Travel medicine : knowledge, attitude, practice and immunisation

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Introduction

General introduction – Travel medicine

In an epoch where every generation travels more frequently and at longer distances than the previous generation, with a mean increase of 30 million travellers per year from 1995 until today [1], physicians throughout the world are confronted with new diseases. From the perspective of Western medicine, the import of highly contagious exotic infections remains an ominous but realistic threat, as shown by a Dutch patient who returned from Uganda carrying Marburg virus [2]. More than just a threat is the fact that approxmately 10% of travellers to developing countries experience a febrile illness, during or immediately after travel [3]. In absolute numbers, this implies that each year, roughly 4 million travellers appeal to specialised health care, either abroad or at home, because of systemic febrile illness, diarrhea or dermatologic disorders [4].

During the last decades, travel medicine has evolved into a distinct discipline of Infectious Diseases, eventhough transmission of infectious agents into vulnerable populations through travel has been well know for centuries. For example when the Spanish conquistadors invaded the Central and South American continents and annihilated (also by murdering) 95% of indigenous populations [5] . In fact, all major epidemics that have afflicted the human race have been spread internationally by travellers. Examples are the plague, which killed one third of the affected population, [6] throughout Europe between the fourteenth and eighteenth centuries, and syphilis, which is believed to have originally been imported into Europe from the New World by Spanish sailors [7]. Scientific medical publications in the field of travel medicine start to appear in the 1950's with mainly topics on the impact of air and space travel on physical conditions and pre-existing illnesses, and individual reports of observed diseases during journeys (PubMed Database, MeSH terms "Travel Medicine", approximately 6300 hits). By the late 1960's the first randomised controlled trial to investigate antimicrobial prevention of traveller's diarrhea was reported [8], as well as case reports on imported infectious diseases by travellers, such as malaria [9]. In 1970, a novel perspective of travel medicine was introduced, in which travellers were defined as short-term travellers (vacational tourists), long-term travellers (e.g. expatriates) and immigrants and travellers visiting friends and relatives (VFRs) (those originating form tropical countries), among whom different risks of acquiring travel-related diseases could be distinguished [10]. Following closely on new travelling trends, specific norovirus outbreaks among cruise ship passengers were reported [11,12]. Since the 1990's, the

number of scientific articles on Travel Medicine has increased almost threefold compared to the preceding decades (figure 1), implicating the increase of importance to and attention by the medical profession of this discipline of Infectious Diseases.

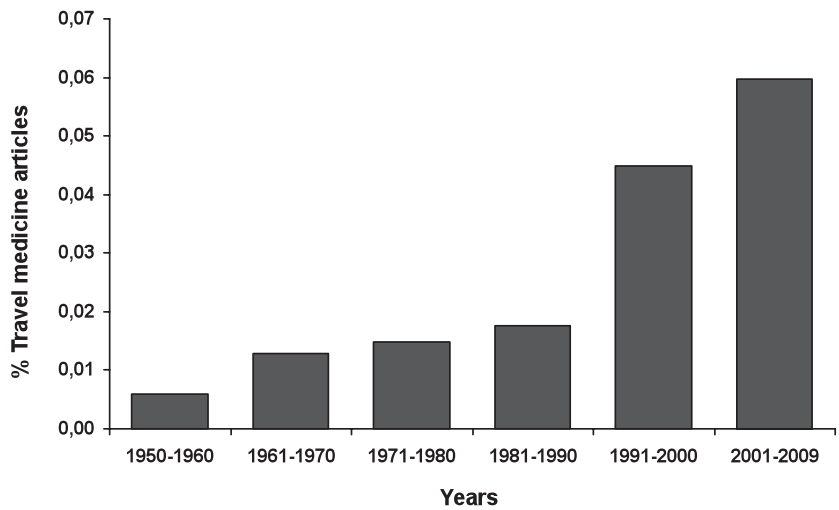

Figure 1 Percentage of articles on travel medicine published (PubMed Database, MeSH Term Travel Medicine, per decade), according to the total number of scientific medical articles published (PubMed Database, total number of articles per decade).

