An Analysis of the Health Risks Associated With International Travel

Dissertation submitted in fulfilment of the degree of MD at the National University of Ireland, Galway

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DECLARATION OF ORIGINALITY

I hereby declare that this thesis is entirely my own work and that I have comprehensively and accurately acknowledged the writings, ideas and work of others. This volume contains material previously published by me and permissions have been received from my co-authors and the publishers to include the work in this thesis. All attributions are elaborated in the text. Where research required the assistance of others, their contributions have been fully acknowledged in the relevant sections of the thesis. Furthermore, this work has not been submitted by me in the pursuance of another degree.

Gerard Thomas Flaherty

January 27, 2015

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DEDICATION

I dedicate this thesis to my sister and Godmother, Geraldine Hession, whose kindness, empathy, and integrity have inspired me throughout my life. Thank you, Geraldine, for all your support, encouragement and excellent example. We both share a belief in the wonderful value of education and you have helped me to achieve my academic potential.

QUOTATION

"Twenty years from now you will be more disappointed by the things you didn't do than by the ones you did. So throw off the bowlines, sail away from the safe harbor. Catch the trade winds in your sails. Explore. Dream. Discover."

Mark Twain (attributed)

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RELEVANT CONFERENCE PRESENTATIONS IN TRAVEL MEDICINE

1. **G Flaherty**, G Fry, T O'Brien. Awareness of the health risks associated with travel to high-altitude destinations. Poster presentation at the 2006 Northern European Conference in Travel Medicine, Edinburgh, Scotland.
2. **G Flaherty**, J Donnellan, T O'Brien. Exploring malaria awareness in the African Visiting Friends and Relatives population in the West of Ireland. Poster presentation at the 2008 Northern European Conference on Travel Medicine, Helsinki, Finland.
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Summary

This thesis, submitted for the award of a doctoral degree in Medicine, represents an attempt to collate all of my original research projects in travel medicine over the last eight years. Chapter 1 presents four projects relating to the theme of knowledge, attitudes and practices in travel medicine, covering the travel health awareness of diverse groups including travel agents and university students. It also explores the issue of itinerary uncertainty and its influence on the pre-travel consultation. Results of a major airport survey conducted in Malaysia complete this chapter. I have a particular interest in the health needs of travellers with pre-existing medical conditions, and Chapter 2 highlights the burden of comorbidities in travellers attending a specialist travel medicine clinic, the risks associated with stem cell tourism, and pre-travel health advice for patients with diabetes mellitus. Chapter 3 is the most extensive chapter in this thesis and it reflects my passionate interest in high altitude medicine. In it I report on projects which examined the awareness of altitude-related health risks among travellers and the quality of advice available online, the issues of travelling with complex underlying medical problems, the pathogenesis of high altitude illness, and high altitude cerebral oedema in particular, the use of pulse oximetry to facilitate a safer ascent profile, and the importance of portable hyperbaric chambers at altitude. Chapter 4 reports the findings of four studies I completed relating to tropical infectious diseases relevant to travel medicine, specifically malaria in the VFR population, prevention of rabies and dengue infection, and the current practices of licensed yellow fever vaccination centres in Ireland. Chapter 5 focuses on issues affecting the returned traveller, including the quality of travel histories recorded when assessing patients with travel-related infectious diseases, and the ability of emergency physicians and nurses to recognise tropical infectious diseases. The pathophysiology and prevention of jet lag complete the chapter. My medical education background has informed my approach to teaching and learning in travel medicine, and Chapter 6 presents some of my educational innovations in this field. The final section of my thesis results from a collaboration with medical students from Brazil and compares travel medicine practice in the British Isles and Latin America.

Anailís ar na Rioscaí Sláinte a Bhaineann le Taisteal Idirnáisiúnta

Achoimre

Is iarracht atá sa tráchtas seo, a leagaim isteach don chéim dhochtúireachta sa leigheas, gach tionscadal taighde i leigheas an taistil a rinne mé le hocht mbliana anuas a chomhtháthú. Cuireann Caibidil a hAon ceithre thionscadal – a bhaineann le téama an eolais, meon agus cleachtais i leigheas an taistil – i láthair. San áireamh anseo, tá feasacht i gcás grúpaí éagsúla, gníomhairí taistil agus daltaí ollscoile, mar shampla. Téann sé i ngleic chomh maith le ceist na neamhchinnteachta maidir leis an gcúrsa taistil agus a thionchar sin ar an gcomhairle réamhthaistil. Cuirtear torthaí mórshuirbhé aerfoirt a rinneadh sa Mhaláis i láthair sa chéad chaibidil freisin. Tá suim faoi leith agamsa i riachtanais taistealaithe a bhfuil galair leighis reatha orthu, agus leagann Caibidil a Dó béim ar ualach na gcomhghalrachtaí ar thaistealaithe ag clinic speisialta do leigheas an taistil; pléitear freisin an baol a bhaineann leis an turasóireacht ghaschille agus comhairle réamhthaistil d'othair a bhfuil diaibéiteas orthu. Is í Caibidil a Trí an chaibidil is mó sa tráchtas agus léiríonn seo an tsuim phaiseanta atá agam sa leigheas airde. Sa chaibidil seo déanaim cur síos ar thionscadail a scrúdaigh feasacht taistealaithe i leith an bhaoil a bhaineann le bheith ar airde agus caighdeán na comhairle atá ar fáil ar líne, cúrsaí a bhaineann le taisteal agus fadhbanna casta leighis ag dul don duine, pataigineas an tinnis ard-airde, éidéime cheirbreach ard-airde ach go háirithe, úsáid tomhais ocsaigine chun modh dreaptha níos sábháilte a éascú, agus tábhacht na gcuasán hipearbarach iniompartha. Déantar tuairisciú ar thorthaí ceithre thionscadal i gCaibidil a Ceathair: tionscadail faoi ghalair thógálacha thrópaiceacha a bhfuil baint acu le leigheas an taistil; maláire i measc an phobail ón Afraic atá lonnaithe in Éirinn ach a thugann cuairt ar a dtír dhúchais, cosc confaidh agus fiabhrais deinge, agus na cleachtais reatha i gcoinne an fhiabhrais bhuí a fheictear in ionaid vacsaínithe in Éirinn. Díríonn Caibidil a Cúig ar na ceisteanna a bhaineann le taistealaithe a thagann ar ais go hÉirinn, caighdeán na staire taistil sna taifid míochaine, agus cumas dochtúirí agus altraí a oibríonn sna Ranna Éigeandála galair thógálacha thrópaiceacha a aithint. Tá mír faoi phataigineas agus cosc tuirse aerthurais ag deireadh na caibidle sin. Sa chaibidil dheiridh, déanaim cur síos ar nuálaíochtaí oideachais a raibh mé freagrach astu i gcás leigheas an taistil. Is comparáid atá sa chuid dheireanach den tráchtas idir staid leigheas an taistil in Éirinn agus an Bhreatain Mhór agus sa Bhrasaíl.

CHAPTER 1

Knowledge, Attitudes and Practices in Travel Medicine

1.1. Travel Agency Awareness of Travel Health Risks

Introduction

Travel agents occupy a central role in the travel industry and may be consulted by intending travellers seeking pre-travel health advice. It is important that front-line travel agency staff are equipped to deal with such queries and have access to sources of reliable travel health information. This is especially important when so-called last minute travellers book their trips with a travel agent very shortly before departure, when insufficient time remains to attend a travel medicine specialist. Travel agencies represent an important potential source of basic information about malaria, recommended travel vaccinations, and other health risks. Little is known about the capacity of travel agency personnel to provide essential health information to travellers. Previous studies highlighted deficiencies in the health-related advice provided by travel agencies in the United Kingdom[1], and in Switzerland.[2] The present study was the first of its kind to examine the situation pertaining to the travel agency sector in the Republic of Ireland.

Aims and Objectives

The aim of this study was to establish the level of knowledge of travel health risks among a sample of Irish travel agents in an effort to identify travel health educational needs in this community.

Specific objectives included the following:

1. To describe the approach of travel agents to clients seeking pre-travel health advice, and their confidence in providing such advice.

2. To assess the level of knowledge of travel agents with regard to the geographical distribution of major tropical diseases and their mode of spread.

