# Health problems and risks encountered among healthy and vulnerable Dutch travelers

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# 1

# General introduction

People are fond of traveling around the globe for leisure, business or other purposes, regardless of their age or health status. In the Netherlands, over 35 million holiday trips were taken, of which 51% were spend outside the country in 2016. This number increased to almost 41 million trips in 2019 with 56% of the trips abroad. [1, 2]

While being abroad, travelers may experience a variety of, mostly self-limiting, travel-related health problems, ranging from infectious diseases to trauma, mental illness or exacerbation of a pre-existing disease. A retrospective study of the Dutch General Practitioners among 600 Dutch travelers revealed that one out of every five Dutch travelers experienced some kind of health complaints while abroad. They strongly advise to be well prepared for the planned journey. [3]

Travel medicine professionals strive to provide travelers with personalized, easy-to-understand risks numbers concerning travel-related health problems. In this way, travelers can make well-informed decisions in adherence to the preventive measures that were advised during the travel health consultation depending on their individual risk thresholds. Compliance with travel health advice while being abroad relies on effective risk communication by the travel health provider and knowledge of the risk perception and risk thresholds of the traveler itself. [4, 5] Hiranrusme et al. demonstrated that images could be a useful tool to enlarge and visualize the risk perception of travel-related health problems in travelers (figure 1). This is particularly the case for 'new' travelers, as experienced travelers often received pre-travel advice(s) in the past. [6] In the Netherlands travelers can contact travel clinics or municipal health services (MHS, in Dutch: GGD) for a pre-travel advice, preferable 4-6 weeks before departure. They receive verbal and written advice and preventive measures concerning various topics, mostly related to infectious diseases, depending on the travel destination(s) that will be visited. Also, the immunization status of the traveler is checked and updated if needed. Guidelines of the foundation named National Coordination Center for Travelers Health Advice (in Dutch: Landelijke Coordinatorcentrum Reizigersadvisering, LCR) are hereby followed. [7] Besides the travel clinic consult, travelers also have other sources for collecting travel information: internet, pharmacies, friends and relatives or travel agencies. The travel health provider should be aware of this as contradictory information can be given, leading to a confused traveler who has less compliance for any preventive measures during travel. [8]

