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In Vitro Activity of Lefamulin against Global Collection of Respiratory Pathogens from Paediatric Patients from the 2015 SENTRY Program

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INTRODUCTION & PURPOSE

Background: Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans. Pleuromutilins are protein synthesis inhibitors which specifically bind to the bacterial peptidyl transferase center (PTC) at two sites via multiple H-bonds resulting in the closing of the binding pocket ("induced fit") around pleuromutilins.[1,2]

In addition to its potent activity against typical respiratory pathogens, lefamulin also covers atypical respiratory pathogens including *Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *Legionella pneumophila*.[3-5] Lefamulin is currently in Phase 3 trials for the treatment of community-acquired bacterial pneumonia (CAP) in adults.

Pneumonia is the most common infectious cause of death in children worldwide accounting for over 2 million deaths annually and 15% of all deaths in children under 5 years old in 2015. The two most common causes of bacterial pneumonia are *S. pneumoniae* and *H. influenzae*, which show increasing resistance to commonly used antibiotics, particularly macrolides class.[7] In addition, use of the fluoroquinolones and tetracyclines is limited in children due to potential adverse effects.

This study investigated the susceptibility of respiratory pathogens collected in 2015 to lefamulin and comparator agents commonly used to treat CAP.

METHODS

1380 unique bacterial isolates were collected worldwide in 28 countries from paediatric patients (≤17 years old) with community-acquired respiratory tract infections (RTI; 900), hospitalized pneumonia (404), blood stream infections (33) or with other infections (43). The majority of isolates were collected in Europe (28.3%) and USA (56.2%); 9.1% and 6.3% were from Asia-Pacific region and Latin America.

Susceptibility testing was conducted using the CLSI broth microdilution method and susceptibility was calculated using EUCAST 2017 breakpoints.[7,8] QC reference organisms were tested concurrently for lefamulin and comparator agents.

Table 1. ***In vitro*** **antibacterial activity of lefamulin against respiratory pathogens from paediatric patients collected worldwide in 2015**

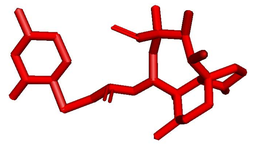

Figure 1. Lefamulin

		Lefamulin MIC [µg/mL]		
Organism	***N***	**MIC_{50}**	**MIC_{90}**	**MIC_{99}**
S. pneumoniae	647	0.06	0.12	0.25
S. aureus	347	0.06	0.06	0.12
H. influenzae	215	0.5	1	2
M. catarrhalis	171	0.06	0.12	0.12

RESULTS

- MIC distributions of lefamulin for isolates collected from paediatric and adult patients are shown in Figure 2. $MIC_{50/90}$ are summarized in Table 2.

Figure 2. MIC distribution of lefamulin collected from paediatric and adult patients.

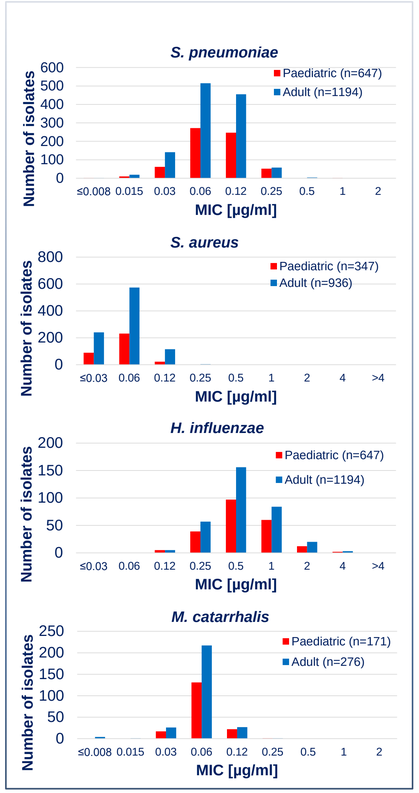

Table 2. ***In vitro*** **activity of lefamulin and comparators against paediatric CAP pathogens.**

