#P1440

A comparative *in vitro* analysis of amoxicillin-clavulanic acid and seven comparative agents in 15,499 peadiatric respiratory isolates

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REVISED ABSTRACT

Background: Several large scale adult surveillance studies have demonstrated the ongoing effectiveness of amoxicillin-clavulanic acid (A/C) even after 20 years of clinical use. This is a retrospective collection of data comprising over 15,000 paediatric respiratory isolates collected from several surveillance studies conducted in 47 countries over a period of 5 years. The *in vitro* activity of A/C and 7 comparators are reported for *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. pyogenes*. Not all antimicrobials were tested in all studies, or against all isolates. **Methods:** Regional reference laboratories used broth microdilution technique according to NCCLS guidelines. **Results:** A/C at the Augmentin ES-600 PK/PD breakpoint of d”4 mcg/mL for *S. pneumoniae*, was the most active agent tested with 96.5% susceptible including 83.5% and 88.6% susceptible for PRSP and ERSP, respectively. **Conclusions:** A/C activity was comparable to or better than comparator agents against all the key respiratory pathogens including resistant strains involved in paediatric respiratory infections

Drug/MIC$_{90}$/%Sus	*H. influenzae* n=5,170	*S. pneumoniae* n=8,040	PRSP n=1,728	ERSP n=1,986
Amox-Clav [c]	2 / 99.2	2 / 96.5 [a] (93.5[b])	8 / 83.5[a] (70.7[b])	8 / 88.6[a] (81.5[b])
Ampicillin	>16 / 74.6	4 / na	8 / na	8 / na
Penicillin	>16 / na	2 / 60.6	4 / 0.0	4 / 18.6
Cefaclor	16 / 84.6	2 / 44.5	>64 / 0.1	>64 / 11.6
Cefuroxime	2 / 96.7	8 / 65.2	8 / 0.7	8 / 26.0
Azithro	2 / 99.1	>32 / 71.4	>32 / 23.0	>32 / 0.3
Erythro	8 / na	>32 / 71.2	>32 / 21.5	>32 / 0.0
Trimeth-Sulfa [c]	>4 / 76.5	8 / 50.2	>8 / 13.8	8 / 24.5

[a] PK/PD breakpoint of =4/2 mcg/mL applied for Augmentin ES-600
[b] NCCLS breakpoint of =2/1 mcg/mL applied for conventional Augmentin.
[c] Amoxicillin-clavulanic acid was tested in a 2:1 ratio; trimethoprim-sulfamethoxazole was tested in a 1:19 ratio; MICs displayed are based on the amoxicillin and trimethoprim content.

INTRODUCTION

After greater than 20 years of use as an oral and parenteral antimicrobial agent, amoxicillin-clavulanic acid has maintained exceptional *in vitro* activity against respiratory tract pathogens [1] in spite of ever increasing resistance reported for other antimicrobial agents. This retrospective analysis provides *in vitro* data from a large global paediatric population for amoxicillin-clavulanic acid and 14 comparator agents against key respiratory tract pathogens, *Streptococcus pneumoniae* (including penicillin- resistant and macrolide-resistant), *Streptococcus pyogenes*, *Haemophilus influenzae*, and *Moraxella catarrhalis* isolates. A compilation of paediatric data (age ≤ 12 years) was collected from six multi-centre global surveillance studies as follows: The Aegus Study; The Augmentin Global Surveillance Study; The International Surveillance Study; Alexander Network Swiss Data; SOAR in Africa and Middle East; and SPARS in Russia. The isolates were collected globally from 183 participating centres in 47 countries during 1998 – 2002. The antimicrobial agents analysed from each study and presented in this report are those which are relevant to paediatric infections.

