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In Vitro Activity of Ceftaroline against *Staphylococcus aureus* Isolates Collected in 2012 from Latin American Countries as Part of the AWARE Surveillance Program

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The *in vitro* activities of ceftaroline and comparators, using broth microdilution, were determined against 1,066 *Staphylococcus aureus* isolates from hospitalized patients. Seventeen medical centers from Latin American countries contributed isolates. Methicillin-resistant *S. aureus* (MRSA) percentages ranged from 46% (Brazil) to 62% (Argentina). All methicillin-susceptible *S. aureus* (MSSA) isolates were susceptible to ceftaroline. Ceftaroline activity against MRSA varied with MIC_{90}s of 0.5 (Venezuela) to 2 (Brazil, Chile, and Colombia) μg/ml, which was the highest MIC value. ST-5 was the most common sequence type.

Staphylococcus aureus is particularly adaptive to antimicrobial pressure and commonly isolated from acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) (1–3). Methicillin-resistant *S. aureus* (MRSA) has been problematic among hospitalized patients, although community-acquired MRSA (CA-MRSA) strains are becoming more prevalent and resistance to commonly used antimicrobial agents is increasing (4–6). A distinction between hospital-associated MRSA (HA-MRSA) infections and CA-MRSA has been based upon genetic characteristics. Clones are migrating globally and disseminating between these environments in recent years. Physicians need to understand the prevalent strains in their area to guide therapy (7–11). Multidrug-resistant (MDR) *S. aureus* requires an alternative therapeutic approach due to lack of effective drugs (12, 13).

Ceftaroline has *in vitro* bactericidal activity against MDR-MRSA, has a good safety profile, and has been approved by the Food and Drug Administration for treating adults with ABSSSI and CABP (14–28). This report from Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) summarizes the *in vitro* activity of ceftaroline against *S. aureus* isolates collected in Latin America during 2012, including molecular characterization of isolates with reduced susceptibility to ceftaroline.

Clinical isolates of *S. aureus* were collected from 17 medical centers in Latin America during 2012. Countries (number of medical centers) included Argentina (3), Brazil (2), Chile (3), Colombia (2), Mexico (5), and Venezuela (2). Single patient isolates were collected prospectively with a targeted number of methicillin-susceptible *S. aureus* (MSSA) and MRSA isolates. The majority of isolates were from skin and skin structure (696 isolates) and respiratory (285) specimens. Isolate identification was confirmed and antimicrobial susceptibility testing was performed by a central laboratory (International Health Management Associates [IHMA], Schaumburg, IL, USA). Susceptibility testing was performed by broth microdilution, and results were interpreted and quality controlled according to the Clinical and Laboratory Standards Institute (CLSI) performance standards (29, 30).

A random sample of 27 of the 130 isolates with ceftaroline MIC values of 2 μg/ml (intermediate MIC) based upon the current CLSI breakpoint was selected for molecular characterization. Whole-genome sequencing was performed to enable sequence-based analyses as previously described (31).

Overall MIC_{50} and MIC_{90} values for ceftaroline were 0.5 and 2 μg/ml against *S. aureus*, respectively, with 87.8% of isolates susceptible to ceftaroline (Table 1). Ceftaroline exhibited MIC_{90} values of 0.25 and 2 μg/ml against MSSA and MRSA, respectively. All of the MSSA isolates and 78.2% of MRSA isolates were susceptible to ceftaroline. No ceftaroline-resistant (MIC, >2 μg/ml) isolates were encountered. MRSA isolates exhibited high resistance to erythromycin, clindamycin, and levofloxacin (56.7%). All isolates were susceptible to linezolid, daptomycin, and vancomycin.

The highest ceftaroline MIC value among MRSA isolates was 2 μg/ml with MIC_{90} values of 0.5 μg/ml in Venezuela, 1 μg/ml in Mexico, and 2 μg/ml in Argentina, Brazil, Chile, and Colombia (Table 2). MRSA isolates with a ceftaroline MIC of 2 μg/ml occurred in Argentina (10.6%), Brazil (25%), Chile (73.2%), Colombia (30.8%), and Venezuela (5.1%), but all MRSA isolates in Mexico were ceftaroline susceptible.

