

COMMUNICATION

Unveiling the prevalence of macrolide resistance genes in *Streptococcus pneumoniae* isolates from Indonesia

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Abstract

The effectiveness of macrolides in the treatment of pneumococcal infections has been increasingly challenged by the emergence and spread of antibiotic resistance mechanisms. This study aims to determine the prevalence of macrolide resistance genes (*mefA* and *ermB*) among *Streptococcus pneumoniae* isolates from selected regions of Indonesia. A total of 703 archived *S. pneumoniae* isolates were screened for both genes using polymerase chain reaction. A total of 11% and 4% isolates were positive for *mefA* and *ermB*, respectively. The major serotype carrying the *mefA* gene was 19F (48%), followed by serotype 23F (39%). The predominant serotype containing the *ermB* genes was 19F (17%). The occurrence of macrolide resistance in *S. pneumoniae* in Indonesia shows a notable pattern, with the most prominent presence observed in serotype 19F.

Keywords: *Streptococcus pneumoniae*; Macrolide resistance; Serotype 19F; Indonesia

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1. Introduction

Streptococcus pneumoniae is a significant pathogen responsible for diseases including pneumonia, bacteremia, and meningitis. However, it has exhibited increasing resistance to macrolide antibiotics in recent years. This trend poses a substantial challenge to public health, as macrolides are commonly used to treat pneumococcal infections.¹ The *ermB* and *mefA* genes are among the principal genetic determinants of macrolide resistance in *S. pneumoniae*. Safari *et al.*² found that the prevalence of isolates carrying the *ermB* and *mefA* genes increased from 10% in 2006 to 25% in 2010 in Taiwan. A recent study from Indonesia revealed that serotypes 19F and 19A have a high prevalence of the *ermB* gene, further underscoring the growing concern of macrolide resistance in the region.³

The changes in macrolide resistance in *S. pneumoniae* can be attributed to selective pressure from macrolide prescribing after the implementation of the pneumococcal

conjugate vaccine (PCV). While these vaccines have been effective in reducing diseases caused by vaccine-covered serotypes, there has been a notable shift in the prevalence of non-vaccine serotypes, some of which exhibit macrolide resistance.⁴ A study analyzing invasive *S. pneumoniae* isolates in the post-PCV era found an increase in non-vaccine serotypes that carried *ermB* and *mefA*. This shift underscores the role of antibiotic selective pressure in the evolving landscape of pneumococcal resistance.⁵ This study aims to identify the prevalence and distribution of macrolide resistance genes (*ermB* and *mefA*) in *S. pneumoniae* isolates, and to evaluate how these gaps affect current antibiotic prescribing practices and treatment outcomes in pneumococcal infections.

2. Materials and methods

2.1. Isolate collection

This study used 703 archived *S. pneumoniae* isolates from different regions of Indonesia (Table S1). The inclusion criteria for this study comprised confirmed *S. pneumoniae* isolates recovered from Indonesian participants and identified by colony morphology on blood agar, together with standard pneumococcal confirmation procedures. Archived isolates were preserved in skim milk–tryptone–glucose–glycerol media and stored at -80°C . Recovered archived isolates demonstrated typical pneumococcal morphology, and optochin susceptibility supported the phenotypic identification of the isolates. As this study used archived isolates from selected regions, the findings may not fully reflect national pneumococcal epidemiology. However, standardized collection, storage, and laboratory procedures were applied to minimize systematic bias.

A total of 21 *S. pneumoniae* isolates were obtained

from an Indonesian population in Padang, West Sumatra, from April 2018 to December 2019.⁶ A total of 269 *S. pneumoniae* isolates were obtained from Lombok Island, West Nusa Tenggara, from March 2018 until June 2019,⁷ and 165 isolates were obtained from Kotabaru, South Kalimantan, from February to April 2019.⁸ Additionally, 163 and 85 *S. pneumoniae* isolates were obtained from Southwest Sumba, East Nusa Tenggara, and Gunungkidul, Yogyakarta, respectively, from February to May 2017.⁹ Previously, serotyping was performed using a multiplex sequence-based polymerase chain reaction (PCR) and partially confirmed by the Quellung reaction.

