tuberculosis meningitis (TBM), including drug-resistant disease, and we wholeheartedly encourage others to continue explore their use further through clinical practice and research endeavors.

The point about the "stickiness" of bedaquiline is valid and important to consider. For additional detail on our CSF collection procedure, we used a prepared lumbar puncture kit; CSF was collected through a 3.5-inch spinal needle and a 3-way stopcock directly into polypropylene specimen vials, pipetted into polypropylene cryovials, and frozen at −80°C until shipment and analysis. While the lack of plastic tubing decreased potential drug loss, it is possible that some of the bedaquiline adsorbed to the polypropylene vials, as has been described previously in a pilot experiment [3]. We applaud the work by Upton and colleagues [4] to test and fine tune collection strategies to more accurately measure CSF bedaquiline concentrations. This provides an invaluable technique for future bedaquiline CSF pharmacokinetic research and will allow for better comparison of results between studies and patients.

Our limit of detection for bedaquiline, delamanid, and clofazamine was validated only to 0.01 μg/mL and not lower, owing to lack of funding for full low-end validation of these drugs in artificial CSF. In our Supplementary Tables 1–5 [2], we categorized CSF drug concentration results as either below the limit of detection or 0, with these below-limit samples having an amount detected below 0.01 μg/mL. More than 50% of the CSF samples we collected had a detectable amount for bedaquiline, clofazimine, and delamanid; however, we chose not to report these values, given lack of validation and potential for inaccuracy. Following the lead of Upton and colleagues, we agree that a lower limit of detection should be validated and used for CSF detection of these drugs to better illuminate the diffusion of free drug into CSF.

We hope that our research stimulates further and innovative research into the clinical pharmacology of TBM. The high mortality rate for drug-resistant TBM shown by our group and others necessitates more investigation aimed at improving treatment options [5, 6]. In a search of clinicaltrials.gov, we found no currently registered TBM trials using bedaquiline, delamanid, or pretomanid. This is stark contrast to the abundance of clinical trial activity in drug-resistant pulmonary tuberculosis [7]. However, innovative translational research in TBM is being done, including work evaluating dynamic positron emission tomography to study drug distribution into brain parenchyma [8, 9].

This work has provided a novel way to evaluate brain concentrations, and results to date have shown promising results for pretomanid and that bedaquiline accumulates at higher concentrations in the brain versus CSF, highlighting that CSF analysis may offer an incomplete picture. We encourage others to use our results as launching pad to further study the clinical pharmacology of TBM.

Notes

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Applying Desirability of Outcome Ranking End Points

To the Editor—We conducted a phase 3 trial in patients with uncomplicated urinary tract infection (UTI), comparing oral sulopenem etzadroxil + probenecid with oral ciprofloxacin [1], and we used the Food and Drug Administration's definition of overall success in studies of UTI, one that requires both clinical cure and microbiologic eradication. In the population of patients with uropathogens that were nonsusceptible to ciprofloxacin, sulopenem was superior to ciprofloxacin (62.6% vs 36.0%; difference, 26.6% [95% confidence interval (CI), 15.1%–37.4%]; $P < .001$). In the patients with ciprofloxacin-susceptible isolates, sulopenem was not noninferior to ciprofloxacin (66.8% vs 78.6%; difference, −11.8% [95% CI, −18.0 to −5.6). This difference could be attributed to a higher rate of asymptomatic bacteriuria after treatment in patients on sulopenem. In the analysis of all patients, sulopenem was noninferior to ciprofloxacin (65.6%

Table 1. Desirability of Outcome Rankings by Treatment Arm

	Patients by Outcome Ranking, No. (%)[a]					
Treatment Arm	1	2	3	4	5	6
Sulopenem (n = 785)	643 (81.9)	139 (17.7)	1 (0.1)	1 (0.1)	0 (0)	1 (0.1)
Ciprofloxacin (n = 794)	608 (76.6)	179 (22.5)	7 (0.9)	0 (0)	0 (0)	0 (0)

[a]One is the most desirable and 6 the least desirable ranking.

