To address the issues raised in the letters, we analyzed the data using time-dependent covariates, and we performed a sensitivity analysis using the suggested stricter survival criteria. We performed a Cox regression analysis with 2 time-dependent covariates for switching to daptomycin adjusting for other covariates that were potential confounders. One time-dependent covariate changed from 0 to 1 on the day a patient initiated daptomycin if it occurred during the first 3 days of hospitalization (intention-to-treat), and the other time-dependent covariate changed from 0 to 1 on the day of the third daptomycin dose during the 3–5 consecutive day window (approximate effective therapeutic level). Three doses of daptomycin were deemed to be an approximate effective therapeutic level based on prior studies that found that blood cultures tend to remain positive within the first 72 hours of anti-staphylococcal therapy [2]. These variables were defined for all study subjects. In this model, the intention-to-treat time-dependent covariate was not significantly associated with mortality (HR = 1.28; 95% CI: .57–2.86). The effective therapeutic level time-dependent covariate was significantly associated with a protective effect (HR = 0.32; 95% CI: .11–0.95), demonstrating that those who received 3 days of daptomycin had a significantly lower hazard of death among early initiators. When both time-dependent covariates were assessed together, early initiation of daptomycin (within 3 days) and receiving an effective therapeutic level significantly lowered the hazard of death (HR = 0.41; 95% CI: .19–.86). A separate sensitivity analysis using patients who survived at least 7 days also found a similar association (HR: 0.54; 95% CI: .27, 1.09), although it was not statistically significant likely due to reduced sample size from excluding patients.

Our results differ somewhat from the small, noninferiority randomized controlled trial (RCT) that compared daptomycin versus vancomycin plus gentamicin for MRSA bloodstream infections and endocarditis [3, 4]. In that RCT of 89 MRSA patients, 4 more daptomycin patients died compared with vancomycin patients (12/45 vs 8/43; $P = .45$). A large RCT powered for superiority is needed, but as stated in our publication, 2 RCTs on this topic have recently been stopped due to low patient enrollment. In contrast to a strictly monitored RCT, our study evaluated how these antibiotics are being used in real-world settings. We agree with Avedissian and colleagues that it is difficult to achieve adequate vancomycin therapeutic doses in some patients. Thus, some of the benefit seen in our study may have been due to ease of dosing daptomycin compared with vancomycin. We attempted to measure vancomycin area under the curve (AUC)/MIC dosing in our database but were unable to accurately collect these data retrospectively.

In conclusion, our analyses have consistently shown a protective association between at least 3 days of daptomycin when given within 3 days and 30-day mortality. However, a large RCT powered for superiority is needed to definitively answer this question.

## Notes

***Financial support.*** M. L. S. and M. P. J. report grants from the Department of Veterans Affairs.

***Potential conflicts of interest.*** All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

**Marin L. Schweizer,[1,2] Kelly Richardson,[1] Michael P. Jones,[1,3] Mary S. Vaughan Sarrazin,[1,2] and Eli N. Perencevich[1,2]**

[1]Center for Access and Delivery Research and Evaluation, Iowa City Veterans Affairs (VA) Health Care System, Iowa City, Iowa USA; [2]Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, Iowa USA; and [3]Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, Iowa USA

## References

1. Schweizer ML, Richardson K, Vaughan Sarrazin MS, et al. Comparative effectiveness of switching to daptomycin versus remaining on vancomycin among patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections. Clin Infect Dis **2021**; 72:68–73.
2. Holland TL, Chambers HF, Boucher HW, et al. Considerations for clinical trials of *Staphylococcus aureus* bloodstream infection in adults. Clin Infect Dis **2019**; 68:865–72.
3. Rehm SJ, Boucher H, Levine D, et al. Daptomycin versus vancomycin plus gentamicin for treatment of bacteraemia and endocarditis due to *Staphylococcus aureus*: subset analysis of patients infected with methicillin-resistant isolates. J Antimicrob Chemother **2008**; 62:1413–21.
4. Fowler VG, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med **2006**; 355:653–65.