3. To explore the awareness of sources of specialised travel health advice among the travel agent community in Ireland.

4. To identify training needs of travel agents in relation to travel health.

Methods

The protocol for this study met the requirements of the local research ethics committee. A 16-item questionnaire was developed and refined following a piloting process. Permission was obtained from the Irish Travel Agents Association (ITAA) to distribute the web-based questionnaire, created on Survey Monkey®, anonymously to its members via an emailed web link. ITAA represents some 100 companies in 140 branches throughout the Republic of Ireland. Data were analysed using descriptive statistical functions in Microsoft Excel.

The questionnaire sought information regarding the travel agents' usual practices in relation to requests for travel health information received from clients. Respondents were asked to estimate the proportion of travellers who had insufficient time remaining before departure to consult a healthcare professional. They were asked if they provided health information leaflets to clients, whether a series of popular holiday destinations presented a risk of contracting malaria, how a series of named tropical infectious diseases were transmitted, and they were asked to rate their level of confidence in providing basic travel health advice on a range of possible exposures, including sun injury, animal bites, insect bites, and food and water safety.

Travel agents were presented with 11 common holiday itineraries and asked to consider whether the travellers concerned should be referred to a specialist travel medicine clinic in each case. They were also asked how frequently they advise travellers to purchase travel medical insurance. The survey also enquired about the travel agents' training, if any, in travel health, and which educational activities they would favour from a list of 6 options provided.

Results

Approach to travel health-related queries

Responses were received from 24 travel agents. 63% of travel agents reported that travellers seek their advice about the health risks faced in their chosen destination frequently, very frequently or always. The majority of travel agents (74%) identified travel medicine specialists as their preferred source of pre-travel health advice, followed by General Practitioners (GPs, 57%) and GP practice nurses (39%). Most travellers (90%) attend their travel agency with sufficient time remaining to consult with a healthcare professional before they depart. The majority of travel agents (81%) welcomed an opportunity to speak to a travel medicine specialist in response to an enquiry from a client. Over two thirds of travel agents (67%) believed that a closer professional relationship with a travel medicine clinic would help them to provide an enhanced service to their own clients.

Travel agent knowledge of travel health issues

The travel agents surveyed demonstrated satisfactory levels of awareness of the global distribution of malaria, but they incorrectly identified a malaria risk in the following popular tourist destinations: Cape Town (42%), Rio de Janeiro (50%), Inca trail (83%), Japan (33%) and Fiji (24%). There was a poor level of knowledge of the mode of transmission of the following infectious diseases to travellers: hepatitis A, polio, Japanese B encephalitis, yellow fever and schistosomiasis. A significant proportion of the travel agents surveyed would not recommend that travellers on the following itineraries obtain pre-travel health advice: a 1-year trip to Australia on a working visa with visits to New Zealand and Fiji (50%); a 2-week Mediterranean cruise (100%); a Trans-Siberian railway crossing (40%); a 2-week trip to Beijing for the 2008 Olympic Games (42%), and a 1-week package holiday in Tunisia (91%).

Travel agents expressed generally low levels of confidence in providing basic pre-travel health advice to travellers relating to a range of travel health risks (Figure 1.1), with the highest levels of confidence recorded for air travel advice and jet lag, and the lowest levels of confidence expressed for provision of

information about animal bites, sexually transmitted infections, insect bites, and altitude.

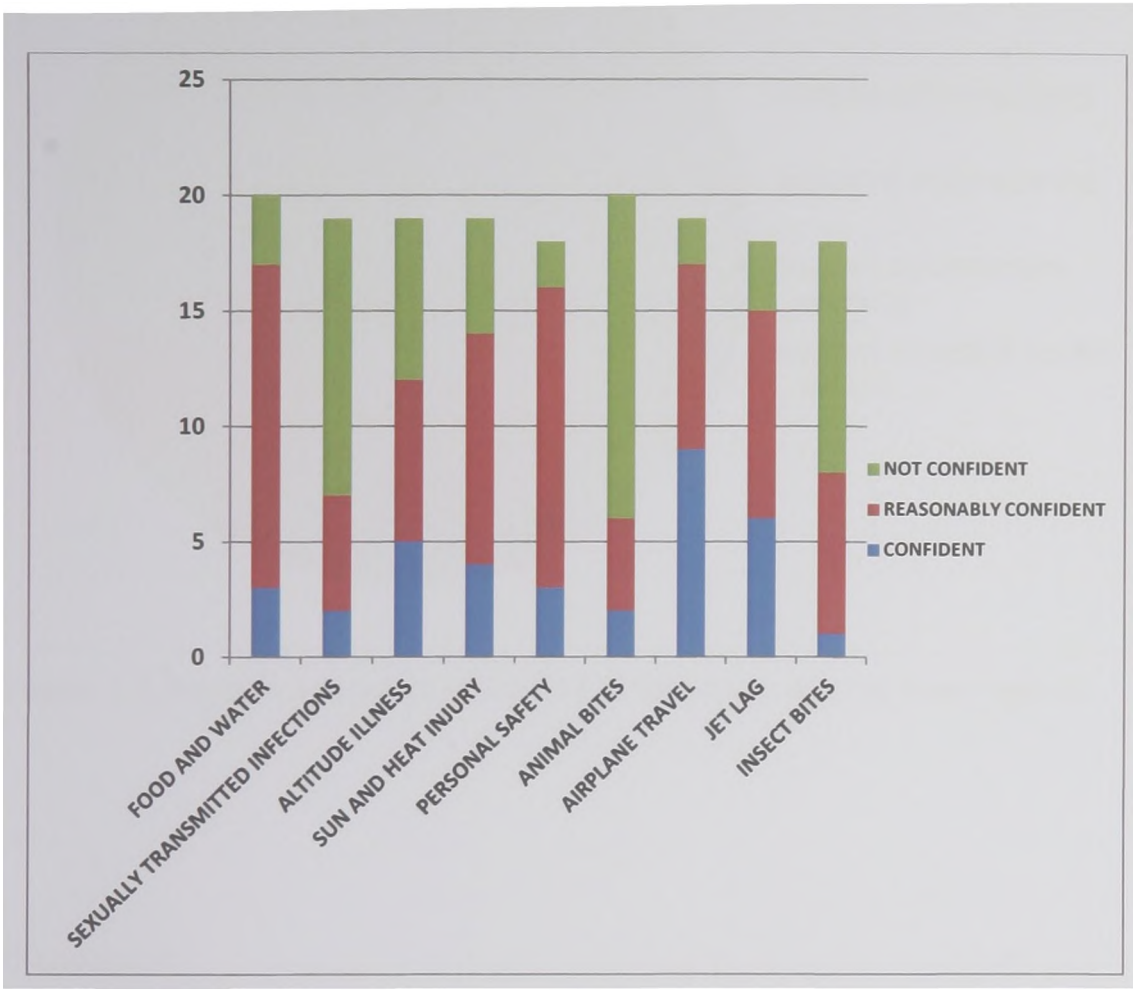

Figure 1.1 Travel agent confidence in the provision of travel health advice

The vast majority of travel agents surveyed expressed a desire to receive or update their existing knowledge in travel health through various educational channels (Figure 1.2), with particular preference given to a user friendly website and an information booklet. A minority of travel agents (32%) provided travel health information leaflets to their existing clients.

