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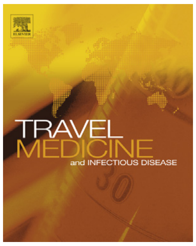

A passage from India: Association between air traffic and reported cases of New Delhi Metallo-beta-lactamase 1 from 2007 to 2012

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Summary *Background:* Highly transmissible genes encoding resistance to carbapenems have demonstrated global spread. The New Delhi Metallo-beta-lactamase 1 gene is hypothesized to have originated in India, with subsequent dissemination by colonized or infected travelers.
Method: We conducted an ecological study evaluating the association between the cumulative air traffic departing India between 2007 and 2012 and published cases of NDM-1. Receiver operator characteristic curves were generated as well as multivariate logistic regression models. 193 countries with complete flight and World Bank data were included in the analysis.
Results: Receiver operator characteristic curves (ROC) of the dichotomous outcome of a published case of NDM-1 were generated, yielding an unadjusted area under the curve (AUC) of 0.88 and adjusted AUC of 0.85. The unadjusted odds ratio of having a reported case of NDM-1, for every percentage increase in cumulative air traffic departing India, was 2.3 (95% CI 1.4 to 3.7) and adjusted was 2.0 (95% CI 1.2 to 3.4).
Conclusions: We demonstrate that flows of international travelers departing India by air is associated with published NDM-1 cases, globally. Countries with high passenger flight traffic from India with no reported cases of NDM-1 may be at increased risk of having unreported transmission of NDM-1.

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1. Introduction

The World Health Organization has identified antimicrobial resistant organisms as one of humanities greatest threats, which could ultimately give rise to a 'post-antibiotic era' [1]. Beta-lactamases capable of breaking down the broad-spectrum carbapenems (termed carbapenemases) have emerged [2]. In 2007, a new carbapenemase was discovered in a Swedish patient after recent travel to the Indian Subcontinent, and was termed New Delhi Metallo-beta-lactamase 1 (NDM-1) [2,3]. Thereafter, the resistance gene was identified in increasing numbers of countries and bacterial species globally, with India being identified as the source country in >70% of travel related cases [3]. It is believed that the resistance gene is transmitted/carried predominantly via asymptomatic carriage of resistant enterobacteriaceae within the gut flora [4]. The seemingly rapid dissemination of this mobile genetic element globally over the last 7 years [5] is concerning and the processes that gave rise to this prolific spread should be investigated.

Recently, air traffic patterns have been used to predict the potential spread of emerging viral pathogens, including Chikungunya and Ebola virus [6,7]. It is possible that these same air traffic patterns could be also be used to predict the spread of bacteria harboring highly transmissible emerging drug resistance mechanisms. Given that India has been hypothesized as a major source country of NDM-1 [8], we sought to identify whether air traffic patterns departing India are associated with the spread of NDM-1, globally.

2. Methods

2.1. Study design

We conducted an ecological study evaluating the percentage of cumulative air traffic departing India between 2007 and 2012 as a predictor of NDM-1 clinical cases (imported and autochthonous) published from 2007 to 2012, with consideration of potential confounding variables including population size and economic status. Given the potential for the establishment of new reservoirs of NDM-1, we did not include cases published after 2012 [3,8,9]. Although publication of the first case did not occur until 2009, we included air traffic data back to 2007, corresponding to the time of occurrence of the first published case.

2.2. Data sources

Reported clinical cases of human NDM-1 infection (not asymptomatic carriage) were identified (from published reports up to December 31st 2012) using a previously published literature review [3]. These data were collected using a pubmed query with keywords 'NDM-1' and 'New Delhi Metallo-beta-lactamase-1' [3], and only contained first published cases, omitting duplicate publications.

We analyzed anonymized flight itineraries of all travelers departing India between the years 2007—2012 for their destination city, using data from the International Air Transport Association [7]. These techniques have been previously described [10]. These anonymized flight itineraries cannot be used to determine the nature of the flight or duration of stay in the destination or origin country. Only final destinations, based flight itineraries, were considered in this analysis. Cumulative air travel from the period 2007—2012 was used to determine the percentage of passengers leaving India attributable to a destination country. 193 countries with complete World Bank economic and population data were included. We excluded Pakistan, Bangladesh, Nepal, and Sri Lanka, Myanmar, and the Bhutan as these countries can be easily traversed by land/sea from India, which was not accounted for in this analysis.

2.3. Analysis

Multivariate logistic regression was performed with a response variable of any (imported or autochthonous) NDM-1 case (yes/no) published from 2007 to 2012. Time of case occurrence was not utilized in the analysis, as these are not reliably reported in this literature. Similarly, response and predictor variables were not analyzed by individual year, as dates of publication were often not reflective of year of case occurrence (where noted). Predictor variables included departing passenger traffic percentage from India from 2007 to 2012, World Bank economic classification, and World Bank population size estimates. World Bank economic classification in the form of 'income level' was used, and was treated as a categorical variable. Receiver operating characteristic curves (unadjusted and logistic regression model) were generated based on a dichotomous outcome of reported NDM-1 case (yes/no) and percentage passenger traffic departing India, based on destination country. All statistical analysis was performed using STATA (Version 14, College Station, Texas).

3. Results

We identified destination countries of travelers departing India from 2007 to 2012 (Fig. 1). Table 1 shows the top destination countries corresponding to nearly 70% of all passenger traffic departing India from 2007 to 2012, along with the country's World Bank population size estimates and economic classification [11], and number of reported cases of NDM-1 published during the same time period [3]. Of these countries, during this time period, the greatest numbers of reported cases of NDM-1 were in the United Kingdom (67), followed by Canada (25), Singapore (16), and Oman (14) [3]. Saudi Arabia, Malaysia, Qatar, and Bahrain reported no published cases of NDM-1 over this time period [3].

Logistic regression analysis of NDM-1 case reports published from 2007 to 2012 yielded an unadjusted odds rate (OR) of 2.3 (95% confidence interval (CI) 1.4 to 3.7) per percentage increase in air traffic departing India. Adjusting for World Bank economic classification and population size yielded an OR of 2.0 (95% CI 1.2—3.4) per percentage increase in air traffic departing India. Unadjusted receiver operating characteristic curve (ROC) analysis for the dichotomous outcome of any reported NDM-1 case (autochthonous or imported) yielded an area under the curve (AUC) of 0.88 (Fig. 2). Using an air traffic volume cut-