Amoxicillin-clavulanic acid (Augmentin) was developed to enhance the activity of amoxicillin against beta-lactamase producing bacteria by the addition of clavulanic acid, a very active beta-lactamase inhibitor. The resistance of *S. pneumoniae* to several antibacterials is increasing world-wide [2, 3]. High doses of amoxicillin have been shown to lead to improved eradication of penicillin-resistant *S. pneumoniae* [4]. Augmentin ES is a novel 14:1 ratio of amoxicillin-clavulanic acid developed to provide improved activity of amoxicillin with serum concentrations above the MIC of the infecting pathogen for a longer proportion of the dosing interval (i.e. higher T>MIC) while retaining the same dose of clavulanate to ensure activity against beta-lactamase producing pathogens. This formulation was developed to provide effective empirical treatment in children with infections where involvement of penicillin-resistant *S. pneumoniae* (PRSP) is suspected and to cover beta-lactamase producing organisms that cannot be ruled out.

MATERIALS & METHODS

- Susceptibility testing was conducted by broth microdilution, according to NCCLS recommended procedures using custom Sensititre (TREK Diagnostics, Westlake, OH) or MicroScan (Dade Behring, CA) panels [5].
- Trays were incubated under ambient conditions at 35°C for 20-24 hours and the lowest concentration showing no growth was read as the MIC.
- Quality control testing was performed daily as specified by the NCCLS using the following QC strains: *E. coli* ATCC 35218, *H. influenzae* ATCC 49247, *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619.
- The results are summarized according to organism and phenotype. MIC$_{90}$s, MIC ranges and susceptibility percentages are reported for all antibiotics as defined by the NCCLS unless otherwise indicated [6].

ACKNOWLEDGEMENTS

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RESULTS

Table 1. List of Countries and Number of Investigative Sites that contributed Paediatric data from 1998 through 2002.

Country	Investigative Sites	Country	Investigative Sites
Argentina	2	Lebanon	1
Australia	7	Luxembourg	1
Austria	7	Mexico	14
Belgium	5	New Zealand	3
Brazil	4	Oman	1
Canada	7	Pakistan	3
Czech Republic	1	Poland	2
Denmark	1	Portugal	1
Egypt	1	Russia	20
Finland	1	Saudi Arabia	7
France	11	Singapore	1
Germany	12	Slovak Republic	1
Greece	2	South Africa	3
Hong Kong	3	Spain	3
Hungary	1	Sweden	7
Indonesia	1	Switzerland	2
Ireland	1	Taiwan	1
Israel	1	The Netherlands	3
Italy	4	Tunisia	1
Japan	1	Turkey	2
Jordan	1	United Arab Emirates	2
Kenya	2	United Kingdom	2
Korea	1	United States	24
Kuwait	1	**Countries = 47**	**Sites = 183**

Table 2. *In Vitro* Activities of Amoxicillin-Clavulanic Acid and Comparative Antimicrobial Agents against 8,040 Paediatric Isolates of *Streptococcus pneumoniae* Susceptible, Intermediate and Resistant to Penicillin and Erythromycin.