Hand in hand with travelling comes protection against travel-related diseases, which can be achieved on an individual and a population level. As preventive travel medicine covers multiple fields, from training to vaccination, individual and population-wide protection can be achieved on these different levels. A model to explain cumulative protective medical measures, and the occurrence of its failures, was proposed by James Reason as the "Swiss cheese" model [13]. According to this metaphor, in a complex system, hazards are prevented from causing human losses or illnesses by a series of barriers. Each barrier has unintended weaknesses or holes, giving the similarity with Swiss cheese (figure 2).

Defences, barriers, and safeguards occupy a key position in this system approach. By defining the barriers, and the (potential) holes, the system can be improved and the

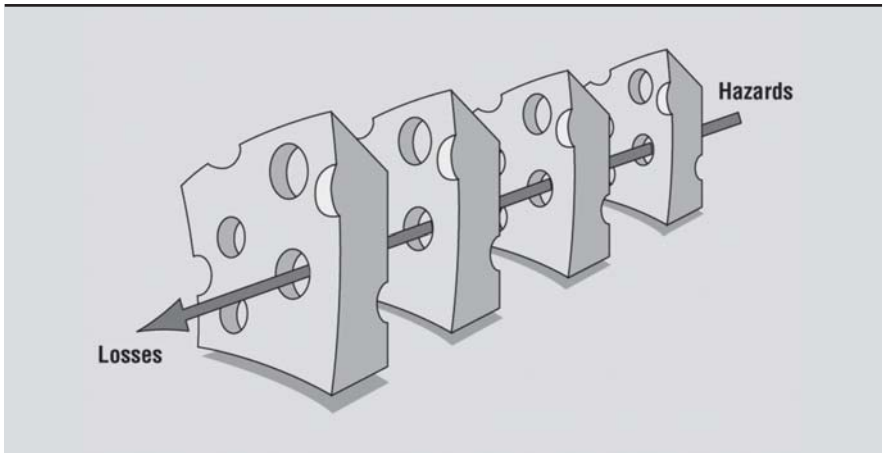

Figure 2 Swiss cheese model of how defences, barriers, and safeguards may be penetrated by an accident trajectory [adapted from 13]. The slices of cheese are schematic and should either be positioned differently, or have different position of the holes, leading to non-overlapping holes.

hazards minimised, which can also be applied to travel medicine. This Swiss cheese model can be applied to the field of travel medicine, in which the slices and holes of the cheese are related to different aspects of protection against travel-related diseases in Table 1.

By applying the model on travel medicine, improvement of the system of protection against travel-related diseases can be achieved through knowledge on the following topics; 1. Epidemiology of travel-related diseases, 2. Morbidity and mortality of these illnesses in specific groups of travellers, 3. Adherence to travel health precautions, 4. Immunological responsivity against vaccination, and 5. Availability of preventive measures, such as vaccines. The research described in this thesis addresses these various topics.

Epidemiology of travel-related disease with regard to specific populations of travellers

Several approaches to inventory the exact burden of these travel-related diseases have shown that the determination of the denominator (i.e. the number of persons exposed to a threat or disease) remains a challenge. A clinically relevant approach to investigate this

Table 1 Application of the Swiss cheese model to travel medicine. Different aspects of the model are related to health care in general and to health care in relation to travel medicine specifically

Swiss cheese model	Representation in health care	Representation in travel health care
Slice of cheese	Health care professional	Health care professional • Travel medicine specialist • General physician • Travel consultant (nurse) • Specialist – Transplant, Rheumatic Diseases, etc.
	Barrier that protects patient	Preventive measures, e.g. • Cook it, Peel it, Boil it or Forget it • Anti-mosquito bite measures • Keep away from stray animals Vaccination Chemoprophylaxis Antibiotics • Preventive • Therapeutic
	Procedure that alleviates the consequences of an error	Information / Training • Travel insurance • What to do when bitten • What to do in case of symptoms • Self-testing • Self-treatment
Error		Lacking scientific data / knowledge Misjudgement of risk by health specialist

