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Commentary

Antibiotic resistance and international travel: Causes and consequences

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1. Background

The discovery of Penicillin by Alexander Fleming in 1928 is generally considered the beginning of the antibiotic era in medicine. Suddenly, bacterial diseases like pneumonia, septicaemia, gangrene or tuberculosis were no longer an inevitable death sentence. Today, decades of much uncontrolled, unwarranted use of antibiotics in both, human medicine and animal husbandry bring us, according to the WHO, to the brink of a post-antibiotic era [1]. A fate which somehow has already been predicted by Alexander Fleming in 1945: When accepting his Nobel Prize for the discovery of penicillin he said: "There is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

1.1. Antibiotic resistance in Gram-negative bacteria

In recent years, multidrug resistant bacteria have become an increasing public health threat worldwide. A decade ago, the worldwide focus was mainly on Gram-positive bacteria. Today, Gram-negative bacteria, mainly *Enterobacteriaceae*, are the main reason for concern: on the one hand the extended-spectrum beta-lactamase (ESBL)- and carbapenemase-producing *Enterobacteriaceae* [2], on the other hand, the *Enterobacteriaceae* carrying the plasmid-mediated colistin resistance gene (*mcr*-1) [3]. ESBL-producing *Enterobacteriaceae* are resistant to penicillin, 1st to 4th generation cephalosporins and aztreonam, carbapenemase-producing *Enterobacteriaceae* show an additional resistance against carbapenems [4]. *Enterobacteriaceae* carrying *mcr*-1 are resistant against colistin [3]. Being plasmidic, all three resistance types can potentially be exchanged between different *Enterobacteriaceae*. They can occur in combination with each other or in combination with resistances against other antibiotics (i.e. quinolones, trimethoprim-sulfamethoxazole), leading to pan-resistance [5–8].

For decades, antibiotic resistance was considered to occur mainly health-care related. However, with regard to multidrug resistant *Enterobacteriaceae*, recent years have shown an increase in the proportion of community-acquired infections, especially with ESBL-producing *Escherichia coli* [9,10]. Furthermore, an increasing trend in the asymptomatic carriage of ESBL-producing *Enterobacteriaceae* in the general population has been observed [11].

1.2. Antibiotic resistance and international travel

International travel is considered to play a major role in the worldwide spread of ESBL-producing *Enterobacteriaceae*. In the past decade, several studies have shown that travellers returning from (sub)tropical countries are colonized with ESBL-producing *Enterobacteriaceae* [6–8,12–15]. Depending on the region visited, colonization rates vary between <10% (Southern Africa) and 75% (Indian Subcontinent) [15]. Moreover, international travel is not only associated with asymptomatic carriage but also with an increased risk for community-acquired infections with ESBL-producing *Enterobacteriace* [16–18]. Suffering from travellers' diarrhoea [6,12–15] and taking antibiotics while travelling [13–15] are the main factors associated with becoming colonized identified so far. With regard to carbapenemase-producing

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Enterobacteriaceae, an association with travel can be observed as well, even though still on a much lower level. In a Dutch study looking at 2001 travellers, only five were colonized with carbapenemase-producing *Enterobacteriaceae* upon return [19]. New Delhi metallo-beta-lactamase, one of the carbapenemases, has its origin in India. The number of clinical cases with NDM-producing isolates reported outside India shows an association with the amount of air traffic reaching the respective countries from India [20]. Similarly, *Enterobacteriaceae* carrying *mcr*-1 have been found to colonize travellers [21–24]. Given that this resistance mechanism has only been described for the first time in November 2015 [3], the exact extent of this problem is not clear yet.

2. Causes and consequences

International travel is a risk factor for becoming colonized with multidrug-resistant *Enterobacteriaceae* [6–8,12–15]. This we know for a fact. However, precariously little is known about the causes and consequences of this phenomenon.

2.1. The human gut microbiome

International travel is known to cause changes in the human gut microbiome [25]. Changes in the gut microbiome can reduce the colonization resistance [26], thereby preparing the grounds for the acquisition of resistant bacteria. Several of the previous studies on colonization while travelling found suffering from travellers' diarrhoea [6,12–15] and taking antibiotics while travelling [13–15] to be associated with an increased risk. While these are both factors which lead to changes in the gut microbiome, too [27,28], the identification of these risk factors obviously provides only part of the answer. Even though, more in-depth knowledge about the role of the human microbiome in acquiring and eradicating resistant bacteria is needed. Especially, as this might lead to the development of new probiotics to be used for preventing colonization.