Organism	Drug	% Sus	% Int	% Res	MIC (mcg/mL) MIC$_{50}$	MIC$_{90}$	Range
S. pneumoniae n=8,040	Amox-Clav (4)[a]	96.5	3	0.5	0.03	2	≤0.015 - >32
	Amox-Clav (2)[b]	93.5	3	3.5	0.03	2	≤0.015 - >32
	Ampicillin	na	na	na	≤0.12	4	≤0.015 - >64
	Penicillin	60.6	17.9	21.5	0.06	2	0.008 - >16
	Cefaclor	44.5	13.4	42.1	2	> 64	≤0.5 - 128
	Cefuroxime	65.2	2.8	32	0.12	8	≤0.015 - >64
	Azithromycin	71.4	0.9	27.7	0.06	> 32	≤0.015 - 128
	Erythromycin	71.2	0.2	28.6	0.06	> 32	≤0.015 - 128
	Trimeth-Sulfa[c]	50.2	19.6	30.2	0.5	8	0.03 - >64
Penicillin-Susceptible n=4,869	Amox-Clav (4)[a]	100	0	0	0.03	0.03	≤0.015 - 4
	Amox-Clav (2)[b]	99.9	0.1	0	0.03	0.03	≤0.015 - 4
	Ampicillin	na	na	na	0.06	≤0.12	≤0.015 - 0.5
	Penicillin	100	0	0	0.03	0.06	0.008 - 0.06
	Cefaclor	77.2	18.3	4.5	1	2	≤0.5 - >64
	Cefuroxime	99.5	0.4	0.1	≤0.06	0.12	≤0.015 - 4
	Azithromycin	91.3	0.3	8.4	0.06	0.12	≤0.015 - 128
	Erythromycin	91.1	0.3	8.6	0.06	0.12	≤0.015 - 128
	Trimeth-Sulfa[c]	67.6	19.7	12.7	0.25	4	0.03 - >64
Penicillin-Intermediate n=1,443	Amox-Clav (4)[a]	100	0	0	0.25	1	≤0.015 - 4
	Amox-Clav (2)[b]	99.1	0.9	0	0.25	1	≤0.015 - 4
	Ampicillin	na	na	na	0.5	2	0.03 - 4
	Penicillin	0	100	0	0.25	1	0.12 - 1
	Cefaclor	17.6	21.8	60.6	4	64	≤0.5 - 128
	Cefuroxime	63.3	11.2	25.5	0.5	4	0.03 - >64
	Azithromycin	62.2	1.8	36	0.12	> 32	≤0.03 - 128
	Erythromycin	62.3	0.3	37.4	0.06	> 32	≤0.015 - 128
	Trimeth-Sulfa[c]	35.1	27.7	37.2	1	8	≤0.06 - >64
Penicillin-Resistant n=1,728	Amox-Clav (4)[a]	83.5	14.1	2.4	2	8	≤0.03 - >32
	Amox-Clav (2)[b]	70.7	12.8	16.5	2	8	≤0.03 - >32
	Ampicillin	na	na	na	4	8	0.5 - >64
	Penicillin	0	0	100	2	4	2 - >16
	Cefaclor	0.1	0.1	99.8	> 64	> 64	1 - 128
	Cefuroxime	0.7	1.8	97.5	8	8	≤0.06 - >64
	Azithromycin	23	1.6	75.4	8	> 32	≤0.03 - 128
	Erythromycin	21.5	0.2	78.3	8	> 32	≤0.015 - 128
	Trimeth-Sulfa[c]	13.8	12.7	73.5	4	> 8	≤0.06 - >64
Erythromycin-Susceptible n=4,851[d]	Amox-Clav (4)[a]	99.2	0.7	0.1	0.03	0.25	≤0.015 - 16
	Amox-Clav (2)[b]	98.3	0.9	0.8	0.03	0.25	≤0.015 - 16
	Ampicillin	na	na	na	≤0.12	2	≤0.015 - 16
	Penicillin	79.2	14.2	6.6	0.03	0.5	0.008 - 8
	Cefaclor	64.5	16.5	19	1	> 16	≤0.5 - 128
	Cefuroxime	86.7	1.2	12.1	0.06	4	≤0.015 - >16
	Azithromycin	99.9	0	0.1	0.06	0.12	≤0.015 - 8
	Erythromycin	100	0	0	0.06	0.06	≤0.015 - 0.25
	Trimeth-Sulfa[c]	59.3	21.9	18.8	0.5	4	0.03 - >32
Erythromycin - Intermediate n=17[d]	Amox-Clav (4)[a]	100	0	0	0.03	2	0.03 - 2
	Amox-Clav (2)[b]	100	0	0	0.03	2	0.03 - 2
	Ampicillin	na	na	na	≤0.12	4	≤0.12 - 4
	Penicillin	64.8	17.6	17.6	0.06	4	≤0.015 - 8
	Cefaclor	44.4	11.2	44.4	2	> 64	1 - >64
	Cefuroxime	66.7	0	33.3	0.12	8	0.03 - 8
	Azithromycin	41.2	11.7	47.1	1	2	0.12 - 2
	Erythromycin	0	100	0	0.5	0.5	0.5 - 0.5
	Trimeth-Sulfa[c]	23.5	35.3	41.2	2	8	0.25 - 8
Erythromycin - Resistant n=1,986[d]	Amox-Clav (4)[a]	88.6	9.9	1.5	1	8	≤0.015 - >16
	Amox-Clav (2)[b]	81.5	7.1	11.4	1	8	≤0.015 - >16
	Ampicillin	na	na	na	2	8	≤0.015 - >16
	Penicillin	18.6	21.2	60.2	2	4	≤0.015 - 16
	Cefaclor	11.6	8.3	80.1	64	> 64	≤0.5 - 128
	Cefuroxime	26	3.5	70.5	4	8	≤0.015 - 32
	Azithromycin	0.3	1	98.7	16	> 32	0.03 - 128
	Erythromycin	0	0	100	16	> 32	1 - 128
	Trimeth-Sulfa[c]	24.5	16.3	59.2	4	8	≤0.06 - >32

