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In vitro activity of lefamulin against a global collection of respiratory pathogens from paediatric patients from the 2015 SENTRY programme

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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. Lefamulin binding is characterized by four H-bonds and other interactions resulting in the shift of certain nucleotides and closing of the binding pocket ("induced fit"). 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 the macrolide class. This study investigated the susceptibility of respiratory pathogens collected in 2015 to lefamulin and comparator agents commonly used to treat CAP.

Material/methods: 1380 unique bacterial isolates were collected 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 other infections (43). Lefamulin and comparators were tested by CLSI broth microdilution methods, and susceptibility was determined using the EUCAST (2016) breakpoints.

Results: 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. Lefamulin demonstrated potent activity against *M. catarrhalis* and *S. aureus* with MIC_{99} of 0.12 mg/L for both organisms. *S. pneumoniae* were highly susceptible to levofloxacin (99.8%), ceftriaxone (85.6%) and amoxicillin/clavulanic acid (94.0%, CLSI) but showed reduced susceptibility to erythromycin (59.5%) and trimethoprim/sulfamethoxazole (77.6%). *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, but only 57.9% and 81.6% were susceptible to erythromycin and levofloxacin, respectively.

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. The results of this study support the continued clinical development of lefamulin for the treatment of RTI, including CAP in adults and paediatric patients.

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

		MIC [mg/L]		
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