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EDITORIAL

Fifty years of travel medicine epidemiology: what have we learnt?

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In the late1950s, Pan Am flight 2 from Calcutta to New York was scheduled to take almost 50 hours. Only after the introduction of jet airliners in the 1960s, did intercontinental travel become more common. Increasingly, that included journeys to developing countries, and tourist hotels and safari lodges were established in Kenya and elsewhere. While anecdotal reports on imported exotic infections were collated, except for military publications, there was a lack of epidemiological assessment of health risks associated with travel. Until chloroquine resistance emerged, that agent was unanimously recommended for prophylaxis of malaria. In contrast, widely differing 'expert opinions' on indicated travel health vaccines, mainly against cholera, plague, typhoid/paratyphoid and typhus, were formulated. As late as 1969, health certificates guaranteeing that travelers were 'not suffering from trachoma, leprosy, dysentery, acute epilepsy and insanity' were required by some authorities.

In the 1970s, researchers on both sides of the Atlantic realized that data were needed to develop evidence-based priorities with respect to preventive measures for travelers. According to a postcard-questionnaire survey among passengers arriving at US airports, almost one in four reported some illness, most often travelers' diarrhea, but the response rate was <30%.[1] A Scottish research group assessed health problems in package tourists, mainly to eastern Europe. Our group in Switzerland systematically investigated health problems abroad in homebound charter flight passengers; the response rate exceeded 80%.[2] We confirmed that travelers' diarrhea was the most frequent illness in any developing country. Rates widely differed depending on the destination. In contrast, in the control group of visitors to North America, constipation was the most frequent ailment. Later, from hospital and public health records and traveler statistics we estimated the incidence rate of hepatitis (at that time 1 per 300 per month), typhoid (greatest risk in South Asia) and other vaccine-preventable diseases.[3] The highest mortality (15 per 100 000) was recorded during treks in Nepal.[4] Injuries were the leading cause of death among travelers in low-income countries, whereas cardiovascular events dominated in the Caribbean and southern Europe where many senior travelers spent the winter season. A completely different approach to illustrate infectious risks abroad was to describe the epidemiological situation in the individual countries while recognizing that risks to visitors and local residents and clinical manifestations of infections may differ between the two groups.[5] With lack of funding these early studies had a simple design; most were retrospective and thus subject to recall bias. Self-reporting of symptoms was suboptimal and many studies did not include statistical analysis. In the few cohort studies, conclusions were drawn on very small numbers. In the absence of good data, case reports, clusters and anecdotes drove decisions.

In 1995 the International Society of Travel Medicine jointly with the U.S. Centers for Disease Control and Prevention established GeoSentinel, a global surveillance network currently including 57 clinics on all continents. These are situated to effectively detect geographic and temporal trends in morbidity among travelers, immigrants and refugees. More than 50 publications describe regional and seasonal trends, specific infections and syndromes, and risks associated with various host factors, such as age or reason for travel. Lacking of denominator data, the network is unable to provide incidence rates, and can document only a relative risk as compared to other diagnoses. But GeoSentinel has recognized sentinel events, prompting enhanced surveillance, and has detected outbreaks (e.g., dengue) before the national authorities had identified them. Thanks to rapid communication, athletes potentially infected by leptospira during an Eco-Challenge race in Sabah, could be alerted in time for intervention.[6]

Since the turn of the century, a myriad of anecdotal reports on travel-related infections have been published, of particular interest are those on very rare ones.[7] Japanese encephalitis affects about one in a million travelers to endemic countries,[7] and it is an illusion to believe that all cases could be collated in some global registry.

Recent observational and cohort studies have documented a decreasing risk of hepatitis A[7,8] and travelers' diarrhea,[7,9] possibly associated with improved sanitary conditions in some destinations. Also, there is increasing interest on sequelae thereof, mainly irritable bowel syndrome.[10] Various groups provided detailed insight in risks among special populations, such as the immunodeficient a population that is growing in size and is also traveling.

Changes in the epidemiology of some infections, increases in antimicrobial drug resistance (e.g., typhoid fever), concerns subsequent to the widespread importation of extended-spectrum beta-lactamase producing Enterobacteriaceae,[11] the availability of new vaccines and malaria chemoprophylactic agents with different efficacy and adverse event profiles require rethinking of recommendations for travelers. Risk is not fixed and potential interventions change; thus, ongoing assessment and analysis is required. The relevant population to study to assess the risk to travelers is all travelers.

The internet and electronic networks allow rapid wide sharing of information but these do not replace the need for systematic collection of data. Although many publications are based on data from travel clinics, these clinics see a minority of travelers, and these travelers may differ substantially from all travelers. Increasingly, the traveling public includes older individuals and those with chronic medical problems. Also, migrants who later visit friends and relatives (VFR) are of particular concern. This group has limited financial means for pre-travel consultations and prophylactic products. VFR often do not perceive infection risks 'back home', which may be a threat particularly for their overseas born children, and for a variety of reasons, e.g., relating to language, there are problems of access to travel health providers.

Despite a rapidly increasing number of publications, travel epidemiology is far from where it should be. Since 2012, WHO has not published the annual *International Travel and Health*, as many recommendations are based on data that are graded to be of substandard quality.[7,12] For the development of modern guidelines we need a risk assessment based on 21st century state-of-the-art trials.[7] Also of concern is the misinterpretation of published results. For example, it is inappropriate to draw conclusions that mainly women should be equipped with stand by antidiarrheal medication, subsequent to the finding that they consulted with GeoSentinel travel clinics that stated that diarrhea occurs more often than in men (OR 1.13; 95% CI 1.09–1.38), when most large previous studies had shown no gender-related differences in incidence. Actually the authors had carefully formulated, 'it is unclear whether women practice travel behavior that increases the risk of acquiring gastrointestinal pathogens or whether they are more likely than men to seek medical help for gastrointestinal problems'.[13]

Many important questions remain unresolved: is the biologically plausible rule, 'boil it, cook it, peel it, or forget it', really useless to avoid diarrhea abroad[14] and, if so, why? Why does travel health advice 'not protect … from travel-related illness,'[15] are our efforts useless? Travel clinics can provide vaccines and drugs, but how does one change behavior? Novel studies, multicenter collaborations to generate large denominators are needed to bring us a step further. Large travel clinics now have the electronic capability to conduct a follow-up on customers, but as this is a biased population we should also find means to recruit departing passengers e.g., at airports. Other questions remain. Can we engage travelers to provide 'during' as well as 'after-travel' data that will allow identification of before and during travel interventions that are effective? Can we harness today's tools to generate data to complement findings from trials?

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