Similar percentages of MRSA were observed among isolates from ABSSI (56%) and respiratory tract infections (RTI) (55%). Ceftaroline susceptibility was higher among the isolates from ABSSI (83.3%) than among those from RTI (69.4%) (Table 3). This trend was also observed when analyzed by country, with the exception of Brazil.

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TABLE 1 Activities of ceftaroline and comparator agents against *S. aureus* isolates from Latin America

S. aureus type (*n*)	Drug	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	% susceptible[a]	% resistant
All (1,066)	Ceftaroline	0.5	2	87.8	0.0
	Ceftriaxone[b]	>32	>32	44.1	55.9
	Erythromycin	1	>4	45.3	44.2
	Clindamycin	0.12	>2	70.5	29.3
	Levofloxacin	0.25	>2	66.8	32.5
	Daptomycin	0.5	1	100	0.0
	Linezolid	2	2	100	0.0
	Vancomycin	1	1	100	0.0
MSSA (470)	Ceftaroline	0.25	0.25	100	0.0
	Ceftriaxone[b]	4	4	100	0.0
	Erythromycin	0.5	>4	68.7	15.7
	Clindamycin	0.12	0.12	99.2	0.6
	Levofloxacin	0.25	0.25	97.7	1.7
	Daptomycin	0.5	1	100	0.0
	Linezolid	2	2	100	0.0
	Vancomycin	1	1	100	0.0
MRSA (596)	Ceftaroline	0.5	2	78.2	0.0
	Ceftriaxone[b]	>32	>32	0.0	100
	Erythromycin	>4	>4	26.9	66.6
	Clindamycin	>2	>2	48.0	51.9
	Levofloxacin	>2	>2	42.5	56.7
	Daptomycin	1	1	100	0.0
	Linezolid	2	2	100	0.0
	Vancomycin	1	1	100	0.0

[a] According to CLSI breakpoint criteria.
[b] Susceptibility based upon methicillin (oxacillin) susceptibility.

MRSA isolates with an intermediate susceptibility to ceftaroline (MIC, 2 μg/ml) were observed across the region (Table 2). Reports of ceftaroline MIC values in the nonsusceptible range (≥2 μg/ml) have been associated with modifications in the *mecA*-encoded penicillin-binding protein 2a (PBP2a) and substitutions in the non-penicillin-binding domain of PBP2a (31). This region has been proposed to be functionally important for interactions with other protein partners or ligands during cell wall biogenesis or in allosteric regulation by a second ceftaroline molecule and has been associated with intermediate ceftaroline MIC values (31, 32). Ceftaroline MIC values higher than 2 μg/ml require additional substitutions in key residues in the transpeptidase pocket of the penicillin-binding domain (31, 32). No ceftaroline-resistant isolates were collected from the region, and modifications in the transpeptidase pocket of the penicillin-binding domain were not observed. Of the random isolates selected for genetic characterization, a single isolate from Brazil carried three substitutions in the non-penicillin-binding domain ($Asn_{146}Lys$, $Asn_{204}Lys$, and $Gly_{246}Glu$), while the remaining 26 isolates, irrespective of the country of isolation, carried the PBP2a substitutions $Met_{122}Ile$ and $Glu_{150}Lys$ (Table 4). Multilocus sequence typing demonstrated that the single isolate from Brazil that carried the three PBP2a substitutions belonged to the ST-239 lineage (Brazilian/Hungarian clone) and carried SCC*mec* type III. All remaining isolates that possessed the $Met_{122}Ile$ and $Glu_{150}Lys$ substitutions belonged to the UK-EMRSA-3 ST-5 lineage and carried SCC*mec* type I.