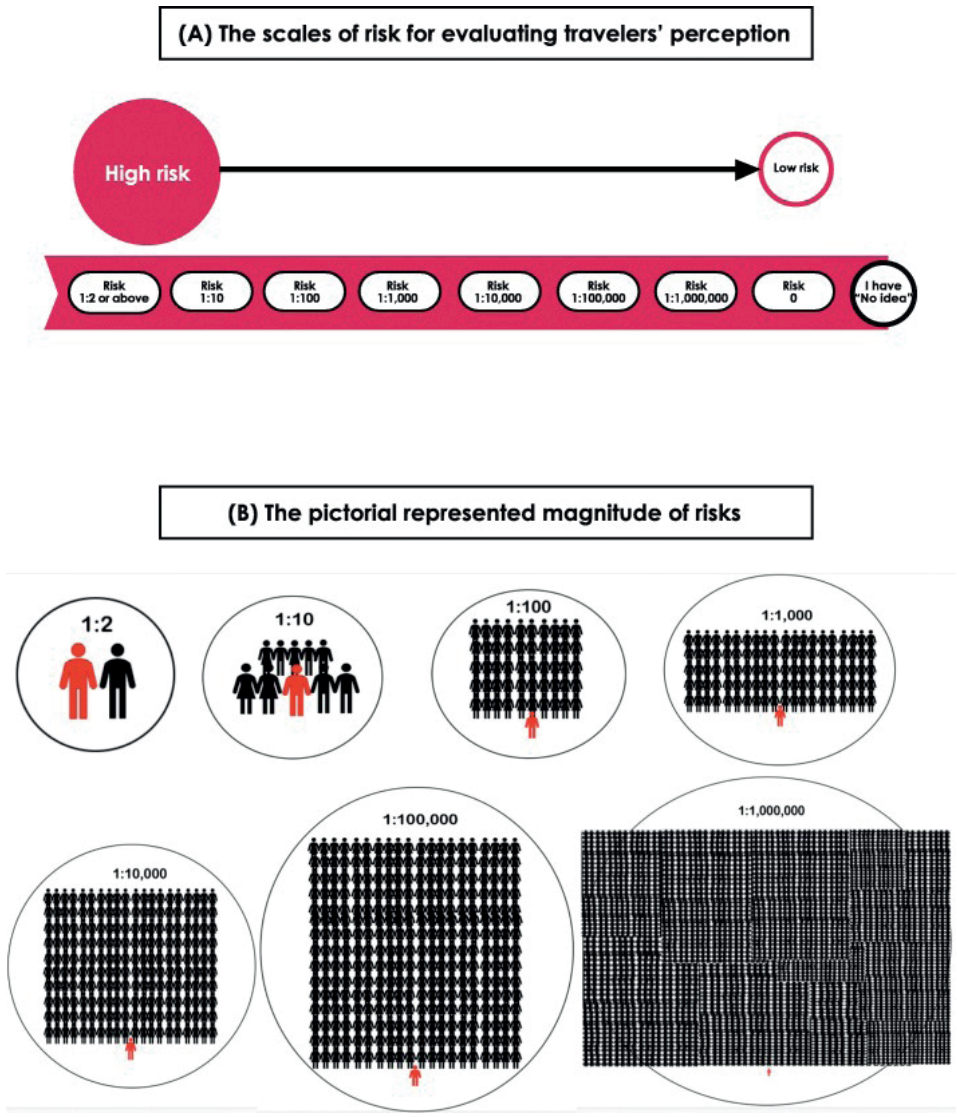


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**Figure 1**. Measurement scales used for risk evaluation in Thai and western travelers who received pre-travel advice at the Thai Travel Clinic in 2019.

**Travel-related health risks**

There are different methods to estimate health risks that can be used, each with their associated advantages and disadvantages. In travel medicine, and also in the research described in this thesis, data is often collected in prospective cohort studies. Associated risk measures reported in cohort studies are incidence rates (i.e. number of new disease cases within a specific at-risk population, expressed per time unit such as per 1,000 travelers per months), or incidence proportions/attack rates (i.e. proportion of at-risk travelers that develops a disease during the foreign journey). Cohort studies are laborious and time-consuming and limited by the fact that most health problems are rare except gastrointestinal complaints and respiratory infections. An alternative option for collecting information is the use of notification data. The number of reported cases among travelers over a specific time period (=numerator) can be compared with the total number of arrivals to a specific destination (=denominator). International registries such as the World Tourism Organization can be used for this purpose. The associated risk measure are case numbers whereby stratification into regions of acquisition can be done. However, under-reporting and under-diagnosis can occur for cases during travel or when a medical diagnosis is missing. [4]

For all types of health-risk estimates it should be kept in mind that travelers are a heterogeneous population. Each traveler is unique and the chance of falling ill depends on many environmental and personal factors such as age, demographics, health status (e.g. comorbidities, medication use), educational level, financial status, and compliance with preventive measures. [4] Travelers to low- or middle-income countries (LOMIC) have higher risk of travel-related morbidity and mortality. In addition, the season of travel (e.g. dry versus rainy season), travel duration, type of journey (e.g. all-inclusive hotels versus low budget hostels), travel purpose (e.g. visiting friends and relatives versus tourism versus medical electives), and risky behavior (e.g. diving, high-altitude hiking) all affect health risks. [9]

In the first part of this thesis we aimed at focusing on health risks and problems and (risk)behavior in specific groups of travelers in order to provide more precise estimates of health risk.

In some cases, travelers require medical assistance while staying abroad, and admission to a foreign hospital or even repatriation to the home country may be necessary. The latter is mostly for medical reasons, but sometimes because of

patient's wishes or high costs of hospital care abroad. Death is the most serious outcome and is often caused by a natural cause (e.g. cardiovascular events) or sustained injuries caused by road traffic accidents, falls, or burns for example. [9-13] Notification data provide an insight on the most serious travel-related health problems that can occur. Regarding travel destinations, these are categorized in geographical regions throughout this thesis, mostly according to the United Nations geographical classification, see figure 2.

In **chapter 2** we explored in a retrospective study how many Dutch travelers received hospital-based care while being abroad or died abroad. We examined the disease burden in a five-year period using data that was retrieved from three medical assistance centers based in the Netherlands and the Dutch Ministry of Foreign Affairs.