Hole	Opportunity for error	Purpose of travel (VFR, expatriate, tourist, migrant) • Altered tendency of seeking health travel advice • Altered conception of risk • Altered motivation for adherence to measures • Itinerary – activities during travelling Adverse events of vaccines or prophylactic medication Self administration of preventive measures • Preventive measures • Chemoprophylaxis
	Weakness in defences against error	Vaccines with <100% protection rate Chemoprophylaxis with <100% protection rate
Arrow	Series of events leading to medical error	Series of events leading to travel-related disease
Adding a slice	Improve health care safety	Identify category of travellers at risk for diseases Extra training for specific groups of travellers Post-travel screening
Plugging a hole		Update scientific data / knowledge Train travel health care specialists / consultants

VFR = Visiting friends or relatives.

burden is to monitor self-reported health problems after travelling to developing countries. However, with this approach, mild or self-limiting illnesses such as diarrhea, mild respiratory infections and skin disorders are either not picked up, or picked up less frequently. In addition, this approach is highly subject to population bias.
Freedman et al. estimated the proportionate morbidity by diagnosis of self reported travel-related disease and geographic region among travellers returning from six developing regions of the world, by using the number of patients with a given diagnosis as the numerator and all ill travellers to a destination as a denominator [4]. Data of 30 GeoSentinel sites, which are specialised travel or tropical-medicine clinics on six continents, contributed to clinician-based sentinel surveillance data on 17.353 ill returned travellers. Besides the limitations of this study, such as probable under-representation of travel-related sexually transmitted diseases and infections with a short incubation period (e.g. dengue), it showed that the proportionate morbidity of diarrhea among returning travellers is highest in all developing regions visited (Southeast Asia, Central Asia, South America, Central America, Caribbean), except for Sub-Saharan Africa, where falciparum malaria accounts for the highest proportionate morbidity [figure 2 from ref 4]. Dengue occurs mostly in visitors to the Caribbean and Southeast Asia, cutaneous leishmaniasis in those who visit Central America and South America, and typhoid fever in travellers to south central Asia. TropNetEurop, a surveillance network of experts in Infectious disease and Tropical medicine throughout Europe, has reported similar trends [14]. Unfortunately, Freedman and colleagues have not analysed in more depth the contribution of the purpose of travel, a well-known risk factor for contracting infectious diseases during travelling.

Bottieau and colleagues, alike the GeoSentinel group [4], investigated self-reported febrile episodes among returning travellers (N=1743), but additionally categorised these travellers into: Western travellers (natives of Western countries visiting the tropics for less than 6 months); expatriates (Western individuals residing for more than 6 months in the tropics); natives of the tropics who have lived for more than 1 year in Europe and returning to their home country to visit friends and relatives (VFR travellers); and foreign visitors or migrants (natives of the tropics arriving for the first time in Europe) [3]. *Falciparum* malaria was more frequently diagnosed in expatriates, VFR travellers, and foreign visitors or migrants, whereas rickettsial infections, dengue, and acute schistosomiasis occurred almost exclusively in Western travellers and expatriates. Prevalence of HIV infection and tuberculosis was much higher in VFR travellers and foreign visitors or migrants. The epidemiology of travel-related diseases generated by these data is important for guiding post-travel diagnosis and empiric therapy as well as

for prioritizing pre-travel intervention strategies. In this thesis, the aim of reducing the risk of malaria in expatriate travellers is discussed in more detail (chapter 4).