Ceftaroline exhibited good *in vitro* activity, with no resistance observed against clinical isolates of *S. aureus* from Latin American countries isolated in 2012. Ceftaroline activity against MRSA was variable in the six countries participating in the Latin America AWARE surveillance program. A previous prospective surveillance study performed under the auspices of the AWARE program in seven Latin American countries reported lower ceftaroline susceptibility (83.6%) against *S. aureus* than did this 2012 study (87.8%), despite collecting a lower percentage of MRSA isolates (42.8% versus 55.9%, respectively) (34). The reasons for the lower susceptibility observed in Latin America remain uncertain but could be due to the inclusion of high numbers of *S. aureus* isolates sourced from respiratory infections (26.7% in this study and 30% in the 2011 AWARE study conducted in the region [34]).

None of the isolates investigated had changes in the penicillin-binding region of PBP2a, which are the types of substitutions observed in ceftaroline-resistant isolates (MIC of >2 μg/ml), and only substitutions in the non-penicillin-binding domain that confer low-level (intermediate) resistance to ceftaroline were detected (31, 32). A recent study has proposed a novel resistance mechanism to explain the observed non-penicillin-binding domain changes and their impact on ceftaroline susceptibility. The hypothesis claims a disruption of an allosteric trigger by the mutations in PBP2a, affecting the ability

TABLE 2 Ceftaroline MIC distributions (cumulative percentages) against *S. aureus* isolates from Latin American countries

		No. of isolates (cumulative %) with MIC (μg/ml)[a]:					
Country (no. of sites)	Organism (*n*)	0.06	0.12	0.25	0.5	1	2
All (17)	MSSA (470)	4 (0.9)	107 (23.6)	**351 (98.3)**	8 (100)		
	MRSA (596)	0 (0)	0 (0)	15 (2.5)	289 (51.0)	162 (78.2)	**130 (100)**
Argentina (3)	MSSA (93)	0 (0)	15 (16.1)	**78 (100)**			
	MRSA (151)	0 (0)	0 (0)	5 (3.3)	118 (81.5)	12 (89.4)	**16 (100)**
Brazil (2)	MSSA (33)	1 (3.0)	10 (33.3)	**22 (100)**			
	MRSA (28)	0 (0)	0 (0)	1 (3.6)	11 (42.9)	9 (75.0)	**7 (100)**
Chile (3)	MSSA (93)	1 (1.1)	29 (32.3)	**60 (96.8)**	3 (100)		
	MRSA (123)	0 (0)	0 (0)	3 (2.4)	20 (18.7)	10 (26.8)	**90 (100)**
Colombia (2)	MSSA (37)	0 (0)	10 (27.0)	**27 (100)**			
	MRSA (39)	0 (0)	0 (0)	2 (5.1)	22 (61.5)	3 (69.2)	**12 (100)**
Mexico (5)	MSSA (141)	1 (0.7)	34 (24.8)	**102 (97.2)**	4 (100)		
	MRSA (156)	0 (0)	0 (0)	2 (1.3)	29 (19.9)	**125 (100)**	
Venezuela (2)	MSSA (73)	1 (1.4)	9 (13.7)	**62 (98.6)**	1 (100)		
	MRSA (99)	0 (0)	0 (0)	2 (2.0)	**89 (91.9)**	3 (94.9)	5 (100)

[a] Boldface values represent MIC_{90} values.

TABLE 3 Activities of ceftaroline against *S. aureus* isolates from skin and skin structure and respiratory tract specimens in Latin American countries