na = NCCLS breakpoints are not defined for this organism/drug combination
[a] PK/PD breakpoints (amoxicillin component) of susceptible ≤4, intermediate = 8 and resistant >16 mcg/mL applied to new formulation of amoxicillin-clavulanic acid (Augmentin ES-600)
[b] NCCLS breakpoints of (amoxicillin component) of susceptible ≤2, intermediate = 4 and resistant > mcg/mL applied for conventional amoxicillin-clavulanic acid; amoxicillin-clavulanic acid was tested in a 2:1 ratio; MICs displayed are based upon amoxicillin content.
[c] Trimethoprim-sulfamethoxazole was tested in a 1:19 ratio; MICs displayed are based on the trimethoprim content.
[d] The International Surveillance Study did not include erythromycin.

Table 3. Penicillin Susceptibility Rates against *S. pneumoniae* by Country.

Country	Total N	Penicillin Susceptible n (%)*	Penicillin Intermediate n (%)	Penicillin Resistant n (%)	Penicillin Non-Susceptible n (%)
Argentina	32	21 (65.6)	7 (21.9)	4 (12.5)	11 (34.4)
Australia	103	68 (66)	22 (21.4)	13 (12.6)	35 (34)
Austria	59	50 (84.7)	5 (8.5)	4 (6.8)	9 (15.3)
Belgium	141	113 (80.2)	13 (9.2)	15 (10.6)	28 (19.9)
Brazil	93	68 (73.1)	22 (23.7)	3 (3.2)	25 (26.9)
Canada	56	44 (78.6)	8 (14.3)	4 (7.1)	12 (21.4)
Czech Republic	24	22 (91.6)	1 (4.2)	1 (4.2)	2 (8.3)
Denmark	31	29 (93.5)	2 (6.5)	0 (0)	2 (6.5)
Finland	19	15	1	3	4
France	325	93 (28.6)	84 (25.8)	148 (45.6)	232 (71.4)
Germany	392	354 (90.3)	30 (7.7)	8 (2)	38 (9.7)
Greece	319	205 (64.2)	58 (18.2)	56 (17.6)	114 (35.7)
Hong Kong	99	14 (14.1)	13 (13.1)	72 (72.6)	85 (85.9)
Hungary	27	5 (18.5)	9 (33.3)	13 (48.1)	22 (81.5)
Indonesia	18	18	0	0	0
Ireland	1	0	0	1	1
Israel	23	11 (47.9)	5 (21.7)	7 (30.4)	12 (52.2)
Italy	66	47 (71.2)	4 (6.1)	15 (22.7)	19 (28.8)
Japan	409	123 (30.1)	99 (24.2)	187 (45.7)	286 (69.9)
Kenya	1	0	1	0	1
Korea	12	2	1	9	10
Luxembourg	15	12	3	0	3
Mexico	369	140 (37.9)	139 (37.7)	90 (24.4)	229 (62.1)
New Zealand	21	18 (85.7)	1 (4.8)	2 (9.5)	3 (14.3)
Oman	19	8	8	3	11
Pakistan	5	4	1	0	1
Poland	67	49 (73.1)	4 (6)	14 (20.9)	18 (26.9)
Portugal	113	68 (60.2)	14 (12.4)	31 (27.4)	45 (39.8)
Russia	2100	1702 (81)	347 (16.6)	51 (2.4)	398 (19)
Saudi Arabia	32	14 (43.8)	14 (43.8)	4 (12.4)	18 (56.3)
Singapore	161	49 (30.4)	34 (21.1)	78 (48.5)	112 (69.6)
Slovak Republic	31	18 (58.1)	6 (19.4)	7 (22.5)	13 (41.9)
South Africa	17	7	7	3	10
Spain	344	112 (32.6)	133 (38.7)	99 (28.7)	232 (67.4)
Sweden	240	203 (84.6)	24 (10)	13 (5.4)	37 (15.4)
Switzerland	48	37 (77.1)	5 (10.4)	6 (12.5)	11 (22.9)
Taiwan	2	0	0	2	2
The Netherlands	80	78 (97.5)	2 (2.5)	0 (0)	2 (2.5)
United Arab Emirates	43	10 (23.3)	29 (67.4)	4 (9.3)	33 (76.7)
United Kingdom	117	107 (91.5)	8 (6.8)	2 (1.7)	10 (8.5)
United States	1966	931 (47.4)	279 (14.2)	756 (38.4)	1035 (52.6)
Total	**8040**	**4869 (60.6)**	**1443 (17.9)**	**1728 (21.5)**	**3171 (39.4)**

