AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy



LETTER TO THE EDITOR

# The Curious Case of TEM-116

**George A. Jacoby,[a] Karen Bush[b]**

Lahey Hospital and Medical Center, Burlington, Massachusetts, USA[a]; Indiana University, Bloomington, Indiana, USA[b]

More than 400 unique TEM β-lactamase variants have been identified (1). Many are derived from one or more mutations at a limited number of positions in TEM-1, the first TEM enzyme to be described (2). Recently, network analysis by Zeil et al. disclosed a second cluster of TEM variants derived from TEM-116 (1). What is so special about this β-lactamase that it has become a second progenitor of this ubiquitous enzyme family?

Since the 1990s, TEM-116 has been described worldwide to occur in a variety of Gram-negative organisms and to be encoded by conjugative plasmids of various sizes (3–8). Although TEM-116 has been characterized microbiologically as an extended-spectrum β-lactamase (ESBL) by some investigators (3, 4, 6, 7), other data do not support this designation based on biochemical and microbiological profiles (9–11). It has been linked on plasmids to the ESBL PER-2, which has an indistinguishable isoelectric point (12) as a possible source of confusion. Other well-established TEM enzymes, whether ESBLs or not, have not given rise to unique clusters of offspring (1). The defining mutations in TEM-116, V84I and A184V, lie in different chains separate from the active site. What is curious about TEM-116 is that $bla_{\text{TEM-1}}$ was engineered in the 1980s to result in precisely these amino acid changes by removing PstI and HincII restriction sites from the wild-type gene to facilitate antibiotic selection using $bla_{\text{TEM}}$ in M13 phage and pUC series plasmids as cloning vectors that came to be widely used in molecular biology (13). The 861 nucleotides of some reported $bla_{\text{TEM-116}}$ genes are completely identical to the constructed $bla_{\text{TEM}}$ gene in pUC vectors. This is concerning because certain commercial *Taq* polymerase preparations used in PCRs to characterize β-lactamases have been contaminated with exogenous DNA, in particular with $bla_{\text{TEM-116}}$ DNA, suggesting that their use might lead to the erroneous description of TEM-116 in organisms that do not contain it (14).

Zeil et al. identified more than 50 TEM variants derived from TEM-116 (1). Almost all contain both mutations. Exceptions are TEM-171, with V84I alone, and TEM-181, with A184V alone, which consequently may be intermediate steps between TEM-1 and TEM-116. TEM-116 had to be present in bacteria to evolve as it has. Despite concern about contaminated reagents, the centrality of TEM-116 in the TEM family network, its wide geographical dissemination, and its establishment on multiple plasmids indicate that TEM-116 is now a naturally occurring enzyme.

