6 Genchi C, Kramer LH, Sassera, Bandi C. *Wolbachia* and its implications for the immunopathology of filariasis. *Endocr Metab Immune Disord Drug Targets* 2012; **12:** 53–56.
7 Li G, Bauer S, Nowak M, et al. Cytokines and epilepsy. *Seizure* 2011; **20:** 249–56.
8 Pietri JE, DeBruhl H, Sullivan W. The rich somatic life of *Wolbachia*. *Microbiol Open* 2016; **5:** 923–36.
9 Mmbando BP, Suykerbuyk, Mnacho M, et al. High prevalence of epilepsy in two rural onchocerciasis endemic villages in the Mahenge area, Tanzania, after 20 years of community directed treatment with ivermectin. *Infect Dis Poverty* 2018; **7:** 64.

Authors' reply

We thank M Teresa Galán-Puchades for her interesting comments. In our study,[1] we considered the worms as a whole to be the relevant entity, because the cutaneous and ocular manifestations of onchocerciasis result from a combination of immune reactions against *Wolbachia* spp (mobilisation of neutrophils), and filarial antigens (mobilisation of eosinophils).[2] Consequently, it seemed artificial to consider the partners of this symbiotic relationship separately.

Galán-Puchades hypothesises that *Wolbachia* spp released during the natural death of *O volvulus* (adults or microfilariae) induce inflammatory processes that trigger epilepsy, which would indeed justify distinguishing wolbachia from the worm in our study. Should this hypothesis be true, the release of *Wolbachia* spp into the blood after treatment with diethylcarbamazine or ivermectin (a demonstrated occurrence)[3] would, as Galán-Puchades suggests, induce an epidemic of seizures after mass treatment with these drugs. However, such an event has never been reported with either drug, even in populations with extremely high microfilarial densities (eg, the Vina valley in northern Cameroon). On the contrary, a decrease in seizure frequency was reported after the first ivermectin distribution in the Kabarole focus, Uganda.[4] Furthermore, the nodding syndrome epidemic in northern Uganda, which Galán-Puchades refers to, started in 2000, whereas war in that region delayed mass ivermectin treatment until 2009. Some factors have been proposed[5] to explain the epidemic pattern of nodding syndrome in Uganda and South Sudan, but these hypotheses are difficult to test.

Galán-Puchades suggests that the inter-foci variability in prevalence and severity of onchocercal ocular manifestations is due to some parasite populations harbouring higher wolbachia burdens. A study[6] published in 2017, in different foci in four west-African countries, showed indeed that this burden can vary considerably between and within foci; however, this variability does not correlate with the ecotype of the focus, even though savanna onchocerciasis causes more blindness than forest onchocerciasis. These results certainly deserve to be complemented by analysis of parasites from areas where a strong association between onchocerciasis and epilepsy has been shown.

As mentioned by Galán-Puchades, a study is ongoing to determine whether doxycyline treatment leads to reduction in symptoms and perhaps reversal of the course of nodding syndrome in affected children. However, doxycycline mass treatment to prevent onchocerciasis-associated epilepsy or nodding syndrome, as Galán-Puchades recommends, does not appear feasible because this requires compliance with daily dosing for 5 weeks to achieve macrofilaricidal effects. Importantly, doxycycline is contra-indicated in children younger than 8 years, and the physio-pathogenic mechanisms that put children with high *O volvulus* microfilaridermia at higher risk of developing epilepsy probably appear before this age.

We declare no competing interests.