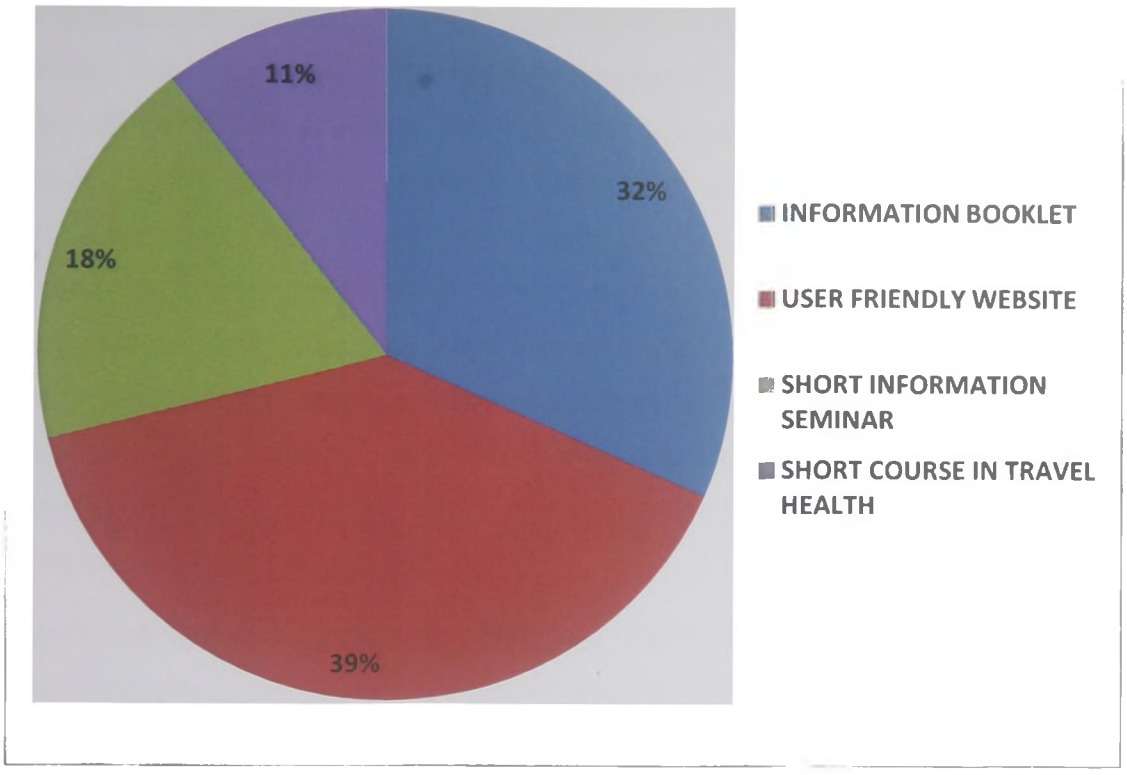

Figure 1.2 Preferred sources of travel health advice among travel agents

Discussion

This study, limited though by its small sample size, provides valuable insights into the current practices of travel agency professionals operating in the Republic of Ireland. The finding that nearly two thirds of travel agents are regularly faced with travel health queries from their client travellers underscores the importance of this group as a source of preventive advice, especially where the traveller has chosen to forgo or bypass advice from a healthcare professional. This is especially critical in the case of a last minute traveller, although these were only encountered about 20% of the time in the sample of travel agents surveyed. In a larger study conducted in 202 travel agencies throughout the UK[1], the researchers found that no spontaneous health advice was offered in 61% of consultations involving destinations which were endemic for malaria. After receiving a prompt from the covert researchers, 71% of the agents surveyed provided general health advice,

67% suggested that the client seek professional malaria advice from a GP, and 37% of agents specified that malaria chemoprophylaxis was indicated for the particular itinerary involved. The authors concluded that travel agents provided health advice in an inconsistent fashion, mentioning travel health risks only when prompted by the traveller. In a study of 88 Swiss travel agencies[2], unprompted health advice was offered in 44% of all consultations. This improved to 99% of all travel agents following prompting by the covert researcher, but only 69% of travel agents suggested the need for travel vaccinations. In a study of 163 registered travel agencies in Cuzco, Peru, it was found that the majority of travel agencies failed to provide adequate information regarding the risks and prevention of malaria and yellow fever to travellers contemplating trips to the southern Amazonian region of Peru.[3]

Underestimation of risk was apparent from the findings of this study, with several popular itineraries being evaluated as low risk. This may have stemmed from a misperception about the likely environmental exposures involved, or from a tendency to attribute low risk to short duration vacations where railway or cruise ship travel is employed, for example. There was a striking lack of confidence among travel agents in their ability to provide basic preventive advice to the travelling public, particularly in relation to sexually transmitted infections, high altitude, insect bites, and animal bites. This is worrying given the potentially devastating consequences of contracting HIV infection, high altitude pulmonary or cerebral oedema, malaria, and rabies, all of which can be avoided by promoting careful behavioural responses in the travelling population. There may be an embarrassment factor at play in the case of sexually transmitted infections, and the travel agent may feel constrained by the restrictions imposed by their commercial relationship with the client and the personal nature of some of the advice required.

The majority of travel agents in this study welcomed a greater level of cooperation between their industry and specialist travel medicine practitioners, and there is scope for distributing standardised health information leaflets to all travellers who book their holidays through travel agencies, especially given the fact that so few travel agents provide health information leaflets of their own. Schwitz and colleagues[2] stressed the need to make accurate information about

travel health risks freely available to travel agencies and to develop structured training for travel agencies in conjunction with healthcare providers. There is a similar need to make reliable information accessible for travellers who arrange their travel plans entirely online without the intervention of a travel agency, and the current practices in this regard are deserving of detailed study.

Conclusions

This study highlights the need to educate travel agents on travel-related health risks and travel health advice provision in order to safeguard the welfare of their travelling clients. Until greater cooperation exists between travel agencies and local travel medicine clinics, travel agents should routinely refer their clients to the patient's GP if their travel plans permit. The study was limited by its small sample size and should be extended to include a larger sample of travel agents using data obtained by a covert researcher recording the actual health information provided, with and without interviewer prompting.

Acknowledgements

I am grateful to the Chief Executive of the Irish Travel Agents Association, Mr. Simon Nugent, for his assistance in providing access to his members for the purposes of distributing the questionnaire used in this study.

1.2. Travel Itinerary Uncertainty and the Pre-Travel Consultation

Introduction

Accurate risk assessment in travel medicine relies on the quality of the information obtained from the traveller during the pre-travel consultation. Inaccurate or misleading information based on uncertainty about the proposed travel itinerary could limit the ability of the travel medicine practitioner to give specific protective travel health advice. There has been very limited discussion in the literature on this important subject. There is a need to determine the extent to which travellers are uncertain about their travel itinerary at the time of their pre-travel consultation and the effect of this uncertainty, if any, on the effectiveness of the consultation.

It is generally accepted in travel medicine practice that pre-travel health advice should be individualised to the specific needs of individual travellers based on a detailed analysis of their anticipated travel itinerary. With the relative ease of modern intercontinental travel and the flexibility offered by the accessibility of web-based travel information, there may be a tendency for the traveller to give suboptimal consideration to the detailed aspects of their travel plans, including exact destinations within countries, visits to altitude or other wilderness environments, mode of transport, accommodation type, access to preventive equipment such as mosquito bed nets, and planned activities, including adventure travel, and participation in water sports. The unwary travel medicine physician may not develop essential elements of the pre-travel consultation if the traveller expresses doubt about their travel intentions. Travellers may have a false sense of security based on previous experience, luxury air travel or hotel accommodation, reassuring online commercial information about their destinations, sanitised reports from friends or relatives, or a desire to avoid reflecting on the potentially negative aspects of a vacation.

Many travellers confirm their travel plans at short notice because of work vacation restrictions or last minute travel deals available online. These so-called last minute travellers may short circuit key steps in their preparation for travel and are less likely to anticipate how their travel plans may be disrupted by unforeseen circumstances such as transport delays or strikes, extreme weather conditions, political unrest, or outbreaks of communicable diseases at or en route to their

proposed destination. It is imperative that the travel medicine practitioner is competent at extracting key points of information from the uncertain traveller and at alerting all travellers to the possibilities of sudden, unplanned changes to their itineraries and the additional preventive measures which should be adopted in these situations. These may include the avoidance of specific exposures, recommendation of additional travel vaccinations, prescription of malaria chemoprophylaxis, and advice regarding the prevention of high altitude illness.

Aims and Objectives

The aim of this study was to explore the degree of uncertainty expressed by a sample of travellers attending a travel medicine clinic in Ireland about aspects of their travel itinerary. Specific objectives included the following:

1. To characterise the level of uncertainty surrounding dates of travel, destinations, mode of transport, accommodation choices, possibility of trekking, and possible travel to malaria endemic areas.

2. To describe any effect of traveller uncertainty on the capacity of the travel medicine specialist to perform a comprehensive risk assessment, select vaccinations, give malaria advice and prescribe malaria prophylaxis.

Methods

This low-risk study met the requirements of the local research ethics committee. A 14-item questionnaire was administered by an experienced travel medicine physician to 83 consecutive travellers attending a specialist travel medicine clinic in Ireland. The travellers were asked to declare their level of certainty about various aspects of their proposed trip. The travel medicine practitioner recorded the extent to which uncertainty about travel plans impacted upon the effectiveness of the travel medicine consultation. Data were entered into a Microsoft Excel database and analysed using descriptive statistics.

