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Risk factors for colonization with extended-spectrum beta-lactamase producing *Enterobacteriaceae* in healthcare students on clinical assignment abroad: A prospective study

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Summary *Background:* The increase of antibiotic resistance in clinically important bacteria is a worldwide threat, especially in healthcare environments. International travel is a risk factor for gut colonization with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE). The risk for healthcare students of being colonized with ESBL-PE when participating in patient-related work abroad has not been previously investigated.
Methods: Swedish healthcare students travelling for pre-clinical and clinical courses outside Scandinavia submitted faecal samples and survey data before and after travel. The faecal samples were screened for ESBL-PE and carbapenemase-producing *Enterobacteriaceae* (CPE). Screening results and survey data were analysed to identify risk factors for colonization.
Results: In the 99 subjects who submitted a full set of samples, 35% were colonized with a new ESBL-PE strain during travel. No CPE was found. The most important risk factor for ESBL-PE colonization was travel destination, and the highest colonization rate was found in the South–East Asia region. Antibiotic treatment during travel was an independent risk factor for ESBL-PE colonization but patient-related work was not significantly associated with an increased risk.

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Conclusions: Patient-related work abroad was not a risk factor for ESBL-PE suggesting that transmission from patients is uncommon. Pre-travel advice on avoiding unnecessary antibiotic treatment during travel is recommended.

1. Introduction

Antibiotic resistance in clinically important gram-negative bacteria is of increasing worldwide concern [1]. This increase is particularly evident for extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE). From being a rare finding among hospitalized patients in Europe in the beginning of the 1980s, faecal carriage rates of over 50% have recently been reported from the WHO South—East Asia region (which includes the Indian subcontinent and countries in South—East Asia) [2,3].

ESBLs render bacteria resistant to, most notably, 3rd generation cephalosporins, and co-occurrence with other resistance mechanisms (e.g. resistance to fluoroquinolones) is common [4—7]. Colonization with multidrug-resistant bacteria in patients has been shown to be associated with increased mortality [8] and infections with ESBL-PE are related to increased mortality, longer hospital stay, and higher healthcare costs [9].

Recent international travel has been identified as a risk factor for clinical infection with ESBL-PE [10—15] and travellers have been shown to become colonized with ESBL-PE during travel with rates between 21 and 30% [5,6,16—21]. A recent emergence of carbapenemase-producing *Enterobacteriaceae* (CPE) that appears to be spread with similar mechanism as ESBLs is especially worrisome due to the limited treatment options given for infections caused by these bacteria. Faecal colonization with CPE in international travellers has recently been demonstrated [22,23], but colonization rates of CPEs are fortunately much lower than those of ESBL-PEs [5,6,16—18].

Previous studies on ESBL-PE faecal colonization in travellers have examined tourists, but no study has considered healthcare workers or healthcare students working or studying abroad. Studying abroad is common. In 2012, 4.5 million students worldwide were enrolled in tertiary education outside their home country [24]. Out of the 357,000 students enrolled in tertiary education in Sweden in the fall of 2012 [25], 28,300 travelled abroad as part of their education [26].

In this study, we investigated the faecal colonization rate and risk factors for acquiring ESBL-PE and CPE among healthcare students taking pre-clinical and clinical courses abroad. We hypothesise that professional healthcare exposure could be related to an increased risk of ESBL-PE colonization during travel.

2. Methods

2.1. Participants and sample collection

This prospective study was open for inclusion between April 2010 and January 2014. The study subjects were consecutively recruited within a survey study investigating health risks when studying outside Scandinavia. Participants were recruited from Universities in Umeå, Stockholm and Gothenburg. Healthcare students -medical, nursing, dental, and pharmacy — participating in the survey study were eligible for participation. Participants submitted faecal swabs (Copan Venturi Transystem®, Copan diagnostics Inc. USA) before and after travel. The instructions included submitting a pre-travel sample close to departure, and a post-travel sample one to two weeks after returning to Sweden using a sampling set sent to the participants. Survey data on demographics, travel characteristics, travel diarrhoea, and antibiotic consumption during travel were collected.

2.2. Detection of ESBL-producing bacteria

Chromogenic culture media (crohmID ESBL, bioMérieux SA, Marcy-l'Etoile France) was used to screen for ESBL-producing bacteria. Positive isolates were analysed with culture-based methods according to EUCAST guidelines (www.eucast.org). The definition of ESBL-producing *Enterobacteriaceae* by Gieske et al. [27] was used. Antibiotic susceptibility testing (including cefotaxime, ceftazidime, piperacillin/tazobactam, and meropenem) was done by disc diffusion (Oxoid Ltd./Thermo Fisher Scientific, Cambridge, United Kingdom) on Mueller-Hinton (MH) agar (Oxoid Ltd.). E-tests® (bioMérieux) were used to test for the presence of the $ESBL_A$ phenotype (CTX-M, SHV and TEM enzymes) [27] with cefotaxime/cefotaxime + clavulanic acid and ceftazidime/ceftazidime + clavulanic acid as well as cefepime/cefepime + clavulanic acid if warranted. If applicable, phenotypic detection of AMPc type beta-lactamases with cloxacillin inhibitable ESBL enzymes (cefotetan/cefotetan + cloxacillin) was performed.

2.3. Detection of carbapenemase-producing bacteria

Supplementary carbapenemase screening was performed to detect OXA-48/OXA-181 producers that do not produce an ESBL [28,29]. Before screening on chromogenic media, all samples were tested by disc diffusion for susceptibility to meropenem (10 μg), piperacillin/tazobactam (30 μg/6 μg), and ceftazidim (10 μg) on MH agar (Thermo Scientific) containing 7.5 mg/L vancomycin. A cut-off value of ≥16 mm for piperacillin/tazobactam susceptibility was used according to the recommendation of Huang et al. [30] instead of the ≥20 mm recommended by EUCAST for *Enterobacteriaceae*. If reduced sensitivity to piperacillin/tazobactam was found, susceptibility testing by disc diffusion to temocillin (30 μg, Rosco Diagnostica, Taastrup,