Source/country (no. of sites)/phenotype (*n*)	MIC (μg/ml)			%		
	MIC_{50}	MIC_{90}	Range	Susceptible[a]	Intermediate	Resistant
Skin and skin structure						
All MSSA (306)	0.25	0.25	0.06–0.5	100	0.0	0.0
All MRSA (390)	0.5	2	0.25–2	83.3	16.7	0.0
Argentina (3)						
MSSA (58)	0.25	0.25	0.12–0.25	100	0.0	0.0
MRSA (116)	0.5	1	0.25–2	90.5	9.5	0.0
Brazil (2)						
MSSA (14)	0.25	0.25	0.12–0.25	100	0.0	0.0
MRSA (6)	0.5	—[b]	0.5–2	66.7	33.3	0.0
Chile (3)						
MSSA (63)	0.25	0.25	0.06–0.5	100	0.0	0.0
MRSA (63)	2	2	0.25–2	28.6	71.4	0.0
Colombia (2)						
MSSA (23)	0.25	0.25	0.12–0.25	100	0.0	0.0
MRSA (24)	0.5	2	0.25–2	87.5	12.5	0.0
Mexico (5)						
MSSA (89)	0.25	0.25	0.06–0.5	100	0.0	0.0
MRSA (100)	1	1	0.25–1	100	0.0	0.0
Venezuela (2)						
MSSA (59)	0.25	0.25	0.06–0.5	100	0.0	0.0
MRSA (81)	0.5	0.5	0.25–2	95.1	4.9	0.0
Respiratory tract						
All MSSA (128)	0.25	0.25	0.06–0.5	100.0	0.0	0.0
All MRSA (157)	1	2	0.25–2	69.4	30.6	0.0
Argentina (3)						
MSSA (25)	0.25	0.25	0.12–0.25	100.0	0.0	0.0
MRSA (22)	0.5	2	0.25–2	86.4	13.6	0.0
Brazil (2)						
MSSA (15)	0.25	0.25	0.06–0.25	100.0	0.0	0.0
MRSA (15)	1	2	0.25–2	86.7	13.3	0.0
Chile (3)						
MSSA (24)	0.25	0.25	0.12–0.25	100.0	0.0	0.0
MRSA (57)	2	2	0.25–2	26.3	73.7	0.0
Colombia (2)						
MSSA (10)	0.25	0.25	0.12–0.25	100.0	0.0	0.0
MRSA (4)	0.5	—[b]	0.5–2	75.0	25.0	0.0
Mexico (5)						
MSSA (44)	0.25	0.25	0.12–0.5	100.0	0.0	0.0
MRSA (46)	1	1	0.5–1	100.0	0.0	0.0
Venezuela (2)						
MSSA (10)	0.25	0.25	0.12–0.25	100.0	0.0	0.0
MRSA (13)	0.5	0.5	0.5	100.0	0.0	0.0

[a] According to CLSI breakpoint criteria.
[b] —, number insufficient to calculate MIC_{90} value.

TABLE 4 Molecular analysis of PBP2a from 27 ceftaroline-nonsusceptible (intermediate) *S. aureus* isolates from Latin America

Country (*n*)	MecA mutations	ST type
Argentina (6)	$Met_{122}Ile$, $Glu_{150}Lys$	ST-5
Brazil (4)	$Met_{122}Ile$, $Glu_{150}Lys$	ST-5
Brazil (1)	$Asn_{146}Lys$, $Asn_{204}Lys$, $Gly_{246}Glu$	ST-239
Chile (7)	$Met_{122}Ile$, $Glu_{150}Lys$	ST-5
Colombia (4)	$Met_{122}Ile$, $Glu_{150}Lys$	ST-5
Venezuela (5)	$Met_{122}Ile$, $Glu_{150}Lys$	ST-5

of ceftaroline to bind within the functional pocket (35). However, other studies have demonstrated no impact of ceftaroline inhibition in purified protein containing non-penicillin-binding domain changes (33).

All isolates, except for one with a ceftaroline MIC of 2 μg/ml, showed the sequence type ST-5. This sequence type, ST-5, was similar to that in a study among *S. aureus* isolates from Brazil that were resistant to tigecycline and daptomycin (36). A possible relationship with this sequence type and increased resistance to these drug classes would require more extensive typing and analysis. However, molecular studies of Latin American *S. aureus*, from Argentina in particular, have documented an epidemic spread of the MRSA ST-5-IV clone (37, 38).

Ceftaroline fosamil is a useful addition to the antimicrobial agents that can be used to treat *S. aureus* infections, especially with the capability of covering MRSA, including CA-MRSA.