Results

Most travellers belonged to the 21-30 year age group and were mainly professionals or skilled workers. Seventy percent of travellers attended their consultation with over a month remaining before departure (Table 1.1). The majority of travellers planned to visit South East Asia (Figure 1.3). The principal reasons for travel were for holidays or backpacking (Figure 1.4). Levels of traveller certainty were highest in relation to the following variables (Figures 1.5, 1.6): travelling companions (95%), intention to obtain travel insurance (93%), and date of departure (92%). Moderate levels of certainty were revealed in relation to countries to be visited (70%), intention to trek (58%), date of return (57%), the need to book internal flights (53%), intention to visit jungle regions (52%), and the order in which they would visit the countries (51%).

Table 1.1 Demographic details of travellers

Traveller characteristic	Frequency (%, n)
Gender	Male: 49% (n=40) Female: 51% (n=41)
Age profile	<20yrs: 1% (n=1) 21-30yrs: 83% (n=67) 31-40yrs: 12% (n=10) 41-50yrs: 1% (n=1) 51-60yrs: 1% (n=1) 61-70yrs: 1% (n=1)
Traveller occupation	Student: 9% (n=7) Unskilled/semi-skilled: 26% (n=20) Skilled worker: 22% (n=17) Professional: 37% (n=29) Unemployed: 6% (n=5)
Time remaining before departure	<7 days: 5% (n=4) 8-14 days: 8% (n=7) 15-21 days: 8% (n=7) 22-28 days: 8% (n=7) 29-35 days: 17% (n=14) 36-42 days: 12% (n=10) 43-49 days: 8% (n=7) 50-56 days: 6% (n=5) >56 days: 27% (n=22)
How was the trip booked?	Internet: 36% (n=28) Travel agents: 64% (n=50)