Besides distinguishing travellers on the basis of the purpose of travel, they can be categorised according to their immune status. Immunocompromised travellers are more likely to experience severe effects of illness, and less likely to mount a significant response to vaccinations than those without immune disorders [15-21]. The divergent group of travellers with a compromised immunity comprises; 1. Patients on immune suppressive therapy such as solid organ or hematopoietic transplant recipients, patients with Crohn's disease, colitis ulcerosa and rheumatic diseases, 2. Patients with human immunodeficiency virus (HIV) infection, 3. Asplenic travellers, 4. Patients with defective barriers such as skin or mucosal disorders or a reduced gastro-intestinal acid barrier [22]. Although the magnitude of the immune disorder is difficult to quantify, except for the use of the $CD4^+$ T cell count in HIV patients, the overall health of immunocompromised patients improves, and so does their motivation for travel along with the need for specific protective measures. In chapter 2 and chapter 3 of this thesis, the susceptibility of travelling solid organ transplant recipients and diabetics to travel-related diseases and their precautions taken, are discussed in more detail.

Prevention of travel-related diseases by vaccination – protecting specific populations

The paradigm in vaccinology, which has existed since the development of vaccines, is that every population will mount comparable (protective) immune responses to similar vaccine doses and number of dose administrations. This approach has led to population-wide immunisations and hence the control of many infectious diseases, and should therefore always be pursued. However, with current advances in knowledge on individual variability in risk and morbidity of infectious diseases and in vaccine response, a more personalised approach could be strived for [23]. For the development of a personalised vaccination approach, the immune response in specific vulnerable groups must be inventoried and new vaccination methods, adjuvants and schedules should be investigated.

Evident groups targeted by this approach would be the previously mentioned immunocompromised travellers, but also apparently healthy individuals can show a diminished response to vaccines. In these healthy persons, genetics, gender and age are well-known factors that can influence the response to specific vaccines [24].
The success of population-wide vaccination programs, suggests that interhuman genetic differences are negligible in the process of vaccine antigen processing,

presentation and lymphocytic response. However, complex interaction of the Human Leukocyte Antigens (HLA) and peptides derived from pathogens or vaccines are believed to play a role in the magnitude and breadth of the immune response [25,26]. HLA class II alleles influence the humoral response after vaccination, since antibody production is mediated by HLA class II-restricted $CD4^+$ T-cell responses, except for polysaccharide antigen vaccines (e.g. pneumococcal vaccine) in which the response is T cell independent [27]. Indeed, for hepatitis B and measles vaccines, genetic profiles were found to be associated with persistent seronegativity or a low antibody response after vaccination [28-30]. The heritability of the immune response against hepatitis B vaccine is caused for 40% by genes within the MHC (Major Histocompatibility Complex), shown by higher intraclass correlations of MHC identical than MHC different dizygotic twins, and 60% by non-MHC genes [28]. Nevertheless, these genetic profiles do not exclusively account for the magnitude of the response. In the development of antibodies against hepatitis B vaccine, higher age, male gender and smoking also predispose for a lower antibody response [31,32].

In this thesis, two allegedly immunocompetent populations are investigated. The first group are individuals who failed to mount a protective immune response to the hepatitis B vaccine (chapter 5), expressed in antibody level. In these non-responders, the intradermal delivery of the vaccine antigen, along with an immune response modifier, was investigated in an attempt to induce a protective response. The second group are travellers of sixty years or older who received the live attenuated yellow fever vaccine (chapter 4). In the case of yellow fever vaccine, older age is associated with an increased susceptibility to serious adverse events which could hypothetically result from a diminished virus neutralising antibody response.

As the global population in Western countries is ageing, so is the travelling population. The elderly suffer from more frequent and severe infections than younger people [33], and this should increase the awareness in the elderly traveller and in those who give travel health advice. One of the main reasons for the increase in infections observed in the elderly is believed to be 'immunosenescence' [33], which refers to the immune system's diminished function with age. Logically, if the elderly show an increased susceptibility to infections, their response to vaccines could be diminished, and this has indeed been found, e.g. in the case of influenza vaccination. In a review, the clinical vaccine efficacy in young adults was 70-90%, compared to an efficacy of 17-53% in the elderly vaccinated [34], depending on the circulating influenza strains. The phenomenon of immunosenescense is not yet well understood, but the following theories have been proposed: 1. Impaired antigen presentation, 2. Thymic involution leading to decreased naïve T cell production and a

