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## Long-Distance Spread of a Highly Drug-Resistant Epidemic Cholera Strain

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1 **Long-distance spread of a highly drug-resistant epidemic cholera strain**

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37 **TO THE EDITOR:** In 2018-2019, Zimbabwe experienced a cholera outbreak with over  
38 10,000 suspected cases caused by a highly drug-resistant (HDR) seventh pandemic *Vibrio*  
39 *cholerae* El Tor (7PET) strain.<sup>1</sup> This strain belonged to the AFR13 sublineage, which was  
40 introduced into East Africa from South Asia in 2013-2014.<sup>1</sup> The Zimbabwean strain contained  
41 an IncC plasmid (pYA00120881) carrying 14 antimicrobial drug resistance (AMR) genes and  
42 the outbreak isolates were resistant to tetracycline, ciprofloxacin, and third-generation  
43 cephalosporins in particular.<sup>1</sup> Fortunately, this HDR strain resistant to two of the three  
44 antibiotics recommended for cholera treatment (doxycycline, ciprofloxacin, azithromycin)<sup>1</sup>  
45 did not spread further. In Yemen<sup>2</sup> in 2018 — after two years of intense circulation (> 2  
46 million suspected cholera cases) of an AFR13 7PET strain essentially susceptible to  
47 antibiotics — the outbreak isolates became HDR after acquiring the IncC plasmid  
48 pCNRVC190243 containing a set of AMR genes different from that of pYA00120881. From  
49 2019 onwards, all Yemeni outbreak isolates were resistant to azithromycin (presence of the  
50 plasmid-borne *mph(A)*, *mph(E)*, and *msr(E)* genes), ciprofloxacin (mutations of the  
51 chromosomal *gyrA* and *parC* genes), and third-generation cephalosporins (presence of the  
52 plasmid-borne extended-spectrum beta-lactamase *bla*<sub>PER-7</sub> gene).<sup>2</sup> In 2022, this HDR strain  
53 was identified in cholera cases in southern and eastern Lebanon.<sup>3</sup> Using the cholera  
54 surveillance systems of several European countries and genomic analyses (Supplementary  
55 Appendix) on the bacterial isolates (Tables S1 to S4), we were able to show that this HDR  
56 AFR13 7PET strain has now spread to Eastern Africa (Figure 1). In 2023, this strain was  
57 isolated from three European travelers returning from Kenya at different times of the year. In  
58 March 2024, this HDR strain was isolated in Mayotte — a French island located off the coast  
59 of Southeastern Africa — initially from patients coming from Tanzania or the Comoros  
60 subsequently from patients contaminated locally. A major cholera outbreak, with 12,120  
61 cases, was reported in Kenya<sup>4</sup> between October 2022 and October 2023. In Tanzania<sup>5</sup>, the

62 number of cholera cases has been increasing since the start of 2024, with 3,032 cases as of  
63 May 26 2024, and in the Comoros<sup>5</sup>, after a lull of more than 20 years, a cholera outbreak  
64 began in February 2024, with 7,335 cases as of May 26 2024. This HDR strain has probably  
65 contributed to the increase in cholera notifications in these countries, but the extent of its  
66 involvement remains to be confirmed in the absence of AMR phenotype data. These findings  
67 argue for a strengthening of laboratory capacity for the rapid diagnosis and surveillance of  
68 cholera (including the regular antimicrobial susceptibility testing of 7PET isolates) in East  
69 Africa. We would also argue more specifically for real-time trans-border surveillance of this  
70 emerging HDR AFR13 7PET strain as the potential acquisition of an additional tetracycline  
71 resistance gene by this strain would jeopardize oral antibiotic treatment of the infections it  
72 causes.

73

74 **Figure 1. Maximum-likelihood phylogeny of 1,523 seventh pandemic *Vibrio cholerae* O1**  
75 **El Tor isolates, including 17 recently obtained highly-drug resistant isolates.** Blue arrows  
76 represent the three genomic waves and the black arrow indicates the acquisition of the *ctxB7*  
77 allele. The double slash (//) indicates an artificial shortening of this branch for visualization.  
78 The color coding in the first column shows the geographic origins (GEO) of the isolates, and  
79 African sublineages (AFR1, AFR3–AFR15) are shown on the right. A magnification of the  
80 AFR13 sublineage (red square) is shown on the right with red text indicating the 17 highly  
81 drug-resistant isolates studied. For each genome, its name (or accession number), the country  
82 in which contamination occurred and the year of sample collection are indicated at the tip of  
83 the branch. The acquisitions of the two IncC plasmids are indicated. Scale bars indicate the  
84 number of nucleotide substitutions per variable site. Blue values correspond to bootstrap  
85 values  $\geq 85\%$  for the main nodes.

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87 **References**

- 88 1. Mashe T, Domman D, Tarupiwa A, et al. Highly Resistant Cholera Outbreak Strain in  
89 Zimbabwe. *N Engl J Med* 2020;383(7):687–9.
- 90 2. Lassalle F, Al-Shalali S, Al-Hakimi M, et al. Genomic epidemiology reveals multidrug  
91 resistant plasmid spread between *Vibrio cholerae* lineages in Yemen. *Nat Microbiol*  
92 2023;8(10):1787–98.
- 93 3. Fayad AA, Rafei R, Njamkepo E, et al. An unusual two-strain cholera outbreak in  
94 Lebanon, 2022-2023: a genomic epidemiology study. *Nat Commun* 2024;15(1):6963.
- 95 4. World Health Organization. Multi-country outbreak of cholera, External situation report  
96 #8 - 2 November 2023 [Internet]. 2023. Available from:  
97 [https://www.who.int/publications/m/item/multi-country-outbreak-of-cholera--external-](https://www.who.int/publications/m/item/multi-country-outbreak-of-cholera--external-situation-report--8---2-november-2023)  
98 [situation-report--8---2-november-2023](https://www.who.int/publications/m/item/multi-country-outbreak-of-cholera--external-situation-report--8---2-november-2023) (accessed 11 Jul 2024).
- 99 5. World Health Organization. Multi-country outbreak of cholera, External situation report  
100 #15 - 19 June 2024 [Internet]. 2024 Available from:  
101 [https://www.who.int/publications/m/item/multi-country-outbreak-of-cholera--external-](https://www.who.int/publications/m/item/multi-country-outbreak-of-cholera--external-situation-report--15---19-june-2024)  
102 [situation-report--15---19-june-2024](https://www.who.int/publications/m/item/multi-country-outbreak-of-cholera--external-situation-report--15---19-june-2024) (accessed 11 Jul 2024).

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