addition to this so-called trojan horse approach, cefiderocol is stable to all classes of carbapenem-hydrolysing enzymes. Therefore, cefiderocol might be suitable for treatment against all Gram-negative species regardless of their mechanism of resistance, including metallo-carbapenemases, porin-channel mutations, and efflux pump overproduction.

In *The Lancet Infectious Diseases*, Simon Portsmouth and colleagues reported the results of a well done multicentre, double-blind, non-inferiority trial that showed superiority of cefiderocol versus imipenem-cilastatin for the composite (microbiological and clinical) primary outcome at test of cure in the treatment of 448 hospitalised adults with complicated urinary tract infections (183 [73%] of 252 patients in the cefiderocol group *vs* 65 [55%] of 119 in the imipenem-cilastatin group). This finding is surprising, because both antibiotics are β-lactams and patients with known carbapenem-resistant infection at screening were excluded. These results were mainly driven by differences in microbiological eradication rates. The differences in outcome at test of cure were shown for all three clinical entities: patients with complicated urinary tract infections without pyelonephritis (85 [70%] of 122 patients in the cefiderocol group *vs* 28 [51%] of 55 in the imipenem-cilastatin group), with uncomplicated pyelonephritis (54 [83%] of 65 patients in the cefiderocol group *vs* 24 [69%] of 35 in the imipenem-cilastatin group), and with complicated pyelonephritis (44 [68%] of 65 patients in the cefiderocol group *vs* 13 [45%] of 29 in the imipenem-cilastatin group); of these, the difference observed in patients with uncomplicated pyelonephritis alone was not significant. These results raise the issue of whether imipenem-cilastatin itself or the dose of imipenem-cilastatin used in this study—although officially recommended—was comparably sufficient for treatment of complicated urinary tract infections with or without pyelonephritis.

About 70% of imipenem, when combined with cilastatin, is excreted in the urine of healthy patients, with a plasma half-life of about 1 h.[4] In a study[5] in healthy volunteers, the administration of cefiderocol with a single dose range between 100 mg and 2000 mg resulted in a mean plasma half-life between 1·98 h and 2·74 h and a geometric mean of urinary excretion between 61·5% and 68·4% as unchanged drug. Although not measured in the study, we can assumed that the urinary concentrations of cefiderocol (dose 2 g three times per day) were substantially higher than those of imipenem (dose 1 g three times per day). Although, to our knowledge, nothing has been published about specific urinary pharmacodynamics of cefiderocol, or those of imipenem-cilastatin, such results would be interesting and could probably explain better the surprising outcome of this clinical study.

Because patients with known carbapenem-resistant infection at screening were excluded, as previously mentioned, the efficacy of cefiderocol, especially in the treatment of complicated urinary tract infections with carbapenem-resistant pathogens, needs still to be established.

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We were pleased to read the generally positive Comment[1] regarding our Article,[2] published in *The Lancet Infectious Diseases*. However, we would like to respond to some of the points raised.

We agree with Angela Huttner that our study did not answer the important question of how this novel antibiotic will address the need for treatment of carbapenem-resistant bacteria. However, we disagree with the statement that "it will fall to us to continue the drug's clinical development". As mentioned in the study summary, the sponsor is currently conducting a randomised, open label study[3] of cefiderocol versus best available therapy in patients with documented carbapenem-resistant infections (NCT02714595), including bacteraemia or sepsis, pneumonia (hospital-acquired, ventilator-associated, and health-care-associated pneumonia), and complicated urinary tract infections. A double blind, randomised controlled study[4] in carbapenem-sensitive infections with hospital-acquired

bacterial pneumonia, ventilator-associated pneumonia, and health-care-associated pneumonia is also underway.

Huttner also states that "unfortunately, neither baseline resistance nor emergence of resistance to cefiderocol was reported". However, baseline resistance to cefiderocol was provided in the appendix. Additionally, we assessed resistance throughout the study and observed no development of resistance to cefiderocol among cases where microbiological failure was present.

Although this study was termed a phase 2 study (first use in human infection), it was also a pivotal study with robust inferential testing, as required for US regulatory review. Our study was adequately powered for non-inferiority, and the finding of superiority over high-dose imipenem clearly shows efficacy in this population of patients with complicated urinary tract infections, many of which were multidrug resistant.

Huttner also mentioned the new US Food and Drug Administration complicated urinary tract infections guidelines,[5] stating that "any trial launched more than 4 months ago (including an ongoing phase 3 cefiderocol trial, NCT02714595)[3] will now be adhering to outdated standards and requirements." However, the new guidelines are not relevant to our ongoing phase 3 trial, because the trial involves carbapenem-resistant infections and is not limited to complicated urinary tract infections. Additionally, applying the endpoints of the new guidelines to our pivotal complicated urinary tract infections study would not have altered the conclusion of superior efficacy observed. Finally, although the catechol moiety of cefiderocol leading to siderophore activity was mentioned, one of the key and additionally unique features of this cephalosporin is its structural stability against all known classes of carbapenemases. It is this combination of unique cell entry and β-lactamase stability that makes cefiderocol so promising.

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Author's reply

The enormous efforts of investigators and trial participants in the pre-market development of cefiderocol should be neither disregarded nor underestimated: thanks to their work,[1] this drug might soon be accessible to patients who might benefit from it. Nonetheless, a drug tested on only a few hundred people and for a few narrow indications will always require additional, postmarket development. As I have stated,[2] because we, the public, have demanded an accelerated path to approval, novel antibiotics are now entering the market on the basis of very thin clinical experience. This is not specific to cefiderocol; the new aminoglycoside plazomicin won FDA approval in 2018, on the strength of a single phase 3 trial with a 15% non-inferiority margin that allowed for a small sample size.[3] If allocation is even in the two ongoing cefiderocol trials mentioned by Simon Portsmouth and colleagues, they will together include a total of 225 patients receiving cefiderocol.

Although baseline resistance to other antibiotics was reported in detail in the study by Portsmouth and colleagues,[1] it was not reported for cefiderocol. For cefiderocol, only a range of minimal inhibitory concentrations (MICs) was provided in the appendix, with no report of the total number of isolates tested, as was carefully done for other antibiotics. Was the reported MIC range representative of all isolates, or only of a selected subset? Why was no denominator provided for cefiderocol, when it was provided for all other antibiotics tested? Because of these gaps in reporting, no conclusions can be drawn. Regarding the development of resistance after therapy, it is reassuring to read Portsmouth and colleagues' statement that none was observed, but the question was not addressed in the Article, where no data pertaining to cefiderocol resistance development are reported.

The merits of the US Food and Drug Administration endpoints in place at the time that the study launched were long subject to debate. The efficacy of cefiderocol, as defined by these endpoints, was certainly demonstrated; yet the value of temporarily reducing a bacterium's count from 10^5 CFU/mL to 10^4 CFU/mL in a follow-up urine culture, when repeat cultures have no place in the clinic, remains questionable. Again, this is a broader regulatory issue that is not specific to cefiderocol, the developers of which are working within the framework they've been given. And there is no simple solution to the problem of defining efficacy in complicated urinary tract infection studies. Outcomes that are meaningful to patients are notoriously