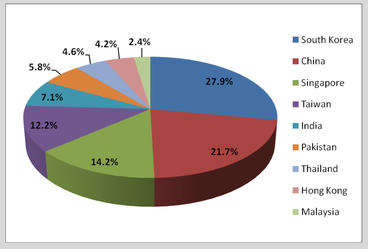
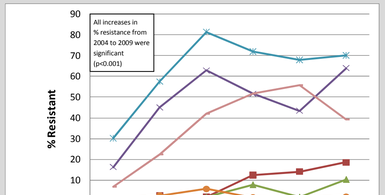


Table 1. *In vitro* activity of antimicrobial agents against *Streptococcus pneumoniae* (n=452) from Asia, 2004 - 2009.

Drug	N	MIC_{50}	MIC_{90}	%Sus [a]	%Int	%Res
Amox-Clav	452	0.5	4	81.86	8.41	9.73
Ceftriaxone	452	0.25	2	82.52	13.27	4.2
Clindamycin	452	2	>64	49.12	0	50.89
Erythromycin	452	64	>64	32.08	0.44	67.48
Imipenem [b]	83	≤0.12	0.5	62.65	28.92	8.43
Levofloxacin	452	1	1	97.35	0.22	2.43
Linezolid	452	≤0.5	1	100*	—	—
Meropenem [b]	369	0.25	1	50.41	22.49	27.1
Penicillin	452	0.5	4	39.82	19.25	40.93
Tigecycline	452	0.015	0.06	93.14*	—	—
Vancomycin	452	0.25	0.5	98.45*	—	—

[a] Breakpoints defined by CLSI document M100-S20 (2010), where applicable. Tigecycline breakpoints are defined by FDA (Tygacil®, 2009).
* Only susceptible breakpoints are defined for linezolid, tigecycline and vancomycin.
[b] Meropenem replaced imipenem in 2006 in the study.

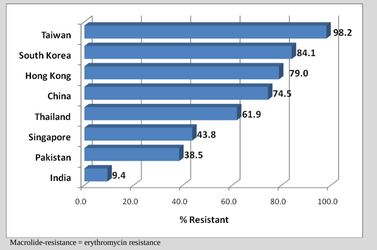
Figure 3. Increasing resistance rates for antibiotics against *Streptococcus pneumoniae* in Asia, 2004 - 2009.



	2004 (n=43)	2005 (n=40)	2006 (n=102)	2007 (n=64)	2008 (n=106)	2009 (n=97)
Amox-Clav	0	2.5	1.96	12.5	14.15	18.56
Ceftriaxone	0	0	1.96	7.81	1.89	10.31
Clindamycin	16.28	45	62.75	51.56	43.4	63.92
Erythromycin	30.23	57.5	81.37	71.88	67.92	70.1
Levofloxacin	0	2.5	5.88	1.56	0.94	2.06
Linezolid*	0	0	0	0	0	0
Penicillin	6.98	22.5	42.16	51.56	55.66	39.18
Tigecycline*	0	0	0	0	0	0
Vancomycin*	0	0	0	0	0	0

* Resistant breakpoints are not defined for these antibiotics by the CLSI (M100-S20, 2010).

Figure 2. Percentage of macrolide-resistance for *Streptococcus pneumoniae* (n=305) in eight Asian countries, 2004 – 2009.



Macrolide-resistance = erythromycin resistance

Table 2. *In vitro* activity of antimicrobial agents against macrolide-resistant *Streptococcus pneumoniae* (n=305) from Asia, 2004 - 2009.

Drug	N	MIC_{50}	MIC_{90}	%Sus [a]	%Int	%Res
Amox-Clav	305	1	8	73.77	12.13	14.1
Ceftriaxone	305	1	2	74.1	19.67	6.23
Clindamycin	305	>64	>64	24.59	0	75.41
Erythromycin	305	64	>64	0	0	100
Imipenem [b]	41	0.25	1	39.02	43.9	17.07
Levofloxacin	305	1	1	96.72	0.33	2.95
Linezolid	305	≤0.5	1	100	—	—
Meropenem [b]	264	0.5	1	35.23	27.65	37.12
Penicillin	305	2	4	22.62	20.33	57.05
Tigecycline	305	0.015	0.06	94.75	—	—
Vancomycin	305	0.25	0.5	97.7	—	—

[a] Breakpoints defined by CLSI document M100-S20 (2010), where applicable. Tigecycline breakpoints are defined by FDA (Tygacil®, 2009).
Only susceptible breakpoints are defined for linezolid, tigecycline and vancomycin.
[b] Meropenem replaced imipenem in 2006 in the study.

Conclusions

- Macrolide resistance (erythromycin) in *S. pneumoniae* has been increasing in Asia for over a decade. The TEST surveillance study documented a 40% increase in macrolide resistance since 2004 to the current level of 70.1% in 2009 ($p<0.001$). Significant increases in resistance rates against *S. pneumoniae* are also seen for amoxicillin-clavulanic acid, ceftriaxone, clindamycin, levofloxacin, and penicillin. 100% of all isolates were susceptible to linezolid.
- Almost all *S. pneumoniae* were recorded as resistant to erythromycin in Taiwan (98%). South Korea, Hong Kong and China had macrolide-resistant rates that are approximately double those of the rest of the world at 84.1%, 79.0% and 74.5%, respectively. India had the lowest macrolide-resistant rate of all the Asian countries at 9.4%.
- Multi-drug resistance was demonstrated in macrolide-resistant isolates with clindamycin (75.4% resistant), penicillin (57% resistant), and meropenem (37.1% resistant). 100% of the macrolide-resistant isolates were susceptible to linezolid and more than 94% were susceptible to vancomycin, levofloxacin, and tigecycline (although resistance for vancomycin and tigecycline against *S. pneumoniae* are not defined by the CLSI or FDA).
- Continued surveillance is warranted in the following of macrolide- and multi-drug-resistant trends against *S. pneumoniae* in Asia.