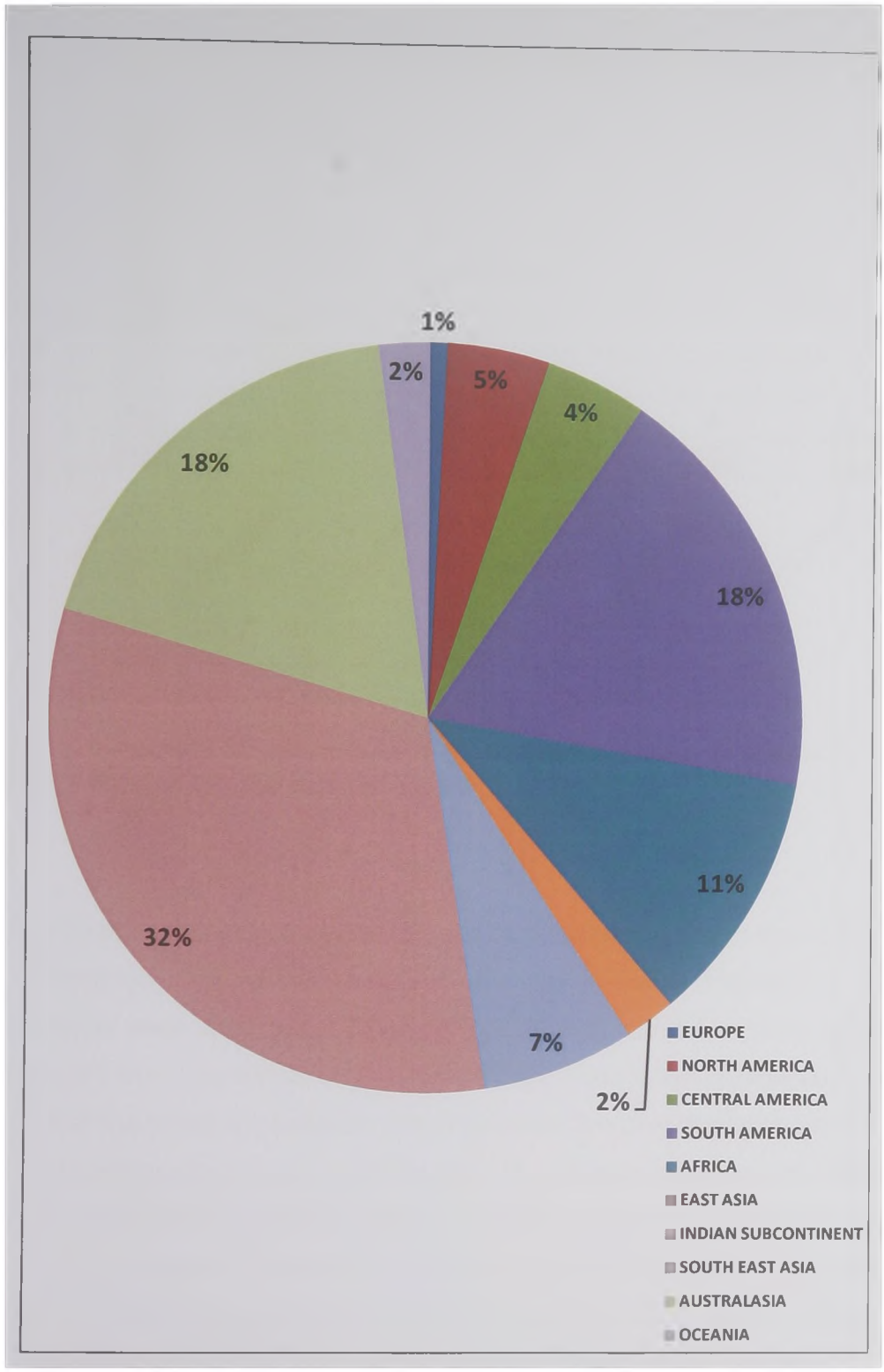

Figure 1.3 Destination profile of study participants

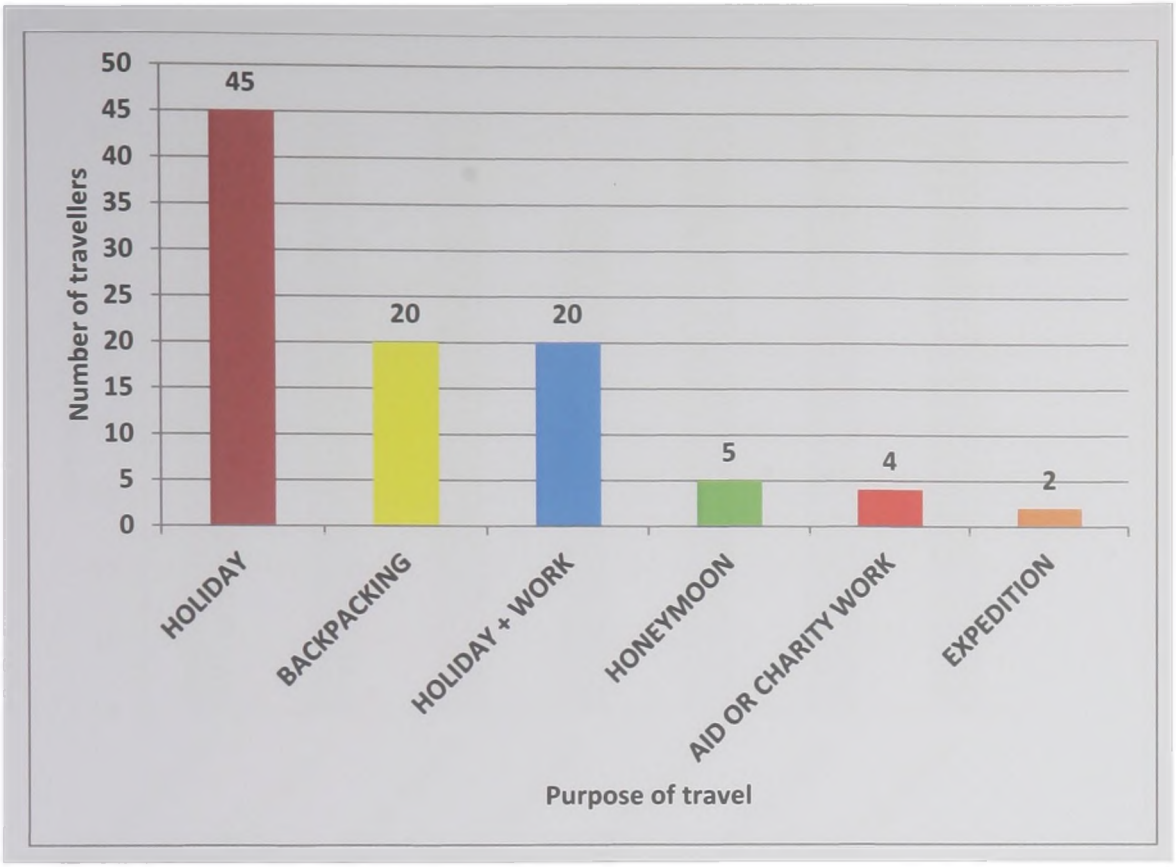

Figure 1.4 Declared purpose of travel

The majority of travellers were uncertain about destinations within the countries, mode of transport within countries or type of accommodation (Figures 1.5, 1.6). Most travellers were uncertain if they would be visiting malaria regions, and 82% were unsure if bed nets would be provided locally. Over a third of travellers believed that the travel consultation which followed the questionnaire helped them to make decisions about their travel itinerary. The degree of uncertainty about itinerary had a significant impact on the ability of the travel medicine specialist (Figure 1.7) to perform an adequate risk assessment (42%), select appropriate vaccinations (33%), counsel about malaria prevention (49%), and prescribe malaria prophylaxis (50%). A repeat malaria consultation due to traveller uncertainty was necessary in 26% of travellers, where a visit to a malaria endemic region was deemed probable (Figure 1.8).

