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Commentary

Should travelers be screened for multi-drug resistant (MDR) bacteria after visiting high risk areas such as India?

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The increasing awareness that antimicrobial resistance is and will continue to be a major threat to human health and welfare now and in the coming decades was underlined in a recent UN debate [1]. The Whitehouse (report) predicting that, by 2050, more people will die from untreatable MDR, than from cancer, illustrate the urgency [2,3]. The control of resistance to antibiotics is a particular concern in low and middle income countries [4], and are spread by travel [5]. We would like to propose screening for certain risk groups but first a brief overview of the milestones in the emergence of MDR bacteria.

1. Global spread of plasmids (mobile bacterial genetic elements) carrying resistance genes

1.1. Carbapenem resistance

1.1.1. Klebsiella pneumoniae carbapenemases (KPC)

KPC were first detected in 1996 and by 1999 have been reported from Israel, China, Greece, Italy, Brazil, France, Colombia, Taiwan [6]. The geographic spread to new areas was often associated with patients transferred from one country to the other [6].

1.1.2. NDM-1, carbapenemases

A new plasmid, NDM-1, carrying resistance genes against carbapenems was reported from India in 2010 [7], and was soon after from Oman [8], a country with approximately 1.5 million guest-workers from the Indian subcontinent and an extensive medical tourism to India and Pakistan. The NDM-1 spread rapidly to the United Kingdom [9], also a country with large immigrant groups and many of the UK NDM-1 positive patients had traveled to India or Pakistan within the past year, or had links with these countries. NDM-1 was mostly found among *Escherichia coli* (n = 36) and *Klebsiella pneumoniae* (n = 111), which were highly resistant to all antibiotics except to tigecycline and colistin [9].

1.2. Acinetobacter baumannii resistance

A baumannii is a saprophytic bacterium that lives mainly in the environment [9,10]. *A. baumannii* is naturally resistant to many antibiotics and strains have acquired additional resistance mechanisms after being subjected to antibiotic selective pressure in hospitals. Some strains are pan-resistant to all available antibiotics, exposing patients to therapeutic failures, particularly when resistance to imipenem is present. *A. baumannii* often affects patients in intensive-care unit and spreads mostly by cross-transmission, with environmental reservoirs often playing a major role. A multi-drug resistant *A. baumannii* (MDRA) epidemic spread in non-ICU area is possible [3,11].

1.3. Colistin resistance MCR-1

Colistin is regarded as one of the last resorts for treating carbapenem resistant bacteria. In 2016, presence of the MCR-1

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plasmid carrying resistance to colistin was reported from China [12], which was rapidly followed by reports of MCR-1 imported from travelers visiting China [13].

The *mcr-1* gene is also found in pigs and poultry and the first European veterinary isolate dates from 2005 [14]. This was soon followed by veterinary reports from most EU countries. The use of colistin in pig and poultry production is widespread in Asia [15].

1.4. Tigecycline resistance

Resistance to Tigecycline has been reported from Asia and includes descriptions of the mutations leading to resistance in *Klebsiella pneumonia.* [16] A study of risk factors for being infected with tigecycline resistant *K. pneumonia* in a hospital setting found that the only independent risk factor was prior use of kinolones [17].

Thus it seems that, in particular, South East Asia is a hotspot for developing and spreading MDR bacteria [18,19], and particularly hospitals are identified a source [20,21], as has also been reported from Greece [22].

An innovative approach to studying the spread of MDR between geographic areas was the use of meta-genomics of toilets contents from long-range flights from Asia and North America to Denmark [23]. The highest number of resistance genes was found in flights originating from Pakistan, Singapore and Thailand. Another study using PCR to study pathogens in stools from tourists before and after travels to Asia, found that most harbored pathogenic bacteria whether symptomatic or not [24]. Thus there is no doubt that travelers are an important route of transmission between countries and continents [25]. The results also underline that the use of antibiotics to treat travelers' diarrhea is not advisable as it may enhance MDR carriage and therefore should be discouraged.