Another major question is how travellers get colonized. Where do the multidrug resistant Gram-negative bacteria come from?

2.2. Antibiotic use in humans

The overuse of antibiotics in human medicine is considered one of the main drivers of resistance development. However, while use of antibiotics certainly increases the risk for resistance development on an individual basis [29], other factors are needed to cause a public health impact: India is considered one of the global hotspots for the emergence of antibiotic resistance. However, while it had the highest absolute consumption of antibiotics in 2010, the per capita use of antibiotics was considerably higher in the United States and Australia (India: 10.7 units per person; USA: 22 units per person; Australia: 87 units per person) [30], both having considerably lower resistance rates than India [11,31]. One of the reasons given in the literature for this apparent contradiction is the discrepancy between the improved access to antibiotics and the lack in improvements if it comes to water, sanitation and public health in India [32]. Furthermore, even though the inadequate over-the-counter use of antibiotics drives resistance development, its restriction has been weight against its benefits of averting death due to infectious diseases [33].

2.3. Antibiotic use in animal husbandry

With regard to the acquisition of multidrug resistant bacteria outside the health-care setting, another one of the main hypotheses discussed in the literature is an animal origin. The massive and indiscriminate use of antibiotics in animal husbandry over the past decades has contributed to the emergence and spread of antibiotic resistance. Studies show a clear association between the amount and type of antibiotics used in animal farming and the prevalence of antimicrobial resistance in animals [34,35]. However, the direct link between resistance development in animals and humans is difficult to establish and discussed controversially. Some studies see a direct link between isolates identified in animals and humans [36–39], others do not [40,41]. However, these discrepancies might partly be due to methodological problems: While some studies take into consideration only the phenotype of the strains found, molecular data are warranted to compare the isolates found in animals and humans, respectively [42]. Either way, given that the global consumption of antimicrobials used in food animal production is estimated to rise by 67% by 2030 [43], more in-depth knowledge about the emergence and spread of antimicrobial resistance at the animal-human interface is urgently needed.

2.4. Resistance acquisition through the food chain and the environment

Originating from food animals, multidrug resistant bacteria can be transferred to the end product, meat. In some studies, up to 95% of broiler meat samples and approximately 10% of pork and beef samples were contaminated with ESBL-*E. coli* [37,44]. Similarly, *mcr*-1-carrying *Enterobacteriaceae* have been found on poultry, beef, and pork [5]. However, not only meat can be contaminated. ESBL-producing *Enterobacteriaceae* have been found on various food products worldwide, e.g. raw milk [45–47], seafood [48], lettuce [49], vegetables [50–52] and herbs [53]. ESBL- and carbapenemase-producing *Enterobacteriaceae* have also been found in drinking water [54,55].

With regard to travellers, to date, only one study has found an association between colonization with ESBL-producing *Enterobacteriaceae* and food habits [8]. However, more information about the potential spread of multidrug resistant bacteria through food is urgently needed, as this would pose an important option for preventive measures. The decades-old advice "*boil it, cook it, peel it or forget it*" to prevent travellers' diarrhoea could potentially serve in avoiding colonization with multidrug resistant bacteria, too.

2.5. Human-to-human transmission

Human-to-human transmission of multidrug resistant *Enterobacteriaceae* occurs within families and in hospitals [56,57]. The question to which extent contaminated surfaces contribute to the spread of multidrug resistant bacteria in the community is difficult to answer: potentially, surfaces like door handles or light switches can be contaminated with bacteria [58]. However, one study looking at handles on the inside of toilet cubicles at several international airports found no ESBL-prod. *Enterobacteriaceae* [59]. More needs to be known about the importance of contaminated surfaces as a means to spread multidrug resistant bacteria, as this could lead to preventive measures like increased hand hygiene.

2.6. Colonization vs. infection

Looking at the consequences of travel-associated colonization, the evidence base is not less fragmentary. There exists some evidence that international travel not only leads to colonization, but increases the risk for infection with multidrug resistant bacteria, too [16–18]. However, data on the absolute risk and risk development over time are completely lacking. However, these information are crucial for developing evidence-based recommendations on empirical antibiotic treatment of travellers presenting with symptomatic disease. Choosing inadequate empirical antibiotic