was not different among centres. In fact, we stated that differences in clinical performance could not be discounted according to the Breslow test. To control for the site effect as a potential confounder (which includes differences in management and also potentially virulence of the isolates), we classified the hospitals into those with high and low mortality using TreeNet and used this variable only to control its effect on the association of treatment and mortality. The division of the cohort into two timeperiods responds to the same argument, because changes in management or virulence determinants of the isolates might have occurred during the study period.

Respectfully, we disagree with Salzberger and Fätkenheuer's recommendation regarding monotherapy or combination therapy according only to clinical experts' decision; this is not evidence-based and is not generalisable by nature. Of course, expert opinions can be relevant in specific situations. We agree that the results of our study need to be replicated; however, these results provide the best available evidence to date regarding the decision between monotherapy or combination therapy for bloodstream infections caused by carbapenemase-producing Enterobacteriaceae.

In another letter about our article, Sara E Boyd and colleagues[2] raised an important issue: combination therapy to avoid the development of resistance. As they state, "combination therapy has also been shown to be efficacious for suppressing emergence of resistance in highly predictive pharmacodynamics models of infection". Unfortunately, such an effect has never been consistently shown in patients with infections due to Enterobacteriaceae.[3] Until suppression of resistance is shown in clinical studies, we would recommend avoiding combination therapy whenever not associated with improved relevant clinical outcomes.

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1 Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. *Lancet Infect Dis* 2017; **17:** 726–34.

2 Boyd SE, Moore LSP, Rawson TM, Hope WW, Holmes AH. Combination therapy for carbapenemase-producing Enterobacteriaceae: INCREMENT-al effect on resistance remains unclear. *Lancet Infect Dis* 2017; **17:** 899–900.

3 Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev* 2014; **1:** CD003344.

High mortality in non-Ebola virus disease cases: need to provide timely and effective care

In their Article in *The Lancet Infectious Diseases*, Matthew Waxman and colleagues[1] report an overall high (8·1%) mortality in patients without Ebola virus disease (EVD) admitted to three Ebola treatment units (ETU) in Sierra Leone; we report a similarly high (6·4%) mortality in non-EVD cases from a Guinean ETU.[2] We agree with the authors that many non-EVD patients succumb to other severe illnesses, probably infectious diseases within a broad differential diagnosis given the high frequency of fever in the context of a negative malaria test.

Several bottlenecks exist, however, in limiting the high mortality associated with non-EVD patients within ETUs. First, the long turnaround time (about 5 h) for receiving negative Ebola results from conventional real-time RT-PCR prolongs the time that a non-EVD patient remains in the ETU. Fortunately, novel point-of-care and automated sample-to-result molecular diagnostic platforms show promise for high sensitivity and faster turnaround time (20 min to 2 h).[3] Second, limited data exist for how to clinically manage non-EVD patients. Novel multiplex molecular diagnostic platforms have been used in some ETUs to help inform diagnosis of undifferentiated febrile gastroenteritis.[4] These tools can guide ETU clinicians to initiate effective empirical or pathogen-specific treatment in non-EVD patients early. Finally, a high risk exists for deterioration of vulnerable health systems during an Ebola outbreak resulting in closure of non-Ebola health facilities to which non-EVD patients need transferring.[5] As part of outbreak preparedness, measures are required to ensure non-Ebola referral hospitals maintain capability to appropriately manage severely ill

patients, including non-EVD patients requiring transfer from an ETU.

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1 Waxman M, Aluisio AR, Rege S, Levine AC. Characteristics and survival of patients with Ebola virus infection, malaria, or both in Sierra Leone: a retrospective cohort study. *Lancet Infect Dis* 2017; **17:** 654–60.

2 Ingelbeen B, Bah EI, Decroo T, et al. Mortality among PCR negative admitted Ebola suspects during the 2014/15 outbreak in Conakry, Guinea: a retrospective cohort study. *PLoS One* 2017; **12:** e0180070.

3 Brown CS, Mepham S, Shorten RJ. Ebola virus disease: an update on epidemiology, symptoms, laboratory findings, diagnostic issues, and infection prevention and control issues for laboratory professionals. *Clin Lab Med* 2017; **37:** 269–84.

4 O'Shea M, Clay KA, Craig DG, et al. Diagnosis of febrile illnesses other than Ebola virus disease at an Ebola treatment unit in Sierra Leone. *Clin Inf Dis* 2015; **61:** 795–98.