2. Medical tourism and hospital as hot-spots for MDR bacteria

“Medical tourism” is the term used for patients traveling for treatment at a medical facility in another country. Because hospitals are hotspots for MDR bacteria, medical tourisms is of particular concern in the spread of MDR bacteria between countries [26,27]. One study found that foreign travel was associated with an increased risk of carriage of MDR Enterobacteriacae [28], while the risk of colonization/infection with MDR bacteria is less well described in travelers who have no history of hospitalization abroad [29].

3. How to tackle patients admitted with history of travel?

This is done mainly by effective infection control and prevention practice and efficient and cost effective screening strategies.

It is essential to have clear infection control polices and practice which include effective environmental cleaning. A case report from Australia clearly demonstrated effective infection control practice, which included, in addition to screening and other infection control measures, an effective environmental cleaning with bleach 1:1000 ppm of chlorine-based disinfectant [30].

Another study recommended that “Healthcare institutions should have sound infection prevention strategies to mitigate the risk of dissemination of MDR organisms from patients who have been admitted to hospitals in other countries“ [31].

In our setting (Oman), if admitted patients have a history of admission to other hospitals in Oman or abroad within the past 12 months, they should be kept in contact isolation until the screening result is known.

4. Screening travelers for MDR bacteria?

Should we employ a systematic or targeted screening? Should we screen all travelers for possible MDR bacteria?

There is no doubt that most travelers returning from several countries in Asia, Turkey and Greece and probably other countries, will be asymptomatic carriers of MDR bacteria. It seems impossible to screen all travelers and the consequences and implications of a positive test are unclear. Clearly they should not receive antibiotics and quarantine or decontamination are not possible.

The decision to screen patients in either way (systematic or targeted) is influenced by the epidemiology of MDR bacteria in the country that the traveler visited, the proportion of a positive screening tests among travelers and the presence of risk factors in the travelers.

In our setting, patients are systematically screened for MDR-GNB (Gram negative bacteria) and Methicillin Resistent *Staphylococci* (MRSA) as our hospital is considered to be endemic with MDR-Carbapenemase Resistant Enterobacteriaceae (CRE) and multidrug resistant Acinetobacter, MDRA. Although on one hand, it might be cost effective not to screen and isolate/cohort all patients coming from abroad, however on the other hand screening will identify novel “superbugs” that will merit enhanced precautions and further evaluation.

The proportion of positive screening tests is also important. In a French study, the yield of positive screening among travelers was reported to be 12% mainly from South Africa, Asia and Europe were mostly Extended Spectrum Beta Lactamases (ESBLs) [27], while it reached up to 20–33% in Sweden, US, Canada and the Netherlands [10,32–36], and Germany [37,38].

Finally, the presence of risk factors in travelers can also influence the decision of the screening approach. While most countries adopt systematic screening, a Swiss study [39], suggested targeted screening based on the low yield of positive screening among travelers (18%) and the specific risk analysis which showed that hospitalization abroad/another hospital with high rate of Multidrug resistant organisms, MDRO, surgical procedure abroad, active infection on admission and presence of skin lesions are specific risk factors associated with higher rate of colonization/infection with MDRO in travelers. Risk factors in the French study [28], were additionally shown to be use of doxycycline as a malaria prophylaxis, antibiotic use for travelers' diarrhea, immunosuppression and severe diseases. Travel medicine specialists and practitioners have a special obligation to inform about the risk of becoming carrier of multidrug resistant bacteria when using antibiotics during their travel especially for travellers diarrhea [40].

Moreover, the time frame of hospitalization abroad is also variable in the definition of travelers' screening. The Australian study used systematic screening and their case definition for travelers is hospitalization abroad in the last 6 months [30]. Although French guidelines recommend placing in contact precautions on patients reporting hospitalization abroad within the last 12 months [28], this 12 month period may be too long as clearance of MDR-GNB could happen [36].

5. What to screen for?

Screening on patients with travel history especially to “hot spots” should include mainly CRE as it is the major concern especially from travelers from India and Pakistan. Additionally, screening can include MDR- *Pseudomonas aeruginosa* and *A. baumanii* and MRSA or Vancomycin resistant *Enterococci* (VRE). Patients admitted and screened should remain contact-isolated until the result of the screening is available.