decreased ability to respond to new antigens, 3. Reduced B cell production or isotype switching, resulting in low affinity antibody production, 4. Increased memory T cell numbers which restrict the diversity of the immune cell repertoire and 5. Ageing of the bone marrow stroma leading to decreased survival of plasma cells [35,36]. With more detailed knowledge on the development of the immune response to travel-related vaccines in the elderly, travel medicine could meet with the needs of this growing population.

Prevention of travel-related diseases by vaccination – increasing vaccine dose availability

In the scope of a population-wide protection through vaccination, the aim is to create herd immunity in order to significantly reduce pathogen transmission and infection. Of all the goals formulated by the World Health Organisation (WHO) with respect to eradication of vaccine preventable diseases, only smallpox eradication has been achieved sofar [37]. Failure of eradication of infectious diseases through vaccination can be attributed to many factors. Evidently, political and financial reasons are the main hurdles to be taken, but from a scientific perspective other reasons can underly this failure. First, if the infectious agent has a non-human host, i.e. a zoonosis such as yellow fever, vaccination of all susceptible humans would still not eradicate the pathogen. Second, not all vaccines provide 100% protection against infection (e.g. vaccination with the capsular polysaccharide of *Salmonella typhi* (Vi) has a protection rate of 75% against typhoid fever in endemic populations) [38]. Third, immunisation is a human interference with nature, and people who believe this interference is wrong on religious or other grounds will refuse to be vaccinated, hampering eradication of the infectious agent. In the Netherlands, small outbreaks of poliomyelitis and measles occur on these grounds [39]. However, these reasons are probably secondary to the lack of resources to obtain the vaccine coverage that is needed for eradication. By reducing the vaccine dose needed for immunisation, vaccine stockpiles will last longer and costs will decrease, possibly leading to higher vaccine coverage.

A recently rediscovered possibility of vaccine dose reduction that receives much attention from vaccinologists, is vaccination in the skin [40-42]. The skin represents the outermost line of defense against mechanical impacts, temperature, UV-radiation, dehydration and pathogenic microorganisms. It is composed of three primary layers: the epidermis, the dermis and the subcutis (figure 3).

The outer part of the epidermis consists of dead cells (stratum corneum), the inner part of live cells such as keratinocytes, melanocytes and, of special interest for immunisation purposes, dendritic cells which are named Langerhans cells (LC) after their discoverer

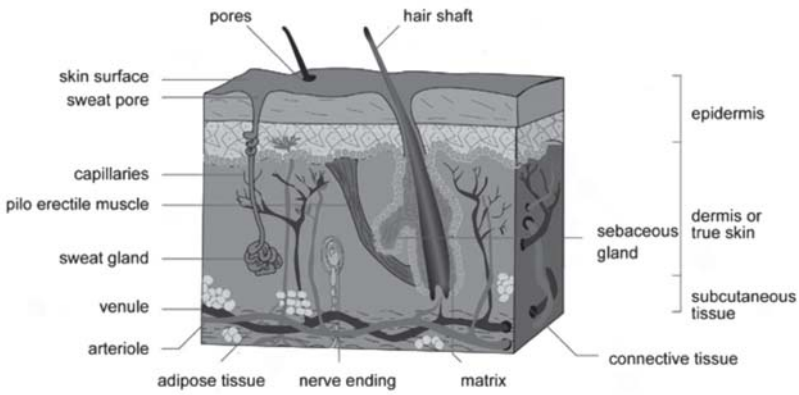

Figure 3 Cross section of the skin. Adapted from the visual dictionary [43].