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REFERENCES

1. **Rodvold KA, McConeghy KW.** 2014. Methicillin-resistant *Staphylococcus aureus* therapy: past, present, and future. Clin Infect Dis **58**(Suppl 1):S20–S27. http://dx.doi.org/10.1093/cid/cit614.
2. **Moet GJ, Jones RN, Biedenbach DJ, Stilwell MG, Fritsche TR.** 2007. Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: report from the SENTRY Antimicrobial Surveillance Program (1998–2004). Diagn Microbiol Infect Dis **57:**7–13. http://dx.doi.org/10.1016/j.diagmicrobio.2006.05.009.
3. **Rubinstein E, Kollef MH, Nathwani D.** 2008. Pneumonia caused by methicillin-resistant *Staphylococcus aureus* Clin Infect Dis **46**(Suppl 5)**:** S378–S385. http://dx.doi.org/10.1086/533594.
4. **Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, Harrison LH, Lynfield R, Dumyati G, Townes JM, Craif AS, Zell ER, Fosheim GE, McDougal LK, Carey RB, Fridkin SK, Active Bacterial Core Surveillance (ABCs) MRSA Investigators.** 2007. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA **298:**1763–1771. http://dx.doi.org/10.1001/jama.298.15.1763.
5. **Ray GT, Suaya JA, Baxter R.** 2012. Trends and characteristic of culture-confirmed *Staphylococcus aureus* infections in a large U.S. integrated health care organization. J Clin Microbiol **50:**1950–1957. http://dx.doi.org/10.1128/JCM.00134-12.
6. **Woods C, Colice G.** 2014. Methicillin-resistant *Staphylococcus aureus* pneumonia in adults. Expert Rev Respir Med **8:**641–651. http://dx.doi.org/10.1586/17476348.2014.940323.
7. **Diekema DJ, Richter SS, Heilmann KP, Dohrn CL, Riahi F, Tendolkar S, McDanel JS, Doern GV.** 2014. Continued emergence of USA300 methicillin-resistant *Staphylococcus aureus* in the United States: results from a nationwide surveillance study. Infect Control Hosp Epidemiol **35:** 285–292. http://dx.doi.org/10.1086/675283.
8. **Levesque S, Bourgault AM, Galarneau LA, Moisan D, Doualla-Bell F, Tremblay C.** 2015. Molecular epidemiology and antimicrobial susceptibility profiles of methicillin-resistant *Staphylococcus aureus* blood culture isolates: results of the Quebec Provincial Surveillance Programme. Epidemiol Infect **143:**1511–1518. http://dx.doi.org/10.1017/S095026881400209X.
9. **Tadros M, Williams V, Coleman BL, McGeer AJ, Haider S, Lee C, Iacovides H, Rubinstein E, John M, Johnston L, McNeil S, Katz K, Laffin N, Suh KN, Powis J, Smith S, Taylor G, Watt C, Simor AE.** 2013. Epidemiology and outcome of pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in Canadian hospitals. PLoS One **8:**e75171. http://dx.doi.org/10.1371/journal.pone.0075171.
10. **David MZ, Daum RS, Bayer AS, Chambers HF, Fowler VG, Jr, Miller LG, Ostrowsky B, Baesa A, Boyle-Vavra S, Eells SJ, Garcia-Houchins S, Gialanella P, Macias-Gil R, Rude TH, Ruffin F, Sieth JJ, Volinski J, Spellberg B.** 2014. *Staphylococcus aureus* bacteremia at 5 US academic medical centers, 2008–2011: significant geographic variation in community-onset infections. Clin Infect Dis **15:**798–807. http://dx.doi.org/10.1093/cid/ciu410.
11. **Tokajian S.** 2014. New epidemiology of *Staphylococcus aureus* infections in the Middle East. Clin Microbiol Infect **20:**624–628. http://dx.doi.org/10.1111/1469-0691.12691.
12. **Kollipara R, Downing C, Lee M, Guidry J, Curis S, Tyring S.** 2014. Current and emerging drugs for acute bacterial skin and skin structure infections: an update. Expert Opin Emerg Drugs **19:**431–440. http://dx.doi.org/10.1517/14728214.2014.955015.
13. **Rincon S, Panesso D, Diaz L, Carvajal LP, Reyes J, Munita JM, Arias CA.** 2014. Resistance to "last resort" antibiotics in Gram-positive cocci: the post-vancomycin era. Biomedica **34**(Suppl 1)**:**191–208. http://dx.doi.org/10.7705/biomedica.v34i0.2210.
14. **Arshad S, Hartman P, Zervos MJ.** 2014. A novel treatment option for MRSA pneumonia: ceftaroline fosamil-yielding new hope in the fight against a persistent infection. Expert Rev Anti Infect Ther **12:**727–729. http://dx.doi.org/10.1586/14787210.2014.908118.