In this study, we included various pneumococcal serotypes; serotype 1 ($n = 3$), 3 ($n = 8$), 4 ($n = 2$), 5 ($n = 2$), 8 ($n = 1$), 13 ($n = 14$), 14 ($n = 28$), 20 ($n = 6$), 21 ($n = 2$), 31 ($n = 1$), 34 ($n = 38$), 39 ($n = 2$), 10A ($n = 3$), sg11 ($n = 16$), sg15 ($n = 70$), 25A ($n = 1$), 33B ($n = 1$), 19B ($n = 1$), 16F ($n = 12$), 17F ($n = 1$), 19A ($n = 14$), 19F ($n = 77$), 22F/22A ($n = 3$), 23A ($n = 9$), 23B ($n = 3$), 23F ($n = 49$), 24F/24A/24B ($n = 3$), 33F/33A/37 ($n = 2$), 35A/35C/42 ($n = 14$), 35B ($n = 9$), 35F/47F ($n = 2$), 38/25F/25A ($n = 1$), 7C/7B/40 ($n = 6$), NT ($n = 137$), Sg6 ($n = 156$), Sg18 ($n = 4$), and 35C ($n = 2$). Antibiotic susceptibility testing was performed by the disc diffusion method and partially assessed by microdilution assay according to the Clinical and Laboratory Standards Institute guidelines (Table 1).

2.2. Detection of *ermB* and *mefA* genes

The *ermB* (639 bp) and *mefA* (348 bp) genes were detected by conventional PCR according to the GoTaq® Green Master Mix protocol (Promega, United States). The PCR mastermix composition contained 12.5 μL of 2 $\times$ GoTaq® Green Mastermix, 0.5 μM for 0.5 μL of forward primer, 0.5 μM for 0.5 μL of reverse primer, 9 μL of nuclease-free

Table 1. Prevalence of macrolide non-susceptibility profile among *Streptococcus pneumoniae* isolated from different regions in Indonesia

Region	Isolate (n)	Macrolide non-susceptible, n (%)	Methodology	Ref.
Kotabaru, South Kalimantan	185	31 (16)	Disc diffusion /microdilution	8
Gunungkidul, Yogyakarta	323	56 (17)	Microdilution	9
Southwest Sumba, East Nusa Tenggara	784	32 (4)	Microdilution	9
Padang, West Sumatra	42	12 (29)	Disc diffusion	6
Lombok, West Nusa Tenggara	497	39 (8)	Disc diffusion	7

water, and 2.5 µL of template DNA. Primers used were:

- (i) *ermB* forward primer: 5'-GAAAAGGTACTCAACCA AATA-3'
- (ii) *ermB* reverse primer: 5'-GTAACGGTACTTAAATTG TTTAC-3'
- (iii) *mefA* forward primer: 5'-AGTATCATTAATCACTA GTGC-3'
- (iv) *mefA* reverse primer: 5'-TTCTTCTGGTACTAAAAG TGG-3'

The PCR was performed using a thermal cycler (Veriti Thermal Cycler, Applied Biosystems, US) under the following conditions: pre-denaturation at 94 °C for four minutes, followed by 35 cycles of denaturation at 94 °C for 30 s, annealing at 50 °C for 30 s, elongation at 72 °C for 1.5 min, and post-elongation at 72 °C for five minutes.²

3. Results

Among the 703 isolates, 76 and 30 were positive for *mefA* (11%) and *ermB* (4%), respectively (Table S1). The distribution of gene-positive isolates by serotype is presented in Figure 1. The total number of isolates that contained both *mefA* and *ermB* genes was 15 (2%). Furthermore, the major serotype harboring the *mefA* gene was 19F (37/77; 48%), followed by serotype 23F (19/49; 39%). The predominant serotype containing the *ermB* genes was 19F (13/77, 17%). In general, serotype 19F emerged as the predominant serotype, with the highest prevalence of carrying both *mefA* and *ermB* genes (12/77;

16%).

In this study, we found that most isolates carried the *mefA* gene ($n = 76$), followed by *ermB* ($n = 30$), and both *mefA* and *ermB* ($n = 15$). The highest prevalence of macrolide non-susceptibility was observed in Padang, West Sumatra (29%) (Table 1). Other areas with significant rates of macrolide non-susceptibility were Gunungkidul, Yogyakarta (17%); Kotabaru, South Kalimantan (16%); Lombok, West Nusa Tenggara (8%); and Southwest Sumba, East Nusa Tenggara (4%).

Among isolates positive for both *mefA* and *ermB*, the highest proportions were observed in Kotabaru (40%), Padang (33%), and Gunungkidul (27%); most were from children aged 1–5 years (93%), and 67% were from males (Table 2). Most of these isolates were from individuals of the 1–5 year-old group (93%). We also found that the prevalence of isolates carrying *mefA* and *ermB* was higher in males (67%) than in females (33%).

