CORRESPONDENCE

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

TO THE EDITOR: From September 4, 2018, to March 12, 2019, a cholera outbreak with more than 10,000 suspected cases caused by a highly drug-resistant seventh-pandemic *Vibrio cholerae* O1 El Tor (7PET) strain occurred in Zimbabwe.[1] This strain belonged to the AFR13 sublineage, which was introduced into East Africa from South Asia during 2013–2014.[1] The Zimbabwean strain contained an incompatibility group C (IncC) plasmid (pYA00120881) carrying 14 antimicrobial drug resistance genes, and the outbreak isolates were resistant to tetracycline, ciprofloxacin, and third-generation cephalosporins.[1] Fortunately, this highly drug-resistant strain, which was resistant to two of the three antibiotic agents recommended for cholera treatment (doxycycline, ciprofloxacin, and azithromycin), did not spread further.[1]

In Yemen during 2018, after 2 years of intense circulation of an AFR13 7PET strain (with >2 million suspected cholera cases), the outbreak isolates became highly drug-resistant after acquiring the IncC plasmid pCNRVC190243, which contained a set of antimicrobial drug-resistance genes different from that of pYA00120881.[2] From 2019 onward, isolates from the outbreak in Yemen were resistant to azithromycin (owing to the presence of the plasmid-borne genes *mph(A)*, *mph(E)*, and *msr(E)*), ciprofloxacin (owing to mutations of the chromosomal genes *gyrA* and *parC*), and third-generation cephalosporins (owing to the presence of the plasmid-borne extended-spectrum β-lactamase gene $bla_{\text{PER-7}}$).[2]

In 2022, this highly drug-resistant AFR13 7PET strain was identified in cholera cases in southern and eastern Lebanon.[3] Using data from the cholera surveillance systems of several European countries and genomic analyses of the bacterial isolates (Tables S1 through S4 in the Supplementary Appendix, available with the full text of this letter at NEJM.org), we found that the highly drug-resistant AFR13 7PET strain has now spread to eastern Africa (Fig. 1). In 2023, this strain was isolated from three European travelers returning from Kenya at different times of the year. In March 2024, this strain was isolated in Mayotte, a French island located off the coast of southeastern Africa, initially from patients coming from Tanzania or Comoros and subsequently from patients infected locally.

A major cholera outbreak, with 12,120 cases, occurred in Kenya between October 2022 and October 2023.[4] In Tanzania, the number of cholera cases has been increasing since the start of 2024, with 3032 cases as of May 26, 2024,[5] and in Comoros,[5] after a lull of more than 20 years, a cholera outbreak began in February 2024, with 7335 cases as of May 26, 2024. The highly drug-resistant AFR13 7PET strain has probably contributed to the increase in cholera notifications in these countries, but the extent of its involvement remains to be confirmed in the absence of data on the antimicrobial drug-resistance phenotype.

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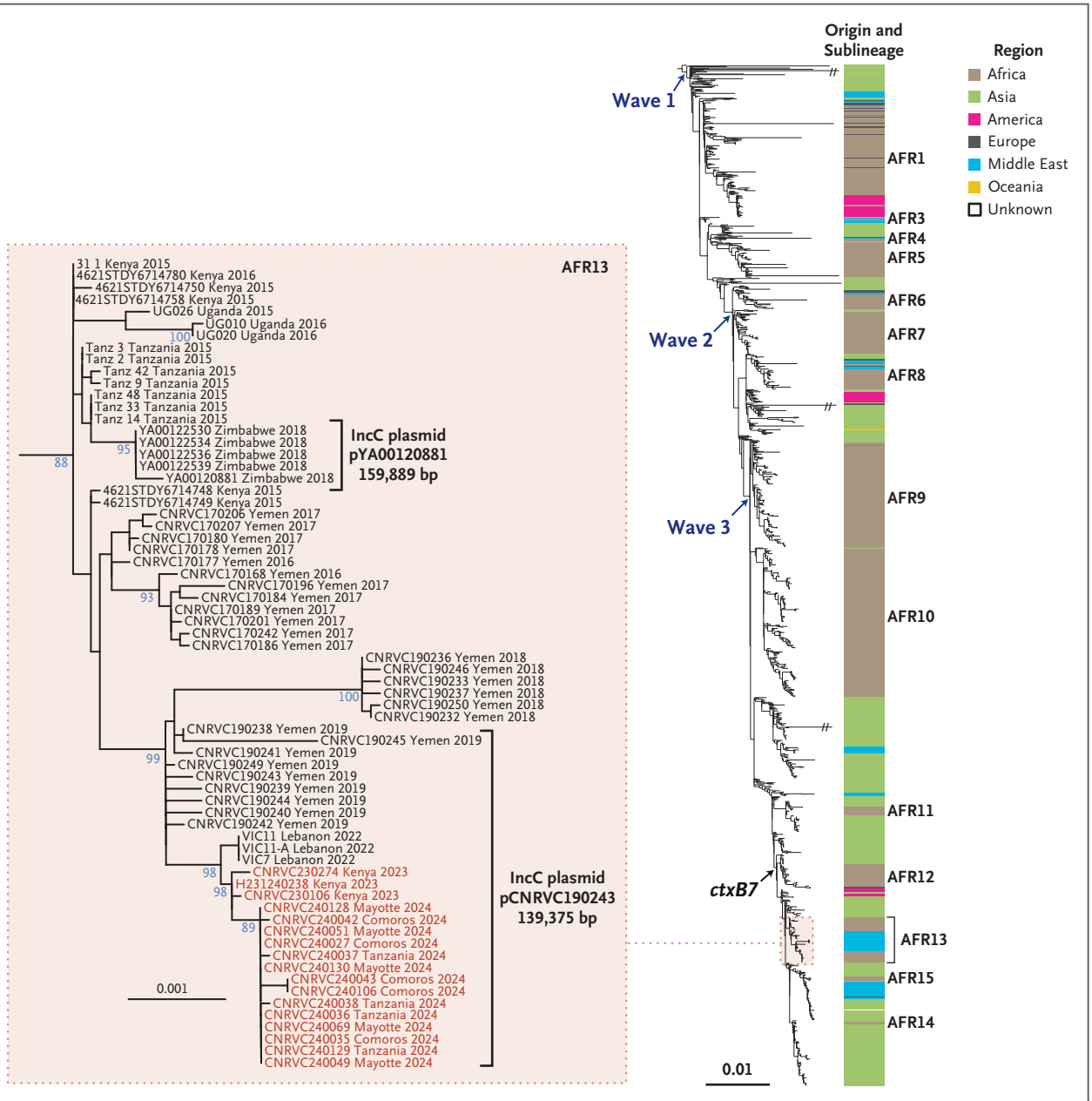