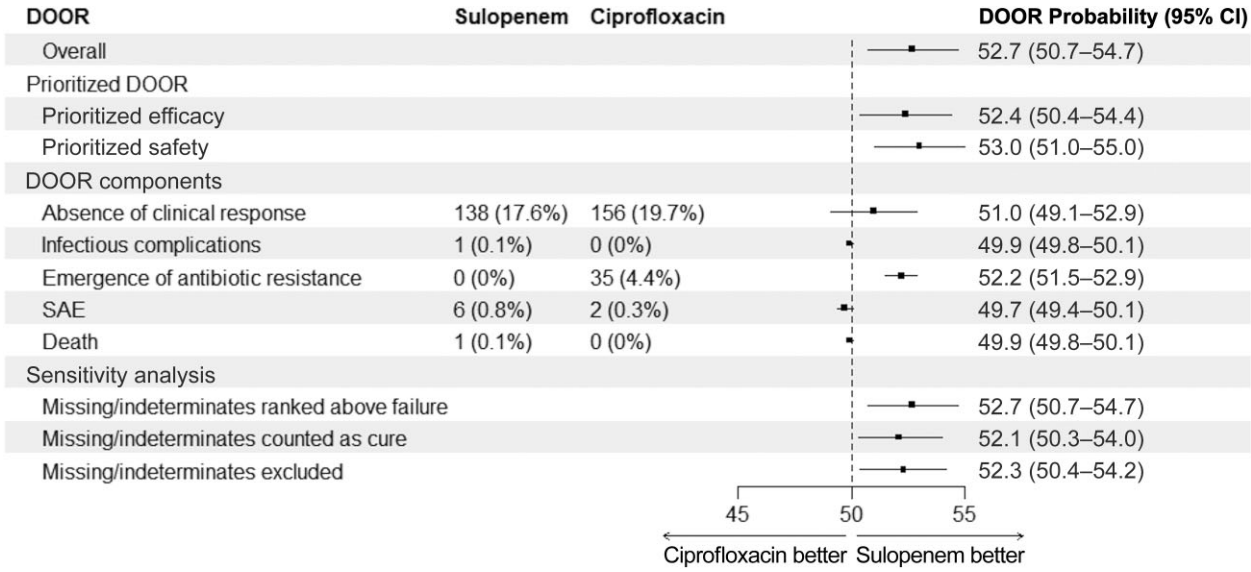

Figure 1. Forest plot demonstrating the desirability of outcome ranking (DOOR) probabilities for the DOOR overall, the DOOR prioritized for efficacy and safety, and the DOOR components. Abbreviations: CI, confidence interval; SAE, serious adverse event.

vs 67.9%; difference, −2.3% [95% CI, −7.9 to 3.3]).

The recent article by Howard-Anderson et al [2], describing the application of a desirability of outcome ranking (DOOR) end point to 3 trials in complicated UTI, was of considerable interest to us. After conducting DOOR analysis on our complicated UTI study [3], we have now performed a desirability of outcome ranking on our uncomplicated UTI study. We added emergence of antibiotic resistance to the DOOR components, generating a total of 6 ranks (Table 1).

The DOOR probability that a patient in the sulopenem arm would have a more desirable outcome than a patient in the ciprofloxacin arm is 52.7% (95% CI, 50.7%–54.7%) (Figure 1), indicating that sulopenem etzadroxil + probenecid was comparably more effective than ciprofloxacin in patients with uncomplicated UTI [4]. The probabilities for the analyses prioritizing efficacy and safety were nearly identical to the original outcome ranking, and those for the individual components of absence of clinical response, infectious complications, serious adverse events, and death were very similar. The component we added, emergence of antibiotic resistance, favored sulopenem etzadroxil + probenecid.

We agree with the opinion, expressed by many at the Food and Drug Administration's June 2022 public workshop on UTI [5], that clinical trial end points should be revised to emphasize symptomatic improvement rather than microbiological eradication. For many physicians, it is standard practice to forgo follow-up urine cultures for patients whose UTI symptoms have completely resolved on antibiotics. The identification of organisms in follow-up cultures, in the form of asymptomatic bacteriuria, may result in inappropriate antibiotic use and the emergence of resistance among posttreatment flora [6].

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Invasive Listeriosis in Southern Switzerland: A Local Problem That Is Actually Global

To the Editor—Recently, Conrad et al [1] reported 10 cases of *Listeria monocytogenes* invasive disease with 3 deaths in a 6-year time frame (2010–2015). Whole-genome sequencing (WGS) demonstrated a link to a widely distributed brand of ice cream, which enabled the source to be narrowed to 2 production facilities, indicating long-standing contamination.

We describe here an outbreak of 6 cases of invasive *L. monocytogenes* infections in Ticino region (a canton of approximately 350 000 inhabitants in the south of Switzerland, close to the Italian border) from July to September 2022. Table 1 provides the demographic and clinical characteristics of the patients; note that 4 patients had *L. monocytogenes* serotype 4b, and 2 had serotype 1/2b. Some weeks before this outbreak, a similar event occurred in Italy [2]; 2 patients, both infected with serotype 4b, had bought fresh cheese in Italy from the same grocery store. However, WGS of the isolates was not performed, so we could not establish whether the strains were related or identify a common source. As for the remaining patients, they denied assumption of cheese or pork derivate in the weeks before hospitalization, and cohabitants did not refer symptoms correlated with *L. monocytogenes* infection.

Invasive listeriosis is associated with a high mortality rate and usually affects immune-compromised individuals. In the present series, antibiotic treatment with amoxicillin and gentamicin was effective, and no deaths were observed 6 months after discharge. We speculate that the isolation of 2 different serotypes in such a short time frame might be due to 2 concomitant outbreaks; nevertheless, we could not identify any confirmed source, nor any correlation among the patients' habits or environment. Although not demonstrated with WGS or other genotypic analysis, it remains plausible that the cases due to serotype 4b have a common source. It would be of interest to compare WGS results from isolates in Ticino with other isolates from recent cases in surrounding areas of Switzerland and Italy. In contrast to the findings by Conrad et al [1], who found serotypes 1/2a, 1/2b, and 3b to be predominant, serotype 4b is commonly associated with outbreaks of invasive disease in Switzerland. As reported with WGS, clinical isolates were traced to environmental contamination of a cheese dairy with *L. monocytogenes* serotype 4b, sequence type 6 [3].

Sporadic outbreaks of *L. monocytogenes* are periodically reported in different countries [4–6], despite control measures and warnings. To identify the source of infection early, we suggest that more effective tracking of the products, thorough analysis of each patient's environment, and a microbiological assessment of the likely involved food should be scheduled as soon as a single case is reported. Given that the Ticino region is so close to the Italian border, it is difficult to draw the supply map, but epidemiological studies should be carried out as most accurately as possible, together with WGS typing of the isolates to enable early recognition of the source. Dealing with outbreaks of *L. monocytogenes* should be a joint effort between public health authorities, local microbiological laboratories, and hospitals.

Note

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