4. Discussion

In *S. pneumoniae*, macrolide resistance is due to ribosomal dimethylation by an enzyme encoded by *ermB*, efflux by a two-component efflux pump encoded by *mefA*, and, less commonly, mutations of the ribosomal target site of macrolides.¹ Our investigation identified serotype 19F as the predominant serotype harboring *mefA* and *ermB* genes. The elevated occurrence of serotype 19F may be attributed to a large number of strains with serotype 19F carrying

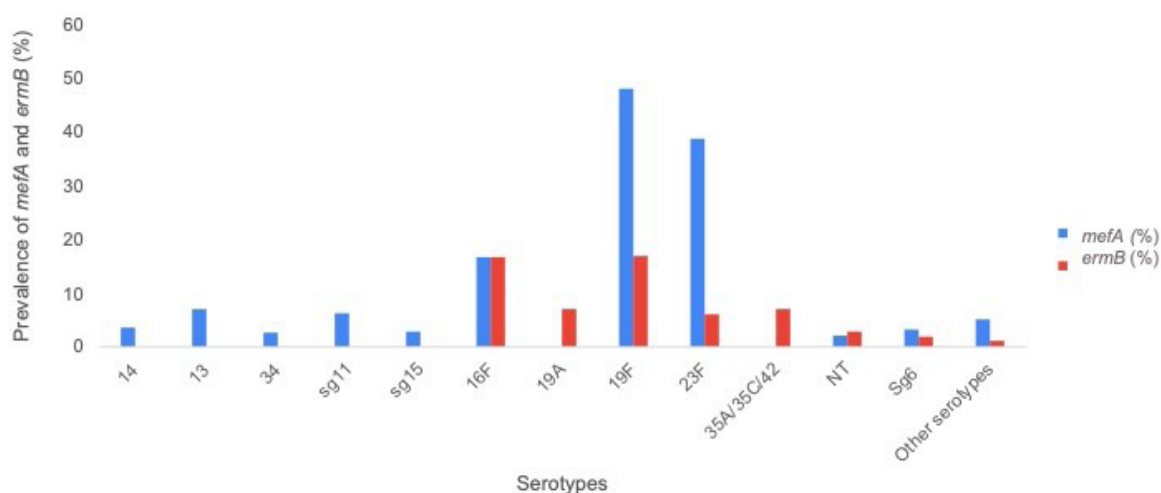


Figure 1. Prevalence of *mefA* and *ermB* genes among different serotypes of *Streptococcus pneumoniae* isolated from the Indonesian population. In total 703 isolates were screened for the presence of *mefA* and *ermB* genes using the PCR including different pneumococcal serotypes: serotype 1 ($n = 3$), 3 ($n = 8$), 4 ($n = 2$), 5 ($n = 2$), 8 ($n = 1$), 13 ($n = 14$), 14 ($n = 28$), 20 ($n = 6$), 21 ($n = 2$), 31 ($n = 1$), 34 ($n = 38$), 39 ($n = 2$), 10A ($n = 3$), sg11 ($n = 16$), sg15 ($n = 70$), 25A ($n = 1$), 33B ($n = 1$), 19B ($n = 1$), 16F ($n = 12$), 17F ($n = 1$), 19A ($n = 14$), 19F ($n = 77$), 22F/22A ($n = 3$), 23A ($n = 9$), 23B ($n = 3$), 23F ($n = 49$), 24F/24A/24B ($n = 3$), 33F/33A/37 ($n = 2$), 35A/35C/42 ($n = 14$), 35B ($n = 9$), 35F/47F ($n = 2$), 38/25F/25A ($n = 1$), 7C/7B/40 ($n = 6$), NT ($n = 137$), Sg6 ($n = 156$), Sg18 ($n = 4$), and 35C ($n = 2$).

Table 2. Characteristics of subjects carrying *ermB* and *mefA* genes

Characteristic	PCR positive for <i>mefA</i> only (n = 61)	PCR positive for <i>ermB</i> only (n = 15)	PCR positive for <i>mefA</i> + <i>ermB</i> (n = 15)
Age (Years)			
<1	6 (10)	4 (27)	1 (7)
1–5	54 (88)	11 (73)	14 (93)
>5	1 (2)	0 (0)	0 (0)
Sex			
Male	30 (49)	7 (47)	10 (67)
Female	31 (51)	8 (53)	5 (33)
Region			
Gunungkidul	11 (18)	4 (27)	4 (27)
Kotabaru	17 (28)	8 (53)	6 (40)
Padang	3 (5)	0 (0)	5 (33)
Sumba	6 (10)	2 (13)	0 (0)
Lombok	24 (39)	1 (7)	0 (0)

Note: Data presented as n (%).