5 Elston JWT, Cartwright C, Ndumbi P, Wright J. The health impact of the 2014–15 Ebola outbreak. *Public Health* 2017; **143:** 60–70.

Spread of a single multidrug resistant malaria parasite lineage (*PfPailin*) to Vietnam

The spread of artemisinin resistance in *Plasmodium falciparum* and the subsequent loss of partner antimalarial drugs in the Greater Mekong subregion[1] presents one of the greatest threats to the control and elimination of malaria. Artemisinin resistance is associated with mutations in the *PfKelch* gene. Initially multiple independent *Kelch* mutations were observed,[1] but in a recent sinister development, a single dominant artemisinin-resistant *P falciparum* C580Y mutant lineage has arisen in western Cambodia, outcompeted the other resistant malaria parasites, and subsequently acquired resistance to piperaquine.[2] Cambodia had adopted dihydroartemisinin-piperaquine as first-line antimalarial treatment, but has now been forced to switch its first line artemisinin combination treatment back to artesunate-mefloquine as a consequence[3]. This dominant multidrug-resistant parasite lineage, identified first in Pailin in western Cambodia and tentatively denoted as *PfPailin*, then spread to northeastern Thailand and southern Laos[2]. We now find that the *PfPailin* lineage, with associated piperaquine resistance (evidenced by amplification in the *PfPlasmepsin2* gene), has spread to the south of Vietnam where it is responsible for alarming rates of failure of dihydroartemisinin-piperaquine—the National first-line treatment (figure).[4] Microsatellite typing of 86 of 152 *P falciparum* isolates from the Binh Phuoc locality in 2016 shows the same flanking sequence surrounding the *PfKelch* C580Y gene as that observed in parasites from the affected areas of the other three Greater Mekong subregion countries.[2] The evolution and subsequent transnational spread of this single fit multidrug-resistant malaria parasite lineage is of international concern.

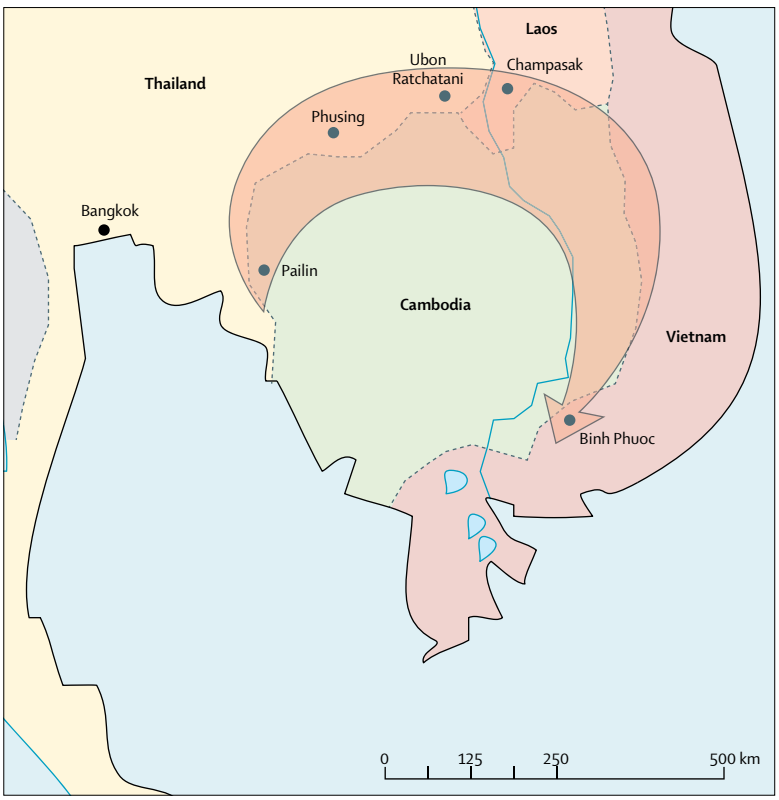

Figure*: Transnational spread of multidrug resistant *PfPailin
The artemisinin resistant *Plasmodium falciparum* C580Y lineage (*PfPailin*) was detected first in Pailin, Western Cambodia, in 2008.[2] It later acquired piperaquine resistance and spread east. 8 years later it has now reached the south of Vietnam encompassing all four countries of the Eastern Greater Mekong subregion.

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