## FUNDING INFORMATION

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

## REFERENCES

1. **Zeil C, Widmann M, Fademrecht S, Vogel C, Pleiss J.** 2016. Network analysis of sequence-function relationships and exploration of sequence space of TEM β-lactamases. Antimicrob Agents Chemother **60:**2709–2717. http://dx.doi.org/10.1128/AAC.02930-15.
2. **Datta N, Kontomichalou P.** 1965. Penicillinase synthesis controlled by infectious R factors in Enterobacteriaceae. Nature **208:**239–241. http://dx.doi.org/10.1038/208239a0.
3. **Jeong SH, Bae IK, Lee JH, Sohn SG, Kang GH, Jeon GJ, Kim YH, Jeong BC, Lee SH.** 2004. Molecular characterization of extended-spectrum β-lactamases produced by clinical isolates of *Klebsiella pneumoniae* and *Escherichia coli* from a Korean nationwide survey. J Clin Microbiol **42:**2902–2906. http://dx.doi.org/10.1128/JCM.42.7.2902-2906.2004.
4. **Song JS, Jeon JH, Lee JH, Jeong SH, Jeong BC, Kim SJ, Lee SH.** 2005. Molecular characterization of TEM-type β-lactamases identified in cold-seep sediments of Edison Seamount (south of Lihir Island, Papua New Guinea). J Microbiol **43:**172–178.
5. **Naiemi NA, Duim B, Savelkoul PH, Spanjaard L, de Jonge E, Bart A, Vandenbroucke-Grauls CM, de Jong MD.** 2005. Widespread transfer of resistance genes between bacterial species in an intensive care unit: implications for hospital epidemiology. J Clin Microbiol **43:**4862–4864. http://dx.doi.org/10.1128/JCM.43.9.4862-4864.2005.
6. **Usha G, Chunderika M, Prashini M, Willem SA, Yusuf ES.** 2008. Characterization of extended-spectrum β-lactamases in *Salmonella* spp. at a tertiary hospital in Durban, South Africa. Diagn Microbiol Infect Dis **62:**86–91. http://dx.doi.org/10.1016/j.diagmicrobio.2008.04.014.
7. **Lahlaoui H, Dahmen S, Moussa MB, Omrane B.** 2011. First detection of TEM-116 extended-spectrum β-lactamase in a *Providencia stuartii* isolate from a Tunisian hospital. Indian J Med Microbiol **29:**258–261. http://dx.doi.org/10.4103/0255-0857.83909.
8. **Maravic A, Skocibusic M, Fredotovic Z, Samanic I, Cvjetan S, Knezovic M, Puizina J.** 2016. Urban riverine environment is a source of multidrug-resistant and ESBL-producing clinically important *Acinetobacter* spp. Environ Sci Pollut Res Int **23:**3525–3535. http://dx.doi.org/10.1007/s11356-015-5586-0.
9. **Sowek JA, Singer SB, Ohringer S, Malley MF, Dougherty TJ, Gougoutas JZ, Bush K.** 1991. Substitution of lysine at position 104 or 240 of TEM-$1_{\text{PTZ18R}}$ β-lactamase enhances the effect of serine-164 substitution on hydrolysis or affinity for cephalosporins and the monobactam aztreonam. Biochemistry **30:**3179–3188. http://dx.doi.org/10.1021/bi00227a004.
10. **Chaibi EB, Peduzzi J, Barthelemy M, Labia R.** 1997. Are TEM beta-lactamases encoded by pBR322 and Bluescript plasmids enzymatically indistinguishable? J Antimicrob Chemother **39:**668–669. http://dx.doi.org/10.1093/jac/39.5.668.
11. **Lin TL, Tang SI, Fang CT, Hsueh PR, Chang SC, Wang JT.** 2006. Extended-spectrum β-lactamase genes of *Klebsiella pneumoniae* strains in Taiwan: recharacterization of *shv-27*, *shv-41*, and *tem-116*. Microb Drug Resist **12:**12–15. http://dx.doi.org/10.1089/mdr.2006.12.12.
12. **Vignoli R, Varela G, Mota MI, Cordeiro NF, Power P, Ingold E, Gadea P, Sirok A, Schelotto F, Ayala JA, Gutkind G.** 2005. Enteropathogenic *Escherichia coli* strains carrying genes encoding the PER-2 and TEM-116 extended-spectrum β-lactamases isolated from children with diarrhea in Uruguay. J Clin Microbiol **43:**2940–2943. http://dx.doi.org/10.1128/JCM.43.6.2940-2943.2005.
13. **Vieira J, Messing J.** 1982. The pUC plasmids, an M13mp7-derived system for insertion mutagenesis and sequencing with synthetic universal primers. Gene **19:**259–268. http://dx.doi.org/10.1016/0378-1119(82)90015-4.
14. **Koncan R, Valverde A, Morosini MI, Garcia-Castillo M, Canton R, Cornaglia G, Baquero F, del Campo R.** 2007. Learning from mistakes: Taq polymerase contaminated with β-lactamase sequences results in false emergence of *Streptococcus pneumoniae* containing TEM. J Antimicrob Chemother **60:**702–703. http://dx.doi.org/10.1093/jac/dkm239.

**Citation** Jacoby GA, Bush K. 2016. The curious case of TEM-116. Antimicrob Agents Chemother 60:7000. doi:10.1128/AAC.01777-16.

Address correspondence to George A. Jacoby, gajacoby50@gmail.com.

For the author reply, see doi:10.1128/AAC.01786-16.