Abbreviation: PCR: Polymerase chain reaction.

both *mefA* and *ermB* genes, resulting in a dual resistance mechanism that contributes to the heightened prevalence of macrolide resistance in these particular serotypes.¹⁰ A study from the Asian Network for Surveillance of Resistant Pathogens reported that *S. pneumoniae* isolates carrying both *ermB* and *mefA* were dominated by serotype 19F, accounting for 61% of isolates.¹¹

Other than serotype 19F, common serotypes that were found in this study included 23F, 19A, 16F, and 35A/35C/42 (Figure 1). Although serotypes 19F, 19A, and 23F are covered by PCV13 (the 13-valent pneumococcal conjugate vaccine), they continue to circulate after its implementation.¹² Additionally, this study found that serotype 16F frequently harbored the *ermB* and *mefA* genes, following serotypes 19F, 23F, and 35A/35C/42. However, serotype 16F is not covered by Indonesia's current national vaccination program (PCV13), but it is included in PCV21.¹³

Vaccine-induced selective pressure contributes to post-vaccination changes in serotype epidemiology, although natural fluctuations in serotype prevalence also play a role.¹⁴ In the study by Desmet *et al.*,¹⁵ serotype 19A re-emerged after switching PCV13 to PCV10 (the 10-valent pneumococcal conjugate vaccine). Re-emergence of serotype 19A, which is not included in PCV13, has an impact on the burden

of invasive pneumococcal disease in the population.¹⁵ Thus, monitoring the distribution of vaccine-type and non-vaccine-type strains following PCV implementation is important for evaluating serotype replacement patterns, particularly for vaccine types associated with high levels of antibiotic resistance.

From a global perspective, macrolide resistance has been common in Asia, North and South America, the United Kingdom, and Africa.¹ In Europe, approximately 90% of macrolide resistance is conferred by the *ermB* gene, whereas in North America, 50–60% of isolates carry the *mefA* gene. Furthermore, in Asia, a significant concern is the presence of isolates harboring both *mefA* and *ermB* genes, with reports indicating that between 12–40% of resistant isolates display both mechanisms¹⁶ (Table 3). However, regional resistance patterns are influenced by factors such as regional antibiotic use patterns, the spread of resistant clones, and the presence of mobile genetic elements that facilitate gene transfer. This study highlights that serotype 19F, which carries most of the *mefA* and *ermB* genes, requires ongoing surveillance to inform future vaccine policy and antibiotic treatment strategies. However, these findings may not fully represent nationwide pneumococcal macrolide resistance patterns and should be interpreted with caution.¹⁷

Table 3. Reported prevalence of isolates carrying the *ermB* and *mefA* genes in different countries

Country	Years of collection	Population	Number of isolates (<i>n</i>)	Prevalence of <i>ermB</i> and <i>mefA</i>	Ref.
Japan	2011–2020	Patients aged 15 years or older	73	<i>ermB</i> = 47%; <i>mefA</i> = 29%; <i>ermB</i> and <i>mefA</i> = 11%	18
Japan	2007	Children	156	<i>ermB</i> = 57%; <i>mefA</i> = 38%; <i>ermB</i> and/or <i>mefA</i> = 83%	19
China	2000–2019	Patients	1,258	<i>ermB</i> = 99%; <i>mefA</i> = 57%; <i>ermB</i> and <i>mefA</i> = 57%	20
China	2011–2014	Pediatric patients	284	<i>ermB</i> = 100%; <i>mefA</i> = 39%; <i>ermB</i> and <i>mefA</i> = 39%	21
Tunisia	2010–2013	Patients	74	<i>ermB</i> = 46%; <i>mefA</i> = 8%; <i>ermB</i> and <i>mefA</i> = 9%	22
Taiwan	2006–2010	Patients	486	<i>ermB</i> = 59%; <i>mefA</i> = 22%; <i>ermB</i> and <i>mefA</i> = 19%	2
Malaysia	1999–2003	Patients	120	<i>ermB</i> = 31%; <i>mefE</i> = 18%	23

5. Conclusion

In this study, the major serotype carrying the *mefA* gene was 19F, followed by serotype 23F. The predominant serotype containing the *ermB* gene was 19F. The occurrence of macrolide resistance in *S. pneumoniae* in Indonesia shows a notable pattern, with the most prominent presence observed in serotype 19F.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

The ethics committee approvals from The Ethical Committee of Faculty of Medicine, Universitas Andalas, Padang, West Sumatra, Indonesia, for nasopharyngeal swab isolate collection were previously obtained with protocol numbers 599/KEP/FK/2018, 618/KEP/FK/2019, and 649/KEP/FK/2018 (Padang, West Sumatra); The Ethical Committee of Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, with the protocol number 1053/UN2.F1/ETIK/2017 (Lombok, West Nusa Tenggara); The Eijkman Institute Research Ethics Commission with the protocol no. 104/2016 (Gunungkidul, Yogyakarta, and

Southwest Sumba, East Nusa Tenggara); and protocol no. 118/2018 (Kotabaru, South Kalimantan). Written informed consent was obtained from the participants/participants' parents or legal guardians prior to enrolment in the study.

Consent for publication

All enrolled participants/participants' parents or legal guardians provided written informed consent, including consent for the publication of anonymized data.

Availability of data

The authors confirm that all supporting data, code, and protocols are provided in the article and Table S1.

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