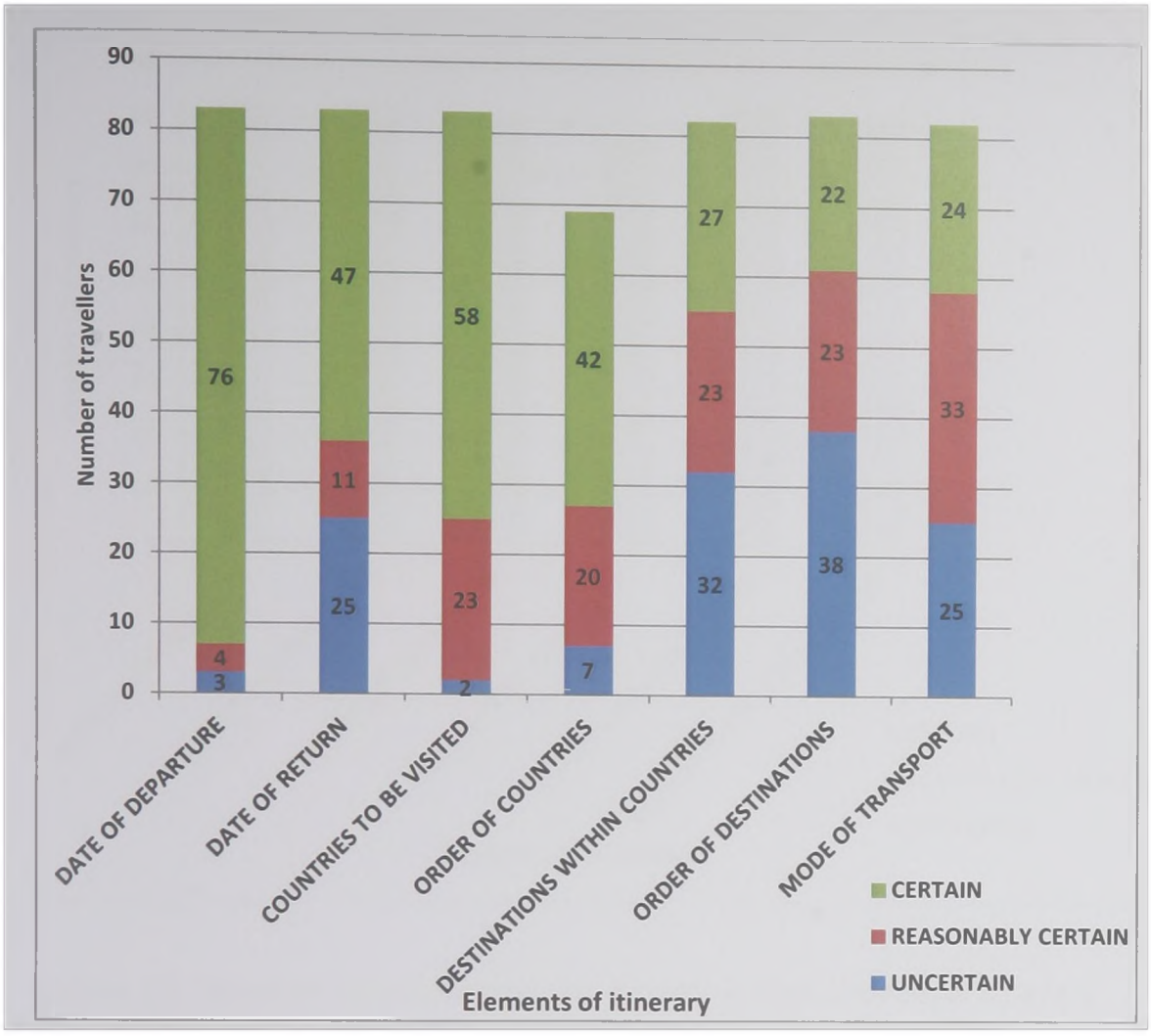

Figure 1.5 Traveller uncertainty levels regarding their travel plans

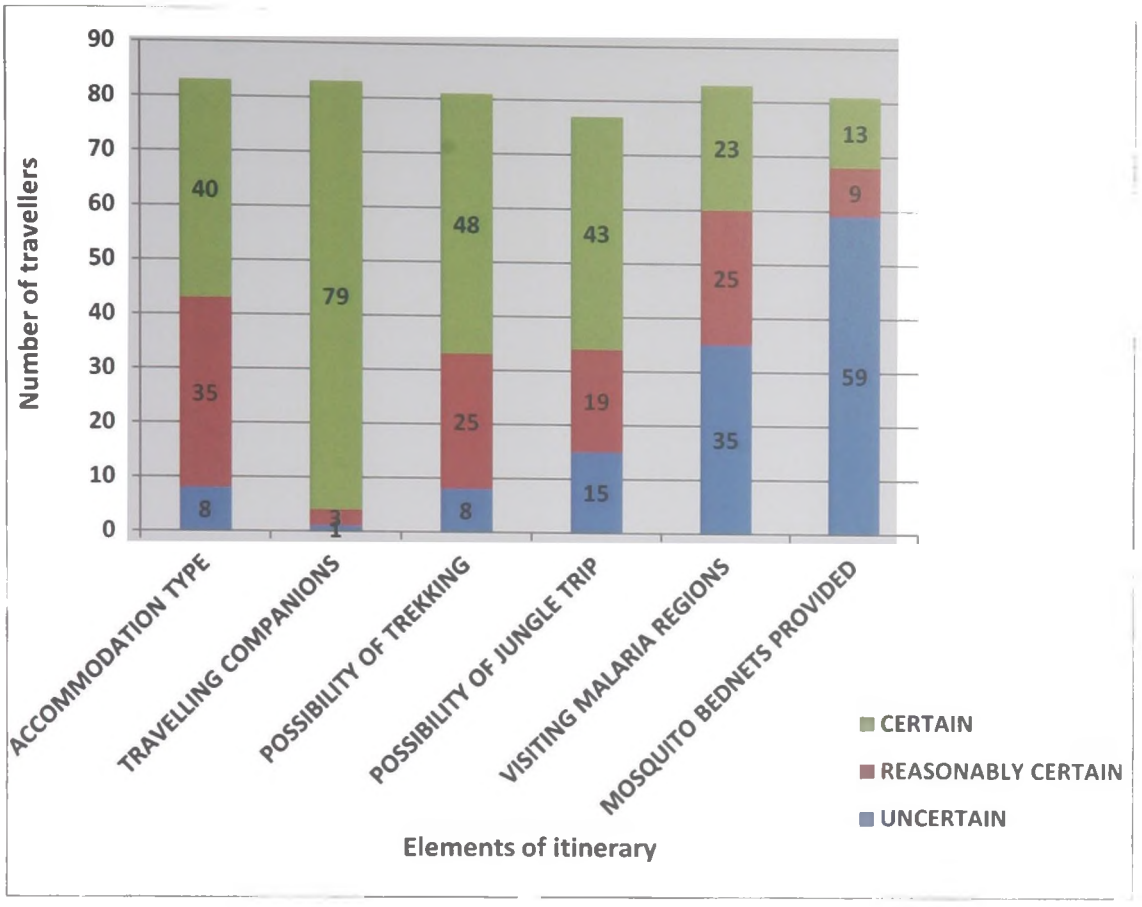

Figure 1.6 Traveller uncertainty levels regarding their proposed itinerary

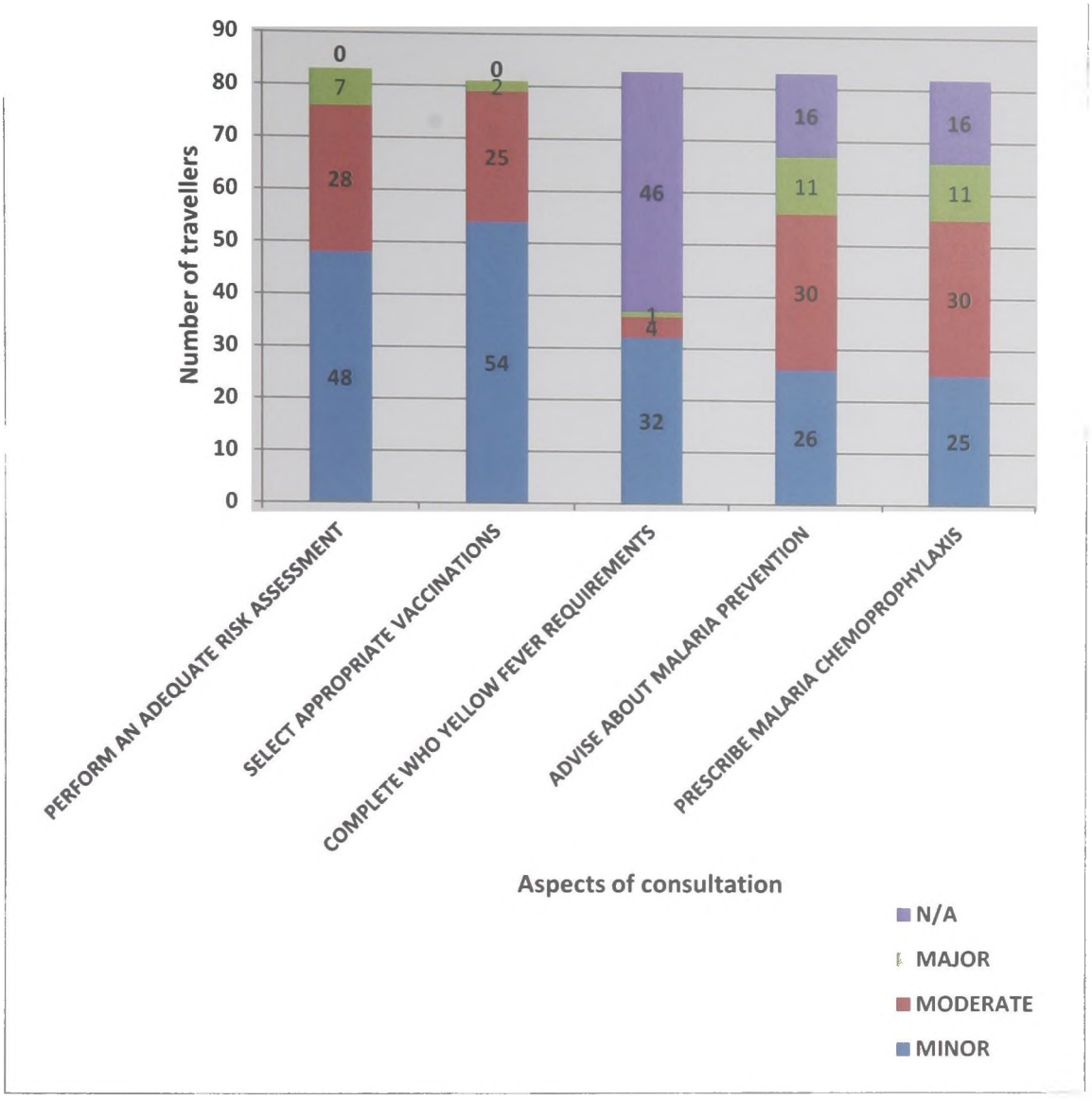

Figure 1.7 Influence of traveller uncertainty on pre-travel consultation

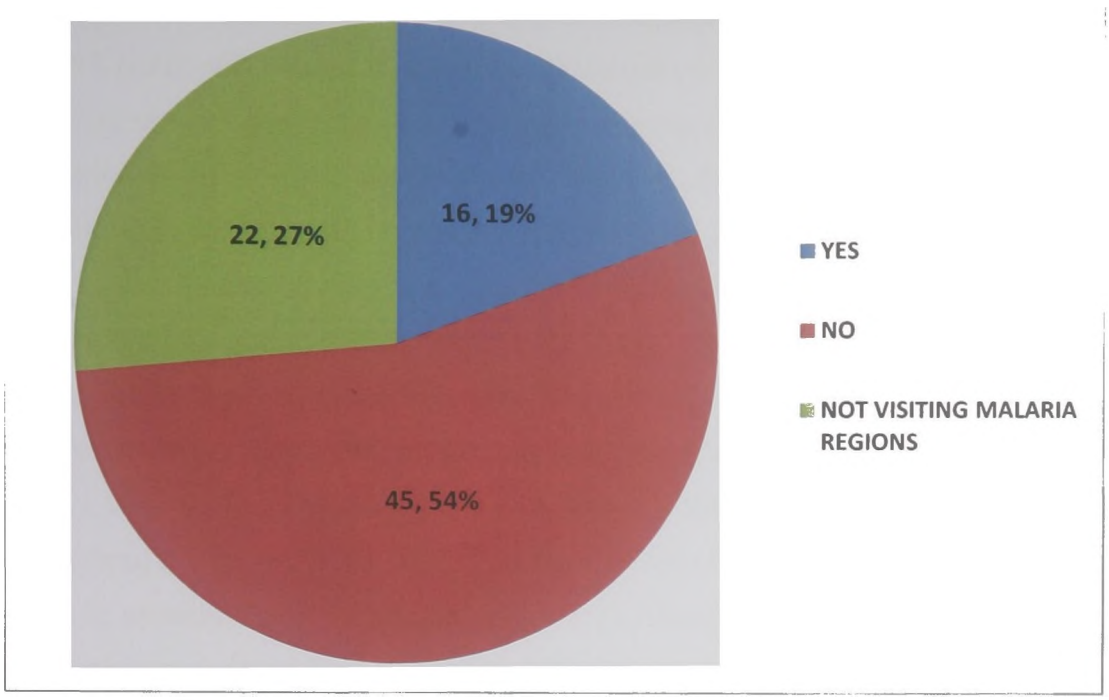

Figure 1.8 "Did traveller uncertainty necessitate a further consultation to prescribe malaria chemoprophylaxis?"

Discussion

Chen argues that for a pre-travel consultation to be effective, it requires due consideration of the medical background of the traveller, the itinerary, duration of travel, travel style, and planned activities during travel.[4] This advice must be personalised to the individual traveller, and should highlight the likely exposures, as well as discussing ubiquitous health risks resulting from injury, ingestion of contaminated food and water, and sexually transmitted infections. The present study exposes an infrequently discussed facet of the travel health consultation, that of travellers' preparation, and specifically knowledge of their travel itinerary.

Almost 30% of travellers interviewed visited the travel medicine clinic with less than 4 weeks remaining before their intended departure date, which itself was certain in the majority of cases. The traveller sample was representative of travellers attending the clinic in question, with 84% being under the age of 30 years. It is the author's impression that the older traveller is generally more prepared for their travels and favours package holidays booked though travel agencies rather than booking their holiday piecemeal online. There was

considerable doubt expressed by the predominantly younger travellers in the present study with regard to some fundamental components of their journey, including country destinations, destinations within countries, and the predicted sequence of travel within and between countries. Duration of travel was even undecided in 43% of travellers surveyed. Such doubt will inevitably hinder efforts by the travel health adviser to conduct a comprehensive travel risk assessment, to provide country-specific information, and to tailor that information to the exact schedule of travel within the countries in question.