**Cédric B Chesnais, Michel Boussinesq*
cedric.chesnais@ird.fr

Institut de Recherche pour le Développement, 34394 Montpellier, France

1 Chesnais CB, Nana-Djeunga HC, Njamnshi AK, et al. The temporal relationship between onchocerciasis and epilepsy: a population-based cohort study. *Lancet Infect Dis* 2018; **18:** 1278–86.
2 Pearlman E. Immunopathogenesis of *Onchocerca volvulus* keratitis (river blindness): a novel role for endosymbiotic *Wolbachia* bacteria. *Med Microbiol Immunol* 2003; **192:** 57–60.
3 Keiser PB, Reynolds SM, Awadzi K, Ottesen EA, Taylor MJ, Nutman TB. Bacterial endosymbionts of *Onchocerca volvulus* in the pathogenesis of posttreatment reactions. *J Infect Dis* 2002; **185:** 805–11.
4 Kipp W, Burnham G, Kamugisha J. Improvement in seizures after ivermectin. *Lancet* 1992; **340:** 789–90.
5 Colebunders R, Nelson Siewe FJ, Hotterbeekx A. Onchocerciasis-associated epilepsy, an additional reason for strengthening onchocerciasis elimination programs. *Trends Parasitol* 2018; **34:** 208–16.
6 Armoo S, Doyle SR, Osei-Atweneboana MY, Grant WN. Significant heterogeneity in *Wolbachia* copy number within and between populations of *Onchocerca volvulus*. *Parasit Vectors* 2017; **10:** 188.

Cefiderocol for treatment of complicated urinary tract infections

Co-trimoxazole, fluoroquinolones, and cephalosporins have been used to treat almost all kinds of complicated urinary tract infections, but this golden age has come to an end. Worldwide, an increase in resistant uropathogens, including those resistant to carbapenems, has been observed.[1,2]

Several new drugs or drug combinations are in development or have been made available, such as new or old cephalosporins or carbapenems combined with new or old β-lactamase inhibitors (ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam), new aminoglycosides (plazomicin), and new fluoroquinolones (finafloxacin).

Another new drug is cefiderocol, the first siderophore-antibiotic conjugate to reach late stage clinical testing, which was developed for treatment of complicated urinary tract infections.[3] Siderophore antibiotics bind to free iron and use the bacterial active iron transport channels to cross the outer membrane of Gram-negative bacteria and reach the periplasmic space. In

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.

FMEW reports personal fees and other support from Shionogi during the conduct of the study; grants from Deutsche Forschungsgemeinsschaft and Deutsches Zentrum für Infektionsforschung; personal fees from Achaogen, Astellas, Bionorica, MSD, Leo-Pharma, Medpace, Merlion, Vifor, Rempex, Rosen Pharma, AstraZeneca, and Janssen; and other support from Enteris BioPharma, Helperby, and Shionogi, outside the submitted work. KGN reports personal fees from Bionorica, DaiichiSankyo, Enteris Biopharma, Helperby, Leo-Pharma, MerLion, MSD, OM Pharma, Paratek, Roche, Rosen Pharma, Zambon, Adamed, Apogepha, Aristo, GlaxoSmithKline, Gruenenthal de Mexico, Hermes, Medice, and Saxonia; and non-financial support from Mission Pharmacal, outside the submitted work.

*Florian M E Wagenlehner, Kurt G Naber
florian.wagenlehner@chiru.med.uni-giessen.de

Clinic for Urology, Pediatric Urology and Andrology, Justus-Liebig University of Giessen, 35390 Giessen, Germany (FMEW); and Technical University of Munich, Munich, Germany (KGN)

1 Zowawi HM, Harris PN, Roberts MJ, et al. The emerging threat of multidrug-resistant gram-negative bacteria in urology. *Nat Rev Urol* 2015; **12:** 570–84.
2 Tandogdu Z, Cek M, Wagenlehner F, et al. Resistance patterns of nosocomial urinary tract infections in urology departments: 8-year results of the global prevalence of infections in urology study. *World J Urol* 2014; **32:** 791–801.
3 Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. *Lancet Infect* Dis 2018; **18:** 1319–28.
4 Rogers JD, Meisinger MA, Ferber F, Calandra GB, Demetriades JL, Bland JA. Pharmacokinetics of imipenem and cilastatin in volunteers. *Rev Infect Dis* 1985; **7** (suppl 3)**:** S435–46.
5 Shimada J, Saisho Y, Katsube T, White S, Fukase H. S-649266, a novel siderophore cephalosporin for gram negative bacterial infections: pharmacokinetics, safety and tolerability in healthy subjects. 54th Interscience Conference on Antimicrobial Agents and Chemotherapy; Washington, DC, USA; Sept 5–9, 2014. F-1564.

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