* Percentages are reported only for countries where Total N > 20.

Table 4. *In Vitro* Activities of Amoxicillin-Clavulanic Acid and Comparative Antimicrobial Agents against 5,170 Paediatric Isolates of *Haemophilus influenzae*, with Beta-lactamase positive and negative strains.

Organism	Drug [a]	% Sus	% Int	% Res	MIC (mcg/mL) MIC$_{50}$	MIC$_{90}$	Range
Haemophilus influenzae n=5,170	Amox-Clav	99.2	0.0	0.8	0.5	2	=0.03 - >32
	Ampicillin	74.6	2.1	23.3	0.25	> 16	=0.06 - >64
	Penicillin	na	na	na	0.5	> 16	=0.015 - >16
	Cefaclor	84.6	8.6	6.8	4	16	=0.5 - >64
	Cefuroxime	96.7	1.8	1.5	1	2	0.03 - >64
	Azithromycin	99.1	0.0	0.9	1	2	=0.015 - >64
	Erythromycin	na	na	na	4	8	0.03 - >64
	Trimeth-Sulfa	76.5	6.2	17.3	0.12	> 4	=0.008 - >64
Beta-lactamase Positive [b] n=997	Amox-Clav	99.8	0.0	0.2	1	2	0.25 - 16
	Ampicillin	0.8	1.2	98.0	> 16	> 16	=0.12 - >64
	Penicillin	na	na	na	> 16	> 16	0.25 - >16
	Cefaclor	69.7	14.7	15.7	8	32	=0.5 - >64
	Cefuroxime	98.6	1.1	0.3	1	2	=0.12 - >32
	Azithromycin	98.8	0.0	1.2	1	2	0.06 - >32
	Erythromycin	na	na	na	4	8	0.25 - >32
	Trimeth-Sulfa	74.2	5.5	20.3	0.12	> 4	0.008 - 32
Beta-lactamase Negative [b] n=3,233	Amox-Clav	99.2	0.0	0.8	0.5	1	0.03 - 16
	Ampicillin	97.2	1.9	0.9	0.25	1	=0.06 - 16
	Penicillin	na	na	na	0.25	1	=0.015 - 8
	Cefaclor	89.3	6.7	4.1	4	16	=0.5 - >64
	Cefuroxime	96.1	2.0	1.9	1	2	0.03 - >32
	Azithromycin	99.3	0.0	0.7	1	2	=0.015 - 64
	Erythromycin	na	na	na	4	8	0.03 - >64
	Trimeth-Sulfa	79.3	6.3	14.4	0.12	4	=0.008 - 32

na = NCCLS breakpoints are not defined for this organism/drug combination
[a] Amoxicillin-clavulanic acid was tested in a 2:1 ratio; trimethoprim-sulfamethoxazole was tested in a 1:19 ratio; MICs displayed are based on the amoxicillin and trimethoprim content.
[b] Not all strains tested were screened for beta-lactamase activity.