15. **Casapao AM, Steed ME, Levine DP, Rybak MJ.** 2012. Ceftaroline fosamil for community-acquired bacterial pneumonia and acute bacterial skin and skin structure infection. Expert Opin Pharmacother **13:**1177–1186. http://dx.doi.org/10.1517/14656566.2012.685718.
16. **Goodman JJ, Martin SI.** 2012. Critical appraisal of ceftaroline in the management of community-acquired bacterial pneumonia and skin infections. Ther Clin Risk Manag **8:**149–156. http://dx.doi.org/10.2147/TCRM.S17413.
17. **Shirley DT, Heil EL, Johnson JK.** 2013. Ceftaroline fosamil: a brief clinical review. Infect Dis Ther **2:**95–110. http://dx.doi.org/10.1007/s40121-013-0010-x.
18. **Casapao AM, Davis SL, Barr VO, Klinker KP, Goff DA, Barber KE, Kaye KS, Mynatt RP, Molloy LM, Pogue JM, Rybak MJ.** 2014. Large retrospective evaluation of the effectiveness and safety of ceftaroline fosamil therapy. Antimicrob Agents Chemother **58:**2541–2546. http://dx.doi.org/10.1128/AAC.02371-13.
19. **File TM, Jr, Wilcox MH, Stein GE.** 2012. Summary of ceftaroline fosamil clinical trial studies and clinical safety. Clin Infect Dis **55**(Suppl 3)**:**S73–S80. http://dx.doi.org/10.1093/cid/cis559.
20. **Actavis, Inc.** 2012. Teflaro (ceftaroline fosamil) prescribing information. Actavis, Inc, Parsippany, NJ. http://www.frx.com/pi/teflaro_pi.pdf.
21. **AstraZeneca.** 2012. Zinforo (ceftaroline fosamil). Summary of product characteristics. AstraZeneca, Luton, United Kingdom. http://www.medicines.org.uk/emc/searchresults.aspx?term=Zinforo&searchtype=QuickSearch.
22. **Bally M, Dendukuri N, Sinclair A, Ahern SP, Poisson M, Brophy J.** 2012. A network meta-analysis of antibiotics for treatment of hospitalised patients with suspected or proven methicillin-resistant *Staphylococcus aureus* infection. Int J Antimicrob Agents **40:**479–495. http://dx.doi.org/10.1016/j.ijantimicag.2012.08.004.
23. **Critchley IA, Eckburg PB, Jandourek A, Biek D, Friedland HD, Thye DA.** 2011. Review of ceftaroline fosamil microbiology: integrated FOCUS studies. J Antimicrob Chemother **66**(Suppl 3)**:**45–51. http://dx.doi.org/10.1093/jac/dkr098.
24. **Frampton JE.** 2013. Ceftaroline fosamil: a review of its use in the treatment of complicated skin and soft tissue infections and community-acquired pneumonia. Drugs **73:**1067–1094. http://dx.doi.org/10.1007/s40265-013-0075-6.
25. **Lodise TP, Low DE.** 2012. Ceftaroline fosamil in the treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections. Drugs **72:**1473–1493. http://dx.doi.org/10.2165/11635660-000000000-00000.
26. **Pasquale TR, Tan MJ, Trienski TL, File TM, Jr.** 2015. Methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia patients treated with ceftaroline: retrospective case series of 10 patients. J Chemother **27:** 29–34. http://dx.doi.org/10.1179/1973947813Y.0000000156.
27. **Santos PD, Davis A, Jandourek A, Smith A, Friedland HD.** 2013. Ceftaroline fosamil and treatment of acute bacterial skin and skin structure infections: CAPTURE study experience. J Chemother **25:**341–346. http://dx.doi.org/10.1179/1973947813Y.0000000144.
28. **Zhong NS, Sun T, Zhuo C, D'Souza G, Lee SH, Lan NH, Chiang CH, Wilson D, Sun F, Iaconis J, Melnick D.** 2015. Ceftaroline fosamil versus ceftriaxone for the treatment of Asian patients with community-acquired pneumonia: a randomised, controlled, double-blind, phase 3, non-inferiority with nested superiority trial. Lancet Infect Dis **15:**161–171. http://dx.doi.org/10.1016/S1473-3099(14)71018-7.
29. **Clinical and Laboratory Standards Institute.** 2012. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standards, 9th ed. CLSI document M07-A9. Clinical and Laboratory Standards Institute, Wayne, PA.
30. **Clinical and Laboratory Standards Institute.** 2014. Performance standards for antimicrobial susceptibility testing; 24th informational supple-