Since many countries in South East Asia, the most visited destination in this survey, and South America have a non-uniform distribution of malaria risk throughout the country, it is difficult even with reference to malaria distribution maps to provide definitive information to the undecided traveller. Practical time constraints may impede the travel health provider from giving advice relating to all of the possible exposures in a given trip, and it is conceivable that, where uncertainty is expressed, the travel health consultation may be too narrow in its scope and too general in its focus.

This study also demonstrated a surprising lack of certainty among travellers about their mode of transport and accommodation arrangements. Since road traffic accidents are the single greatest cause of travel-related mortality[5], it is worrying that travellers do not give due attention to their prevention. Uncertain travellers may be more likely to hire a motor vehicle after arriving jetlagged at an international airport, take an unplanned journey on a local ferry boat to save time driving, or choose to be passengers on motorcycle taxis, where frequently the driver is seen to wear a helmet but the passenger is not offered one.

Travel to exotic destinations may increase risk-taking behaviour and encourage travellers to engage in adventurous activities they would eschew in their own countries. In this study, 42% of travellers were uncertain about whether they would be trekking during their trip, and 48% were unsure if their travel itineraries would include a visit to a jungle environment. High altitude trekking may expose the traveller, particularly the inexperienced traveller, to a wide range of health risks, including trauma from rock falls or avalanches, high altitude illness, frost bite and hypothermia, while jungle treks carry a multitude of risks including mosquito-borne infections such as malaria, envenomations, heat injury and drowning. The responsible traveller should avoid embarking on travel where due attention has

not been given to these possible excursions, even if they are completed under supervision from licensed commercial tour operators. There may be an unrealistic perception on the traveller's part that the local tour operators will mitigate all such health risks and that evacuation capabilities are highly developed even in remote wilderness locations.

This study also attempted to analyse the effect of traveller uncertainty on the effectiveness of the travel health consultation. There may be a degree of observer bias at play as the researcher was conducting the travel health consultation and this aspect of the study should be explored in follow up studies where the researcher is independent from the consultation. Nevertheless, some interesting trends were observed which are worthy of reflection. Traveller uncertainty was deemed to negatively influence the quality of the risk assessment in 42% of cases, the ability to appropriately prescribe travel vaccinations in 33% of travellers, and to prescribe malaria chemoprophylaxis with confidence in half of all cases.

Where it was established that the traveller was likely to visit an area endemic for malaria, the degree of itinerary uncertainty prompted the travel health physician to arrange a follow up brief malaria consultation during one of the traveller's return visits to the clinic for the purposes of receiving booster doses of travel vaccines. Clear direction was provided about the most common travel scenarios in the country or countries involved and colour malaria distribution maps were provided to the traveller to study in the interim. Whether or not the finalised itinerary presented during the return visit truly represents the actual itinerary is unknown and deserving of further study.

David Schlim, a former President of the International Society of Travel Medicine, encourages travel medicine providers to advance an understanding of the concept of traveller commitment, whereby certain inherent travel-related risks must be accepted, such as the difficulty or impossibility of rescue from a remote trekking environment.[6] He also challenges travel medicine practitioners to reflect on their own risk perception and tolerance, so that they can counsel travellers to find their own comfort level when reaching decisions about destination itineraries, activities, and preventive actions. Much attention has been given in the recent travel medicine literature to the concept of applying numerical risk data to the health advice conveyed in the pre-travel consultation in order to empower travellers to make informed decisions about the uptake of preventive measures.[7]

The quality of vaccine-preventable travel risks has been graded and consideration given to incorporating graded risk assessments into future versions of the "International Travel and Health" handbook, published by the World Health Organisation.[8] This study underscores the need to educate the travelling public to a greater extent about the requirements of responsible travel, which must include careful elaboration of travel plans, a greater sense of self reliance, and improved collaboration with the travel health provider so that all reasonable travel health risks may be adequately signalled in the pre-travel consultation.

Conclusions

This study reveals high levels of traveller uncertainty about important aspects of the travel itinerary which may compromise the effectiveness of the pre-travel health consultation. Travellers should be informed of the importance of planning their itineraries carefully in order to derive maximum benefit from the pre-travel consultation. The travel medicine community must be keenly aware of the limitations imposed on the travel health consultation by lack of certainty about the travel itinerary and their advice must be comprehensive enough to prepare the traveller for a wide range of possible health risks.

1.3. Travel Health Risk Awareness and Practices of University Students

Introduction

Students attending third level educational institutions represent a vulnerable group of travellers. An increasing number of students are encouraged and enabled to travel for course credit and as service volunteers.[9,10] Backpackers tend to comply with mosquito bite prevention and chemoprophylactic strategies but adherence to other travel health advice may be sub-optimal.[11] Previous travel medicine training seems to correlate with a greater quality of pre-travel health advice provided to third level students.[12] This study examines the travel patterns of university students and explores the extent to which they are aware of, and protect themselves from, travel health risks.

Methods

The protocol for this research project met the requirements of the local research ethics committee. A questionnaire was distributed electronically to all registered undergraduate Biomedical Science students attending the National University of Ireland, Galway. The survey recorded demographic information, sources of pre-travel health advice, and perceived barriers to accessing such advice. Respondents were invited to rate their likelihood of following various travel health precautions.

Results

314 students (63% response rate) responded to the survey, the majority of whom were female (71%). For students who had previously travelled outside Europe, 21% had received pre-travel health advice, 20% had received vaccinations, and 40% did not receive any form of pre-travel health preparation. The most frequently cited barrier (Figure 1.9) to obtaining pre-travel health advice was finance (44%). Students were most likely to consult family (47%), their GP (46%), and websites (43%) for travel health information. There was poor awareness (Figure 1.10) of the biting pattern of the malaria-carrying mosquito (26%), or malaria symptoms (33%). Several personal safety and security measures were not commonly observed by

these students (Figure 1.11). Several recommended travel risk reduction strategies were not routinely followed by students (Table 1.2). In particular, students were less likely to wear MedicAlert® bracelets, seek pre-travel health advice, take steps to reduce their risk of traveller's thrombosis, and avoid excessive alcohol consumption (Figure 1.12).