Table 4. *H. influenzae* beta-lactamase Positive Rates by Country.

Country [a]	Strains tested for Beta-lactamase (n)	Beta-lactamase Positive (n)	% Beta-lactamase Positive (%) [b]
Argentina	21	2	9.5
Australia	94	20	21.3
Austria	42	1	2.4
Belgium	126	25	19.8
Brazil	96	16	16.7
Canada	24	8	33.3
Czech Republic	25	5	20
Denmark	20	0	--
France	192	76	39.6
Germany	215	17	7.9
Greece	106	14	13.2
Hong Kong	49	16	32.7
Ireland	4	1	--
Israel	25	7	28
Italy	54	1	1.9
Japan	434	34	7.8
Mexico	328	76	23.2
New Zealand	9	1	--
Poland	39	3	7.7
Portugal	150	31	20.7
Russia	77	1	1.3
Saudi Arabia	53	12	22.6
Singapore	176	42	23.9
Slovak Republic	14	2	--
South Africa	25	1	4
Spain	48	11	22.9
Sweden	220	28	12.7
Switzerland	42	7	16.7
Taiwan	6	4	--
The Netherlands	197	7	3.6
United Kingdom	45	7	15.6
United States	1274	521	40.9
Total	**4230**	**997**	**23.6**

[a] Not all studies required testing for beta-lactamase in *H. influenzae*
[b] Percentages are reported only for countries where Total N > 20.

Table 6. *In Vitro* Activities of Amoxicillin-Clavulanic Acid and Comparative Antimicrobial Agents against 995 Paediatric Isolates of *Moraxella catarrhalis* with Beta-lactamase positive and negative strains.*

Organism	Drug [a]	MIC (mcg/mL MIC$_{50}$	MIC$_{90}$	Range
Moraxella catarrhalis n=995	Amox-Clav	0.25	0.25	=0.015 - 16
	Ampicillin	4	> 16	=0.06 - >64
	Penicillin	8	> 16	=0.015 - >16
	Cefaclor	2	8	=0.5 - 32
	Cefuroxime	2	4	=0.015 - >64
	Azithromycin	=0.06	0.12	=0.015 - >64
	Erythromycin	=0.5	=0.5	0.03 - 4
	Trimeth-Sulfa	0.25	1	=0.015 - >64
Beta-lactamase Positive [b] n=639	Amox-Clav	0.25	0.25	=0.015 - 0.5
	Ampicillin	8	16	=0.06 - >16
	Penicillin	16	> 16	=0.015 - >16
	Cefaclor	2	8	=0.5 - 32
	Cefuroxime	2	4	=0.015 - 8
	Azithromycin	0.03	=0.12	=0.015 - 0.5
	Erythromycin	=0.5	=0.5	0.03 - 4
	Trimeth-Sulfa	0.25	1	=0.015 - 8
Beta-lactamase Negative [b] n=23	Amox-Clav	=0.12	0.5	=0.015 - 1
	Ampicillin	=0.12	2	=0.12 - 4
	Penicillin	0.25	16	=0.015 - 16
	Cefaclor	=0.5	1	=0.5 - 2
	Cefuroxime	0.5	2	0.03 - 4
	Azithromycin	0.03	0.5	=0.015 - 1
	Erythromycin	=0.5	2	0.03 - 4
	Trimeth-Sulfa	0.12	0.5	0.03 - 1

* Breakpoints are undefined for *M. catarrhalis*, NCCLS (M100-S14), 2002.
[a] Amoxicillin-clavulanic acid was tested in a 2:1 ratio; trimethoprim-sulfamethoxazole was tested in a 1:19 ratio; MICs displayed are based on the amoxicillin and trimethoprim content.
[b] Not all strains tested were screened for beta-lactamase activity.