[44]. These professional antigen presenting cells (APC) account for only 1% of cells, but cover nearly 20% of the surface area due to their horizontal orientation and long protrusions [45]. The dermis is primarily composed of extracellular matrix, and like the epidermis contains dendritic cells (dermal dedritic cells – dermal DC), besides fibroblasts, macrophages and granulocytes. In the dermal layer reside the most superficial glands and lymphatic and blood vessels of the body. LC and dermal DC constantly monitor the (epi)dermal microenvironment by taking up antigen and processing it into fragments that can be recognised by effector cells of the adaptive immune system. LC have classically been thought to be essential for initiating T cell responses to cutaneous antigens, accounting for the success of intradermal vaccination [46]. However, recent data have also highlighted the importance of dermal DC in cutaneous immunity [47,48]. Zhao et al. investigated the contribution of vaginal APCs in immune induction to HSV-2 (Herper Simplex Virus), and revealed that only the $CD11b^+$ dermal DCs, but not Langerhans cells, presented viral antigens to $CD4^+$ T cells and induced Interferon γ (IFN)secretion. Following on these results, Allan et al. provided in vivo evidence that priming of HSV-specific CTLs (Cytotoxic T cells) after skin infection does not require antigen presentation by LCs. Although these results are confined to HSV and may not apply to other pathogens, they do undermine the hypothesis of overall dominance of LCs in an (epi)dermally initiated immune responses.

For immunisation purposes, both could be relevant, as both LC and dermal DC process and present the injected antigen to naïve T cells in the draining lymph nodes [49]. Itano and colleagues demonstrated that after subcutaneous inoculation of antigen, unprocessed antigen drains to lymph nodes within several hours and does not require cell-mediated transport [50]. DC that reside in the lymph node take up and process this antigen and then activate naïve T lymphocytes. A second wave of antigen is delivered to lymph nodes approximately 24 hours later by an influx of dermal DC that express high levels of the antigen. Although extensive T cell proliferation is induced by the first wave of antigen, complete $CD4^+$ T cell differentiation requires the presence of dermal DC. [50].

LC and DC represent the principal APC under steady state condition, which is disrupted during cutaneous vaccination. The inflammatory state initiated by immunisation might induce influx of plasmacytoid DC into the site of injection, contributing to the induction of an adaptive immune response [51]. Based on these data, the success of intradermal vaccination is attributed to efficient vaccine antigen presentation to APC and hence T and B cells, whereas with subcutaneous or intramuscular vaccine administration, the probability of antigen – APC contact is lower. This hypothesis has recently been studied in mice, in which Virus-like particles (VLPs) of simian-human immunodeficiency virus (SHIV) were inoculated intramuscularly, intraperitoneally, subcutaneously and intradermally. With an optical imaging approach to directly visualize the trafficking of the VLPs after immunisation, Cubas et al. showed convincingly that the intradermal immunisation led to the largest level of lymph node involvement for the longest period of time, which correlated with the strongest humoral and cellular immune responses [52].

Historically, the route of vaccine administration by needle, i.e. intradermal, subcutaneous or intramuscular, has been reached on arbitrary grounds. The first scientific evidence of vaccination was provided by Edward Jenner, an English doctor who in 1796 successfully inoculated the content of a cowpox bulla -containing vaccinia virus- into the skin of a young boy, rendering him protected against a challenge with the human pox virus (variola) [53]. Almost 100 years later another vaccinology pioneer, Louis Pasteur, developed a post-exposure rabies vaccine, which was administered under a fold of the skin (i.e. subcutaneously) [54]. Apparently, intramuscular injection was initially not the standard immunisation route, and is still not the immunisation route for vaccines as Bacille Calmette Geurin (BCG) and vaccinia. Increased knowledge on vaccine-induced immunity, and enhanced laboratory techniques have contributed to a more ‘educated’ monitoring of immune response, although these measured responses often remain surrogates for protection against infection [55].

In this thesis, the intradermal delivery of Hepatitis B vaccine (chapter 5), yellow fever vaccine (chapters 6 and 7) and rabies vaccine (chapter 8) is discussed, as a method to reduce vaccine dose or enhance vaccine-induced immunity.

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