Background: S. pneumoniae is a key causative pathogen of community-acquired respiratory tract infections. The clinical management of these infections is complicated by the worldwide emergence and spread of resistance to commonly used antibiotics. Resistance to macrolides in S. pneumoniae is mediated by two major mechanisms: modification of the ribosomal macrolide target site, encoded by ermA or ermB, or efflux by medA or mefE. ErmB typically confers high-level resistance to macrolides, lincosamides and streptogramin B, whereas MefE or Mef confers low-level resistance to macrolides only. The aim of this study was to determine the prevalence of such mechanisms of resistance in various geographical regions. Methods: A total of 648 macrolide-resistant (erythromycin MIC ≥ 1 mg/L) S. pneumoniae clinical isolates collected through the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) from 2004 to 2008 were tested. Detection of genes conferring macrolide resistance (ermB, mefE and mefA) was performed by multiplex PCR. Results: Among these 648 isolates, 58.6% were isolated in North America, 24.7% in Europe, 7.1% in Asia, 6.5% in Latin America, 1.5% in Africa and 0.6% in Middle East and South Pacific. Of the 648 isolates studied, 35.2% were ermA-positive. 32.2% were mefE-positive. 25% were positive for both erm and mef and 4.5% were mefA-positive. 2.5% of the isolates were negative for any of these mechanisms. MefE was the most common gene identified in North America (41.8%) while in Europe the most frequent was ermA (67.5%), and a high prevalence of mefE/mefA genes (25%) can be highlighted in North America. Conclusions: The distribution of pneumococcal macrolide resistance is an important phenomenon because of the diversity of prevalence by region. A rapid increase in isolates containing both erm and mef has been noted in the last several years in the United States.

Introduction

Resistance to macrolides in S. pneumoniae is mediated by two major mechanisms [2]:

- Target modification caused by a ribosomal methylase encoded by the erm gene.
- Drug efflux encoded by the mef gene.

High-level macrolide resistance (MIC ≥ 8 mg/L) is usually associated with ermA, whereas mefA-positive resistance is the most prevalent mechanism in the United States (5) usually results in lower-level resistance (MIC = 0.15-1.1).

- Resistance to macrolides in S. pneumoniae has increased dramatically during the last decade [4, 10].

- This study will investigate the incidence of macrolide resistance mechanisms (erm and mef genes) in a worldwide collection of isolates.

Materials and Methods

- 648 macrolide-resistant S. pneumoniae clinical isolates from 2004-2008 collected through the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) were tested. All the isolates included in the study were Erythromycin-resistant (MIC ≥ 4 mg/L).
- 4 control strains were used in this study: erythromycin-sensitive isolate, mefE-positive isolate, mefE-negative isolate and ermA-positive/mefE double-positive isolate.

- **Regions/Clusters:**
  - Europe
  - South Pacific
  - Middle East
  - North America
  - Africa
  - Asia
  - 648 isolates

- **Site Location:**
  - Respiratory: 32.3%
  - Blood: 0.7%
  - HEENT: 0.6%
  - Other: 2.7%

- **Site:**
  - Medical: General (24.9%) and ICU (33.3%)
  - Critical Care: 14.2%
  - Emergency Room: 12%
  - Pediatric: General (8.8%) and ICU (2.3%)
  - Surgery: General (18.5%) and ICU (2.8%)
  - Trauma: 8.9%
  - Non-Given: 8.5%

- **Detection:**
  - Multiplex PCR
  - QAGEN Multiplex PCR kit

- **Oligonucleotide primers used in this study:**

- **Materials & Methods**

- **Table 1: Phenotypic and genotypic data for the 648 macrolide-resistant S. pneumoniae isolates.**

- **Table 2: Multiplex PCR components**

- **Table 3: Oligonucleotide primers used in this study**

- **References**

- **Results**

- **Figure 1: Global prevalence of macrolide resistance mechanisms among 648 S. pneumoniae isolates.**

- **Figure 2: Distribution of Erythromycin MICs among mefA and mefE-positive isolates.**

- **Figure 3: Worldwide incidence of macrolide resistance mechanisms among S. pneumoniae isolates from 2004 to 2008.**

- **Figure 4: Geographic differences in the prevalence of macrolide resistant mechanisms.**

- **Figure 5: Incidence of macrolide resistance isolates in US during 2004-2008.**

- **Conclusions**

- In this study, resistance to macrolide antibiotics in S. pneumoniae worldwide is typically mediated equally by ermA and mefE.

- However, the worldwide distribution of resistance is very different by region:
  - North America: mefA/E and increase of ermA/mefE
  - Europe: ermA

- In addition, in this study isolates carrying only the mefA/E gene showed a higher-level resistance (MIC≥8 mg/L) than expected. Recent data have suggested that the macrolide MICs for a growing proportion of mef/E/A isolates exceed 6 mg/L. However, further investigations are needed to elucidate the precise mechanism involved.

- Our study confirms that the prevalence of mef/E/A is decreasing in United States and isolates harboring ermA and mef/E/A genes are becoming increasingly common as already described (6, 7).

- These findings indicate that macrolide resistance may not have plateaued as previously thought. Continued surveillance of erythromycin resistance in general and of highly resistant ermA+mefE strains in particular, is warranted.

#P995

C. Lascor, M. Hackell, A. Werbowetzki, D. Hostenb, B. Johnson, J. Johnson, M. Dowdley

*International Health Management Associates, Schaumburg, IL, USA*

*University of Manitoba, Winnipeg, Canada*

*Pfizer Inc., Collegeville, PA, USA*

**Worldwide Prevalence of Macrolide Resistance Genotypes among Streptococcus pneumoniae from 2004 to 2008**


**Materials & Methods**

- **Detection of genes conferring macrolide resistance (ermB, mefE and mefA) was performed by multiplex PCR.**
- **Materials:**
  - Multiplex PCR: QAGEN Multiplex PCR kit
  - Detection of genes encoding macrolide resistance (ermB, mefE and mefA) was performed by multiplex PCR.**

**Results**

- **Table 1: Oligonucleotide primers used in this study**

- **Table 2: Multiplex PCR components**

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IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL 60173
Tel: 847.303.5003
Fax: 847.303.5601