Correspondence: M. Schweizer, Iowa City VA Health Care System (152), 601 Highway 6 West, Iowa City, IA 52246 (Marin-schweizer@uiowa.edu).

**Clinical Infectious Diseases® 2021;73(6):1129–30**



DOI: 10.1093/cid/ciab249

## Toward the Spread of the New L2b/D-Da Hybrid *Chlamydia trachomatis* Strain in Men Who Have Sex With Men in France?

To the Editor—We read with great interest the article by Borges et al reporting recently lymphogranuloma venereum (LGV) cases in Portugal, Israel, and Canada caused by a recombinant LGV strain with L2b/D-Da hybrid *omp*A sequence [1, 2]. This hybrid variant was first identified in 2017 in Portugal and mostly affected human immunodeficiency virus (HIV)-positive men who have sex with men (MSM) with proctitis and engaging with high-risk sexual practices [1] and also recently reported in Italy [3]. In France, as part of the sentinel surveillance of *Chlamydia trachomatis* anorectal infections [4], molecular epidemiology of genovar L strains did not identify the hybrid variant between 2010 and 2015 [5, 6]. Interestingly, in 2017, we reported 4 cases of MSM pre-exposure prophylaxis (PrEP) users infected with strains harboring *pmp*H gene of genovar L and *omp*A sequence of D/Da genotype [7]. It is worth mentioning that the *omp*A sequence of the 4 strains was subsequently found to be identical to that of the hybrid variant. Three patients were from Paris and had anorectal symptoms. We therefore investigated if there was a potential increase of LGV outbreak involving the L2b/D-Da hybrid in France.

All LGV-positive anorectal specimens collected in the French National Reference

Centre for Bacterial Sexually Transmitted Infections in 2018 from HIV-positive MSM with anorectal symptoms were analyzed.

The criteria for collecting specimens were based on clinical symptoms (rectal syndrome, rectal pain, rectal tenesmus, anal discharge, rectal bleeding), on HIV-positive status and a positive specific LGV real-time polymerase chain reaction (PCR) targeting the *pmp*H gene [8]. A 1.100-bp fragment of *omp*A gene was amplified directly on clinical specimens by nested PCR and sequenced in both directions [9]. The obtained sequences were compared by alignment with currently available chlamydial L genovar-*omp*A gene sequences from GenBank.

Overall, 184 LGV-positive anorectal specimens matched the selection criteria. The *omp*A gene was successfully sequenced for 146 specimens. Most had *omp*A sequences identical to that of *C. trachomatis* L2/434/Bu (41.7%, 61/146) and L2b/UCH-1/proctitis reference strains (36.3%, 53/146). We also identified several genovariants: 27 (18.4%) L2b *omp*A variants (4 already described and 2 new, L2b variant C340G (GenBank MW653320) and L2b variant A997G (GenBank MW653319)), 2 (1.3%) L2 *omp*A variants (L2h and 1 new L2 variant with G868A substitution (GenBank MW653321)) [5, 10] and 6 (4.1%) L2b/D-Da hybrid variants. One specimen belonged to L1 genotype.

Among the 6 patients infected with the new hybrid variant, only one had concurrent sexually transmitted infections (STIs) (active syphilis). From a geographical perspective, there was no evidence of a cluster as specimens came from 4 different French cities. Patients reported having been infected in France, not abroad.

These findings confirm that the L2b/D-Da hybrid variant has been circulating in France since 2017. Indeed, the hybrid variant represents 16.9% of LGV cases in Italy since 2018; 12.5% and 16.5% of LGV cases in Portugal in 2017 and 2018, respectively, with a decrease in 2019 (3.1%); and 26.3% in Canada in 2019 [1–3]. The proportion remains low in Israel in 2018 and 2019 [2]. Although we have described only a few cases, monitoring should continue in France.