Figure 1. Maximum-Likelihood Phylogeny of Seventh-Pandemic *Vibrio cholerae* O1 El Tor Isolates.

Shown is a maximum-likelihood phylogenetic tree for 1523 *V. cholerae* isolates, including 17 recently obtained highly drug-resistant isolates. Blue arrows indicate the three genomic waves of the seventh pandemic, and the black arrow indicates the acquisition of *ctxB7*, the most recent variant of the gene encoding the B subunit of cholera toxin. Double slashes indicate an artificial shortening of the branch to enhance visualization. The column shows the geographic origins of the isolates and the African sublineages (AFR1 and AFR3 through AFR15). A magnification of the branch for the AFR13 sublineage is shown on the left, with the red text indicating the 17 recently obtained highly drug-resistant isolates. For each genome, the name (or accession number), the country in which infection occurred, and the year of sample collection are indicated at the tip of the branch. The acquisitions of the two incompatibility group C (IncC) plasmids are also indicated. Scale bars indicate the number of nucleotide substitutions per variable site. Blue numbers correspond to bootstrap values of at least 85% for the main nodes.

These findings argue for a strengthening of laboratory capacity for the diagnosis and surveillance of cholera (including antimicrobial susceptibility testing) in East Africa. More specifically, real-time transborder surveillance of this emerging highly drug-resistant AFR13 7PET strain is needed because the potential acquisition of an additional tetracycline-resistance gene by this strain would jeopardize the effectiveness of oral antibiotic treatment as currently recommended.

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1. Mashe T, Domman D, Tarupiwa A, et al. Highly resistant cholera outbreak strain in Zimbabwe. N Engl J Med 2020;383:687-9.
2. Lassalle F, Al-Shalali S, Al-Hakimi M, et al. Genomic epidemiology reveals multidrug resistant plasmid spread between *Vibrio cholerae* lineages in Yemen. Nat Microbiol 2023;8:1787-98.
3. Abou Fayad A, Rafei R, Njamkepo E, et al. An unusual two-strain cholera outbreak in Lebanon, 2022–2023: a genomic epidemiology study. Nat Commun 2024;15:6963.
4. World Health Organization. Multi-country outbreak of cholera: external situation report #8. November 2, 2023 (-https://www.who.int/docs/default-source/coronaviruse/situation-reports/20231102_multi-country_outbreak-of-cholera_sitrep_8.pdf).
5. World Health Organization. Multi-country outbreak of cholera: external situation report #15. June 19, 2024 (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20240619_multi-country_outbreak-of-cholera_sitrep_15.pdf).

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Four Years of Screening for Prostate Cancer with PSA and MRI

TO THE EDITOR: The randomized trial by Hugosson et al. (Sept. 26 issue)[1] evaluated the effect of magnetic resonance imaging (MRI)–targeted biopsy of MRI-positive lesions as compared with the standard approach of MRI-targeted biopsy plus systematic biopsy in patients with a prostate-specific antigen (PSA) level of 3 ng per milliliter or higher with respect to the detection of clinically insignificant prostate cancer (primary outcome) and clinically significant prostate cancer (secondary outcome). The authors found that detection of clinically insignificant and significant prostate cancers was reduced with MRI-targeted biopsy as compared with the standard approach, with a significant reduction in the former case (relative risk, 0.43; 95% confidence interval [CI], 0.32 to 0.57; P<0.001) but not the latter (relative risk, 0.84; 95% CI, 0.66 to 1.07).

A point for consideration is that among patients undergoing MRI-targeted biopsy of MRI-positive lesions plus systematic biopsy, we found a significant association between the presence of Gleason grade group 1 (GGG1) prostate cancer in more than 50% of systematic biopsies and an increased risk of PSA failure (biochemical recurrence) within 18 months after radical prostatectomy (adjusted hazard ratio, 2.88; 95% CI, 1.04 to 7.97),[2] which supports the presence of clinically significant prostate cancer.[3,4] It would be interesting to know the results for the detection of clinically significant and insignificant prostate cancers in the two trial groups when GGG1 prostate cancer