Table 7. *In Vitro* Activities of Amoxicillin-Clavulanic Acid and Comparative Antimicrobial Agents against 1,294 Paediatric Isolates of *Streptococcus pyogenes.*

Organism	Drug [b]	% Sus	% Int	% Res	MIC (mcg/mL) MIC$_{50}$	MIC$_{90}$	Range
Streptococcus pyogenes n=1,294	Amox-Clav	na [a]	na	na	=0.03	0.03	=0.015 - >32
	Ampicillin	99.9	0.0	0.1	=0.06	=0.12	=0.015 – 2 [c]
	Penicillin	100	0.0	0.0	=0.015	0.03	=0.015 - 0.12
	Cefaclor	na [a]	na	na	=0.5	=0.5	=0.5 - 4
	Cefuroxime	na [a]	na	na	0.03	0.06	=0.015 - >64
	Azithromycin	80.2	0.8	19.0	0.12	16	=0.015 - >64
	Erythromycin	82.2	0.0	17.8	0.06	>32	=0.015 - >32
	Trimeth-Sulfa	na	na	na	0.12	1	0.03 - >64

na = NCCLS breakpoints are not defined for this organism/drug combination.
[a] Streptococcal strains that are susceptible to penicillin are considered susceptible to this beta-lactam –NCCLS document note (M100-S14), 2004.
[b] Amoxicillin-clavulanic acid was tested in a 2:1 ratio; trimethoprim-sulfamethoxazole was tested in a 1:19 ratio; MICs displayed are based on the amoxicillin and trimethoprim content.
[c] One strain had a MIC of 2 mcg/mL against ampicillin but could not be recovered for confirmation.

Table 8. Frequency Distribution (n) and Cumulative Percents Inhibited of Amoxicillin-Clavulanic Acid against 15,499 Paediatric Respiratory Pathogens. [a]

MIC (mcg/mL) / n / % [b]							
=0.12	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**=16**
7432	1891	2687	1456	1331	369	280	53
47.89	60.07	77.45	86.89	95.47	97.85	99.66	99.92

[a] Includes all *S. pneumoniae* (n=8,040), *H. influenzae* (n=5,170), *M. catarrhalis* (n=995) and *S. pyogenes* (n=1,294) in this study.

[b] Amoxicillin-clavulanic acid was tested in a 2:1 ratio; MICs displayed are based on the amoxicillin content.

CONCLUSIONS

- The percentage of *S. pneumoniae* isolates that are non-susceptible to penicillin is 39.4% in this global study. Penicillin non-susceptibility rates varied by country (where n's >20) from the lowest rate of 2.5% in The Netherlands to the highest rate of 85.9% in Hong Kong.
- The global rate of beta-lactamase positive *H. influenzae* was 23.6% in strains screened for beta-lactamase production. Beta-lactamase positive rates varied by country (where n's >20) from 1.3% in Russia to 40.9% in the United States.
- Using the PK/PD breakpoint of ≤4/1 mcg/mL for high dose amoxicillin/clavulanic acid (Augmentin ES) for *S. pneumoniae*, 97% of all the *S. pneumoniae* paediatric respiratory strains evaluated in this study are susceptible to Augmentin ES; 83.5% of penicillin-resistant *S. pneumoniae* are susceptible; and 89% of erythromycin-resistant *S. pneumoniae* strains are susceptible.
- Augmentin ES demonstrates excellent *in vitro* activity against all strains of *H. influenzae*, *S. pneumoniae*, *M. catarrhalis* and *S. pyogenes* with MIC$_{90}$s of 2, 2, 0.25 and 0.03 mcg/mL, respectively.
- Amoxicillin-clavulanic acid inhibited 97.9% and 95.5% of all paediatric respiratory strains at a MIC of ≤4 mcg/mL and ≤2 mcg/mL, respectively.
- Augmentin ES should be considered in the empirical treatment of children with infections where involvement of penicillin-resistant *S. pneumoniae* is suspected, or possible, and beta-lactamase producing pathogens cannot be ruled out.