Organism (*N*)	**MIC_{50}**	**MIC_{90}**	**% S[a]**	**% R[a]**
S. pneumoniae **(647)**				
Lefamulin	0.06	0.12	-	-
Amoxi/Clav	≤0.03	2	-	-
Azithromycin	0.06	**>4**	59.2	**40.3**
Ceftriaxone	0.03	1	85.6	1.1
Clindamycin	≤0.12	**>1**	82.8	**17.2**
Levofloxacin	1	1	99.8	0.2
Linezolid	1	1	100.0	0.0
Penicillin	≤0.06	2	60.6	4.3 [b]
Vancomycin	0.25	0.25	100.0	0.0
S. aureus **(347)**				
Lefamulin	0.06	0.06	-	-
Azithromycin	0.5	**>4**	56.2	**42.4**
Ceftaroline	0.25	0.5	99.4	0.6
Clindamycin	≤0.25	**>2**	87.3	**11.8**
Levofloxacin	0.25	**4**	81.6	**18.4**
Linezolid	1	1	100.0	0.0
Oxacillin	0.5	**>2**	73.5	**26.5**
Vancomycin	0.5	1	100.0	0.0
H. influenzae **(215)**				
Lefamulin	0.5	1	-	-
Amoxi/Clav	0.5	2	96.3	3.7
Ampicillin	0.25	**>8**	76.3	**23.7** [c]
Azithromycin	1	2	0.5	2.3
Cefepime	0.06	0.12	96.7	3.3
Levofloxacin	≤0.015	≤0.015	97.2	2.8
Trimethoprim-sulfa	0.12	**>4**	67.9	**29.8**
M. catarrhalis **(171)**				
Lefamulin	0.06	0.12	-	-
Amoxi/Clav	0.12	0.25	100.0	0.0
Azithromycin	0.015	0.03	100.0	0.0
Ceftriaxone	0.25	0.5	100.0	0.0
Levofloxacin	0.03	0.03	100.0	0.0

[a], Susceptible (S), Resistant (R) Criteria as published by EUCAST [2017]
[b], Non-meningitis breakpoints applied for penicillin;
[c], ß-lactamase positive, reported as resistant for penicillins without inhibitors

RESULTS (continued)

- Lefamulin displayed potent antibacterial activity with 99.7% of all *S. pneumoniae* inhibited at concentrations of ≤0.25 mg/L and 99.1% of *H. influenzae* isolates at ≤2 mg/L (Table 1, Figure 2).
- Lefamulin demonstrated potent activity against paediatric *M. catarrhalis* and *S. aureus* with MIC_{99} of 0.12 mg/L for both organisms.
- *S. pneumoniae* from paediatric patients were highly susceptible to levofloxacin (99.8%), and amoxicillin/clavulanic acid (94.0%, CLSI) but showed reduced susceptibility to ceftriaxone (85.6%), erythromycin (59.5%) and trimethoprim/sulfamethoxazole (77.6%).
- Paediatric *H. influenzae*, 20.5% of which were ß-lactamase positive, were susceptible to amoxicillin/clavulanic acid (96.3%) and levofloxacin (100%) while 29.8% displayed resistance to trimethoprim/sulfamethoxazole. Azithromycin activity against *H. influenzae* was limited (97.2% intermediate, 2.3% resistant).
- *S. aureus* isolates (26.5% MRSA) were 100% susceptible to vancomycin and linezolid. The susceptibility to azithromycin was 56.2%, to clindamycin 87.3% and to levofloxacin 81.6%.
  - Among MRSA (*n*=92) the susceptibility to azithromycin (22.8%), to clindamycin (70.7%) and levofloxacin (41.3%) was lower than among MSSA.

CONCLUSIONS

- **Lefamulin displayed potent *in vitro* antibacterial activity against respiratory pathogens collected globally from paediatric patients regardless of their susceptibility phenotype to commonly used antibiotics.**
- **MIC distributions of paediatric isolates were similar to that collected from adults.**
- **The results of this study support the continued clinical development of lefamulin for the treatment of RTI, including CAP in adults and paediatric patients.**

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27th European Congress of Clinical Microbiology and Infectious Diseases, Vienna, Austria, 22-25 April 2017