**Chapter 3** describes the degree of inconvenience of travelers' diarrhea experienced in adult Dutch travelers to (sub)tropical destinations using web-based questionnaires. This is meaningful because many travelers have to deal with gastrointestinal complaints during one of the trips they undertake in their life. Travelers' diarrhea is mostly caused by bacterial pathogens such as *Escherichia coli (E.coli)* and has a mean duration of three to five days. Young children and elderly with diarrhea are more at risk for dehydration. During the pre-travel consult it is therefore important for the travel health provider to highlight preventive measures a traveler can take: good hygienic measures, drinking bottled water that is properly sealed, and avoiding raw and uncooked vegetables, meat and salads. [8, 14] This advice is also summarized in the traditional recommendation "Peel it, cook it, boil it or forget it". Unfortunately this turns out not to be the Holy Grail in practice and travelers still develop health complaints. [15] A travel medical kit should always contain oral rehydration solution (ORS) to prevent dehydration and the antimotility agent loperamide. Antibiotics (i.e. azitromycine or ciprofloxacine) are only prescribed for self-treatment in special groups such as immunocompromised or long-term travelers. Travelers should also be informed when they should visit a physician when having additional complaints (i.e. fever, bloody stools, increased thirst, infrequent/ little urination, or drowsiness) with the diarrhea. [14] In order to get a better understanding of the impact of gastrointestinal complaints, the study in **chapter 3** was performed.

**Figure 2**. World map according to the geographical regions assigned by the Statistics Division of the United Nations. Data were adopted from https://unstats.un.org/unsd/methodology/m49/. World map is created using https://mapchart.net.

Alongside the “ordinary” travelers, many medical schools offer their students the opportunity to perform an elective abroad. Students often choose for an institution in LOMIC countries and can be exposed to specific work- and travel-related health risks that can have serious impact on their long-term stay abroad. Therefore, we performed a web-based questionnaire study in **chapter 4** that highlights various aspects that Dutch and Belgian medical students may face before, during and after their elective in a LOMIC country, such as pre-travel preparation, culture shock, health problems and post-travel screening for several infectious diseases.

In thirty years, the Dutch population aged older than 65 years increased from 13% in 1990 to 20% in 2019 (n=3,484,216). Of this, 57% of the older Dutch citizens are between 65 and 75 years of age. [16] Travel-related morbidity in this group of travelers is expected to differ from that of younger travelers due to medical, physiological, and behavioral differences.[17-19] Older persons are more susceptible to infections due to waning immunity, impaired immune responses, and limited effectiveness of received pre-travel vaccinations. [20-24]

**Chapter 5** contains a study in which we try to identify predictors for the development of (travel-related) morbidity in Dutch travelers aged 60 years and older that needs to be taken into account during the pre-travel consult in their home country. Pre-travel physical performance was measured with hand grip strength and a cognition performance test. Questionnaires and a paper diary were used to register health complaints at different moments. We performed this study since the increase in life expectancy and vitality has led to a growing population of older adults traveling internationally over the past decades. [25]

The second part of this thesis addresses the occurrence of antimicrobial resistance in international travelers.

Antimicrobial resistance (AMR) is a complex health problem and is a growing global public health treat, fueled by the use and misuse of antimicrobial agents. [26] With the lack of new antimicrobials, treatment of common infections may become a challenge, and this can lead to higher morbidity and mortality. [27] For years there was no proper global surveillance system and countries ‘created’ their own routine surveillance that was mainly based on samples that were taken from patients with severe infections. In 2014, the World Health Organization (WHO) started to collect resistance surveillance data from 129 member states. *E. coli* and *Klebsiella pneumoniae* (*K. pneumoniae*) were identified as the main bacterial causes of urinary

tract infections, and a frequent cause of blood stream infections in hospitals and in the community, with resistance against fluoroquinolones and 3rd generation cephalosporins. Due to this resistance, severely ill patients can probably only be treated with expensive and limited available carbapenems. Although carbapenem resistance already have been reported. [26] Antimicrobial Resistance Collaborators across the world generated a world map with raw and modelled estimates for the percentage of pathogen isolates of *E. coli* and *K. pneumoniae* that are drug resistant in 2019, see Figure 3.