## Notes

***Financial support.*** This study was supported by an internal funding.

***Potential conflicts of interest.*** The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Mathilde Carrer,[1] Bertille de Barbeyrac,[2,3,4] Cécile Laurier-Nadalié,[2] Cécile Bébéar,[2,3,4] Arabella Touati,[2,a] and Olivia Peuchant[2,3,4,a]**

[1]Centre Hospitalier Universitaire (CHU) Bordeaux, Infectious and Tropical Diseases Department, Bordeaux, France; [2]CHU Bordeaux, Department of Bacteriology, National Reference Centre for bacterial Sexually Transmitted Infections, Bordeaux, France; [3]Universitaire Bordeaux, USC EA 3671 Mycoplasmal and Chlamydial Infections in Humans, Bordeaux, France; and [4]INRA, USC EA 3671 Mycoplasma and Chlamydial Infections in Humans, Bordeaux, France

## References

1. Borges V, Cordeiro D, Salas AI, et al. *Chlamydia trachomatis*: when the virulence-associated genome backbone imports a prevalence-associated major antigen signature. Microb Genom **2019**; 5:1–11.
2. Borges V, Isidro J, Correia C, et al. Transcontinental dissemination of the L2b/D-Da recombinant *Chlamydia trachomatis* lymphogranuloma venereum (LGV) strain: need of broad multi-country molecular surveillance. Clin Infect Dis **2021**.
3. Marangoni A, Foschi C, Tartari F, Gaspari V, Re MC. Lymphogranuloma venereum genovariants in men having sex with men in Italy. Sex Transm Infect **2020**.
4. de Barbeyrac B, Laurier-Nadalié C, Touati A, et al. Observational study of anorectal *Chlamydia trachomatis* infections in France through the lymphogranuloma venereum surveillance network, 2010–2015. Int J STD AIDS **2018**; 29:1215–24.
5. Peuchant O, Touati A, Sperandio C, et al. Changing pattern of *Chlamydia trachomatis* strains in lymphogranuloma venereum outbreak, France, 2010–2015. Emerg Infect Dis **2016**; 22:1945–7.
6. Touati A, Peuchant O, Hénin N, Bébéar C, de Barbeyrac B. The L2b real-time PCR targeting the pmpH gene of *Chlamydia trachomatis* used for the diagnosis of lymphogranuloma venereum is not specific to L2b strains. Clin Microbiol Infect **2016**; 22:574.e7–.e9.
7. Peuchant O, Touati A, Laurier-Nadalié C, et al. Prevalence of lymphogranuloma venereum among anorectal *Chlamydia trachomatis*-positive MSM using pre-exposure prophylaxis for HIV. Sex Transm Infect **2020**; 96:615–7.
8. Morré SA, Spaargaren J, Fennema JS, de Vries HJ, Coutinho RA, Peña AS. Real-time polymerase chain reaction to diagnose lymphogranuloma venereum. Emerg Infect Dis **2005**; 11:1311–2.
9. Lan J, Ossewaarde JM, Walboomers JM, Meijer CJ, van den Brule AJ. Improved PCR sensitivity for direct genotyping of *Chlamydia trachomatis* serovars by using a nested PCR. J Clin Microbiol **1994**; 32:528–30.
10. Cole MJ, Field N, Pitt R, et al. Substantial underdiagnosis of lymphogranuloma venereum in men who have sex with men in Europe: preliminary findings from a multicentre surveillance pilot. Sex Transm Infect **2020**; 96:137–42.

[a]A. T. and O. P. contributed equally to this work.

Correspondence: O. Peuchant, Department of Bacteriology, French National Reference Centre for Bacterial STIs, CHU de Bordeaux, Place Amélie Raba Léon, 33076 Bordeaux Cedex, France (olivia.peuchant@u-bordeaux.fr).

**Clinical Infectious Diseases® 2021;73(6):1130–1**

DOI: 10.1093/cid/ciab253