Title: Imported extensively-drug resistant typhoid fever in a child travelling to Spain from Pakistan

Running Title: Imported XDR typhoid fever

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Since 2016 an outbreak of extensively drug-resistant (XDR) typhoid has emerged from Sindh province in Pakistan.¹ Imported cases have been identified in the US, Canada, UK and Denmark.^{2,3} We report the first case in Spain.

An 11 year-old boy was seen in December 2018 at Hospital del Mar in Barcelona, Spain, due to fever for 4 days and right iliac fossa pain. He lived in Pallandri (Azad Kashmir, Pakistan), until 3 weeks ago when he arrived to Spain. He had non-complicated typhoid fever 4 years ago. Laboratory evaluation revealed 4870 white

blood cells, aneosinophilia, C-reactive protein (CRP) 3 mg/dL. Abdominal ultrasound showed mesenteric adenitis. Cefotaxime was started due to suspicion of enteric fever. One day later, blood culture grew XDR *Salmonella enterica* serovar Typhi, sensitive to azithromycin and carbapenem (Table 1).

Antibiotic regime was changed to meropenem. Six days later he was still febrile, with a coated tongue, CRP 7,6 mg/dL, ALT 69 UI/L, AST 118 UI/L.

The dose of meropenem was increased (120 mg/kg/day) and azithromycin (20 mg/kg/day) was added. Fever subsided on day 7 of combined treatment. Stool culture on admission and 2 months following treatment was negative. The patient has remained well, with no complications or relapse.

Until July 2019, 9822 XDR typhoid cases have been confirmed in the Sindh province, mainly in Karachi.¹ The patient we report lived in an area that is 1500 km from Karachi, he had not travelled anywhere else other than Islamabad before coming to Spain. This case suggests that a traveller from any region of Pakistan can potentially carry this strain.

The Sindh strain is sensitive to azithromycin and carbapenem. Azithromycin is the antibiotic of choice for non-complicated cases. Meropenem is reserved for severe disease.² Some authors suggest that meropenem should be combined with an antibiotic that provides an intracellular mode of action e.g. azithromycin, since there can be antibiotic tolerance and persistence.⁴ There is limited evidence from randomized trials to use combination therapy. It is sometimes used when response to treatment is slow, as it may have synergistic effects.⁵ We used initially meropenem because the patient had been vomiting. Later on, we added azithromycin and increased the dose of meropenem due to persistent fever. We were also worried about antibiotic tolerance after having

used an inappropriate low dose of meropenem (30 mg/kg/day instead of 30 mg/kg/dose every 8 hours).

More than 80% of XDR cases in the Sindh area are children under 15 years and 18% are under 2 years. A new prequalified typhoid conjugated vaccine, that is suitable for children from 6 months of age, is now being used to control the outbreak.¹ This vaccine should be recommended to all travellers, although it is not yet available in many countries. Adhering to hygienic practices may not be enough to prevent typhoid. Even drinking bottled water can be a risk in Pakistan. Some local brands have been reported to be contaminated with faecal material.⁶

Enteric fever should be considered in the differential diagnosis of fever in travellers coming from endemic regions, even if vaccination and safe practices have been applied. Empiric treatment of a suspected imported case from any region of Pakistan should cover XDR strains. We suggest to use azithromycin, add meropenem if complications are present, and adjust therapy once susceptibility results are obtained. Travellers to Pakistan need to know about the current XDR outbreak, how to prevent typhoid and plan ahead for vaccination before visiting the country.

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Table 1. Antimicrobial susceptibility testing results of isolated XDR *S. enterica* ser. Typhi in a child travelling to Spain from Pakistan

Antibiotic	Minimum inhibitory concentration (µg/mL)
Ampicillin	Resistant ≥32
Azithromycin	8*
Amoxicillin-clavulanate	Intermediate 8
Ceftazidime	Resistant ≥64
Cefotaxime	Resistant ≥64
Cefoxitin	Sensitive ≤4
Ciprofloxacin	Resistant 2
Cefepime	Resistant ≥64
Cefuroxime	Resistant ≥64
Ertapenem	Sensitive ≤0.5
Imipenem	Sensitive ≤0.25
Nalidixic acid	Resistant ≥32
Piperacillin-tazobactam	Intermediate ≤4
Trimethoprim-Sulfamethoxazole	Resistant ≥320
Tigecycline	Sensitive ≤0.5

*Isolates with a Minimum inhibitory concentration ≤16 µg/mL are considered responsive to azithromycin