ment. CLSI document M100-S24. Clinical and Laboratory Standards Institute, Wayne, PA.
31. **Alm RA, McLaughlin RE, Kos VN, Sader HS, Iaconis JP, Lahiri SD.** 2014. Analysis of *Staphylococcus aureus* clinical isolates with reduced susceptibility to ceftaroline: an epidemiological and structural perspective. J Antimicrob Chemother **69:**2065–2075. http://dx.doi.org/10.1093/jac/dku114.
32. **Otero LH, Rojas-Altuve A, Llarrull LI, Carrasco-López C, Kumarasiri M, Lastochkin E, Fishovitz J, Dawley M, Hesek D, Lee M, Johnson JW, Fisher JF, Chang M, Mobashery S, Hermoso JA.** 2013. How allosteric control of *Staphylococcus aureus* penicillin binding protein 2a enables methicillin resistance and physiological function. Proc Natl Acad Sci U S A **110:**16808–16813. http://dx.doi.org/10.1073/pnas.1300118110.
33. **Long SW, Olsen RJ, Mehta SC, Palzkill T, Cernoch PL, Perez KK, Musick WL, Rosato AE, Musser JM.** 2014. PBP2a mutations causing high-level ceftaroline resistance in clinical methicillin-resistant *Staphylococcus aureus* isolates. Antimicrob Agents Chemother **58:**6668–6674. http://dx.doi.org/10.1128/AAC.03622-14.
34. **Flamm RK, Sader HS, Jones RN.** 2014. Ceftaroline activity tested against contemporary Latin American bacterial pathogens (2011). Braz J Infect Dis **18:**187–195. http://dx.doi.org/10.1016/j.bjid.2013.11.005.
35. **Fishovitz J, Rohas-Altuve A, Otero L, Dawley M, Carrasco-Lopez C, Chang M, Hermoso JA, Mobashery S.** 2014. Disruption of allosteric response as an unprecedented mechanism of resistance to antibiotics. J Am Chem Soc **136:**9814–9817. http://dx.doi.org/10.1021/ja5030657.
36. **Dabul AN, Camargo IL.** 2014. Molecular characterization of methicillin-resistant *Staphylococcus aureus* resistant to tigecycline and daptomycin isolated in a hospital in Brazil. Epidemiol Infect **142:**479–483. http://dx.doi.org/10.1017/S0950268813001325.
37. **Sola C, Saka HA, Cordoba MRSA Collaborative Study Group, Vindel A, Bocco JL.** 2008. Emergence and dissemination of a community-associated methicillin-resistant Panton-Valentine leucocidin-positive *Staphylococcus aureus* clone sharing the sequence type 5 lineage with the most prevalent nosocomial clone in the same region of Argentina. J Clin Microbiol **46:**1826–1831. http://dx.doi.org/10.1128/JCM.01949-07.
38. **Sola C, Paganini H, Egea AL, Moyano AJ, Garnero A, Kevric I, Culasso C, Vindel A, Study Group of CA-MRSA in Children, Argentina-2007, Lopardo H, Bocco JL.** 2012. Spread of epidemic MRSA-ST5-IV clone encoding PVL as a major cause of community onset staphylococcal infections in Argentinean children. PLoS One **7:**e30487. http://dx.doi.org/10.1371/journal.pone.0030487.