Traveling to a high-prevalence area of extended-spectrum beta-lactamase-producing *Enterobacteriaceae (ESBL-E)* or carbapenemase-producing *Enterobacteriaceae* (CP-E) may have a significant impact on the gut flora in travelers up to several months after return. [28] Tängdén et al. was the first who reported on the relationship between international travel and the risk of colonization with ESBL-E in 2010. [29] In the same year, CP-E was reported for the first time in the Netherlands in three travelers who visited Greece and India. [30]

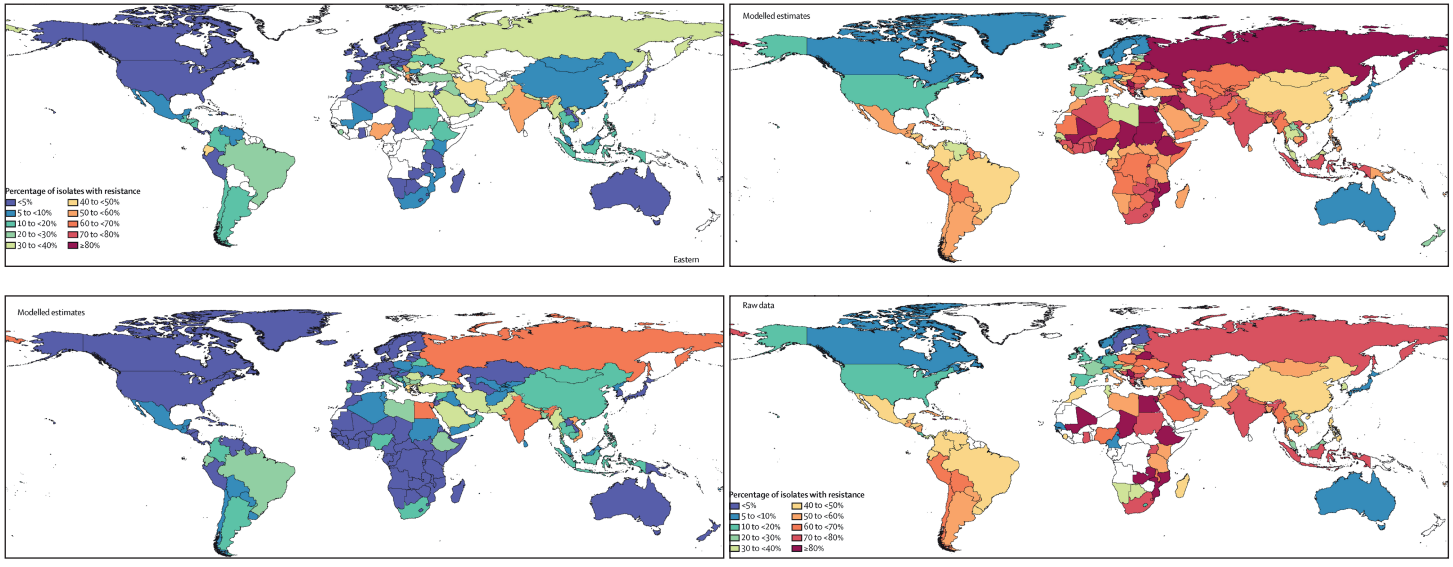
In **Chapter 6** we focus on the acquisition and duration of post-travel rectal carriage of (multi)resistant *Enterobacteriaceae* and on the identification of risk factors in a prospective cohort of Dutch travelers. For this study we were interested in the role of travelers' diarrhea, antibiotic use and the local hygiene- and sanitation level in relation to the spread of resistant organisms such as ESBL-E and CP-E .

In **Chapter 7**, data of the African travelers described in **chapter 6** were combined with comparable data from Finland and another study from the Netherlands to assess colonization rates and risk factors in this specific group of travelers.

The third part of this thesis consists of **chapter 8**, in which the findings are summarized and discussed, and **chapter 9**, which contains a Dutch summary.

A. Third-generation cephalosporin-resistant *E.coli*

B. Fluoroquinolone-resistant *E.coli*




C. Carbapenem-resistant *K. Pneumoniae*

D. Third-generation cephalosporin-resistant *K. Pneumoniae*

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**Figure 3**. Raw data and modelled estimates for the percentage of *E. Coli* and *K. Pneumoniae* isolates that are resistant by country in 2019. Locations with no raw data or modelled estimates are presented in white.

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