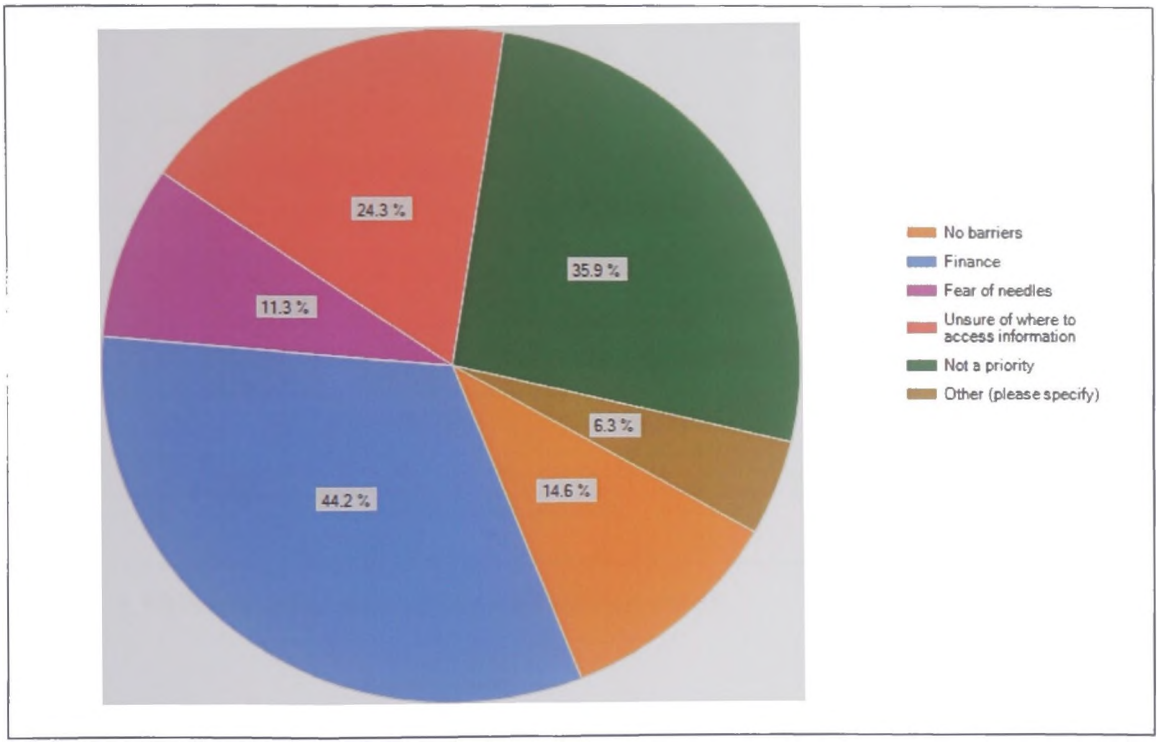

Figure 1.9 Perceived student barriers to accessing pre-travel health advice

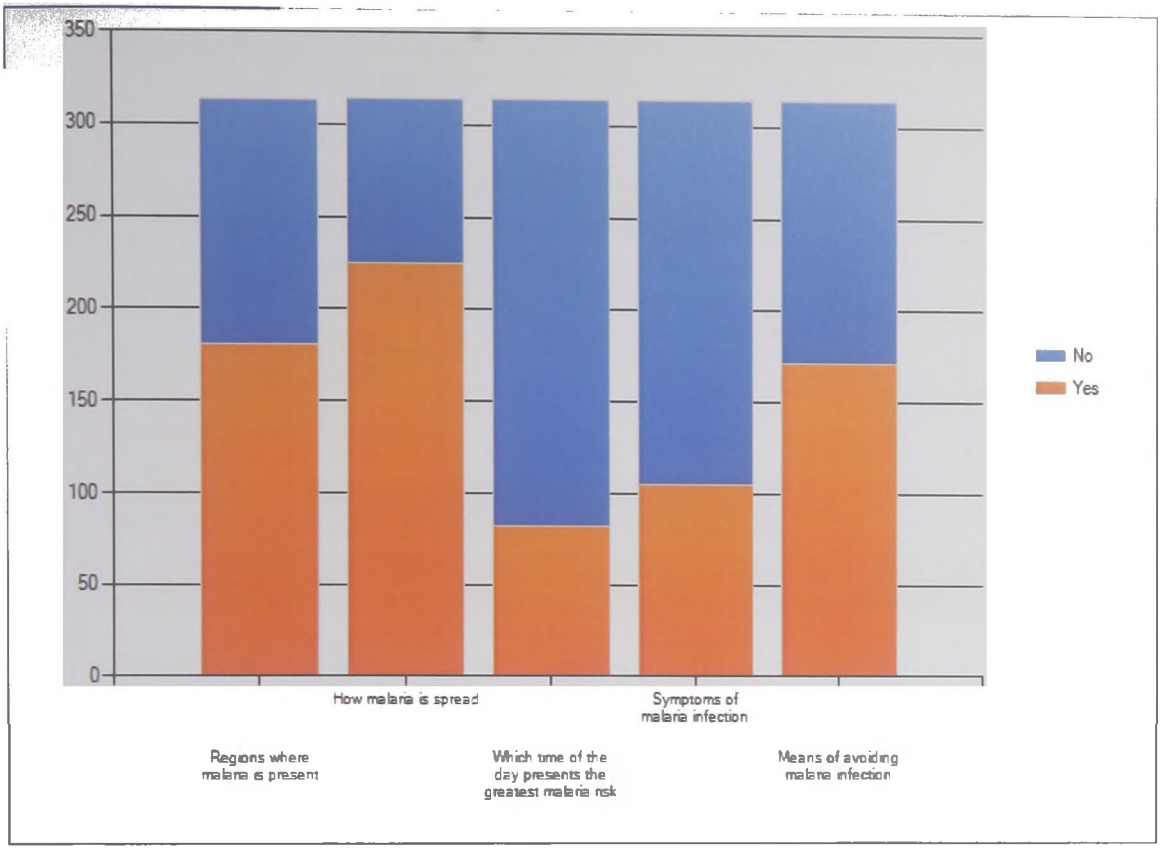

Figure 1.10 Students' awareness of malaria risk

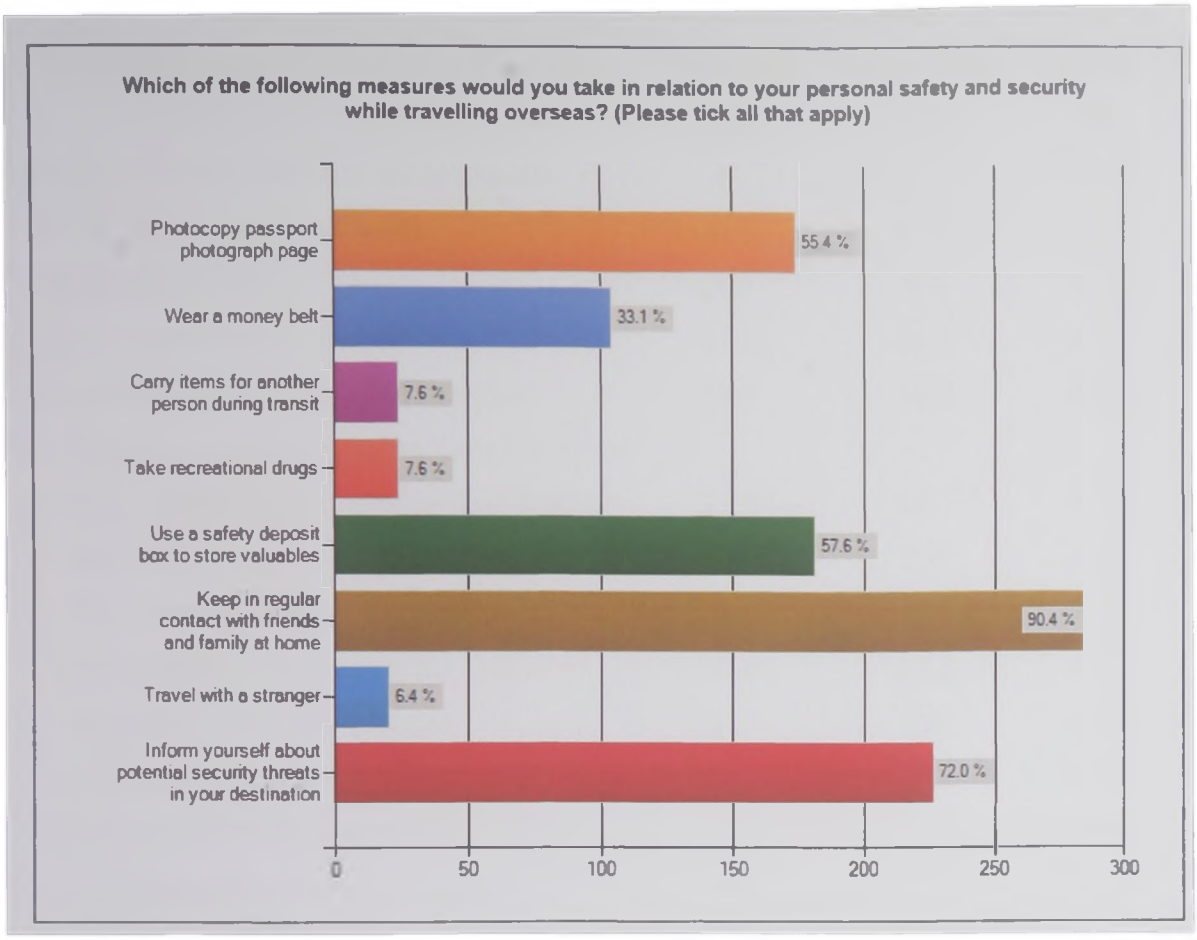

Figure 1.11 Students' awareness of traveller security and safety concerns

Table 1.2 Self-reported observation of travel health preventive measures

Recommended Preventive Measure	Unlikely (%)	Uncertain (%)	Likely (%)	N/A (%)
Avoid excessive alcohol consumption	41	9.9	45.9	4.1
Avoid unsafe food and water	6.4	6.1	87.2	0.3
Avoid unsafe sex	2.0	6.4	87.8	3.8
Hire a vehicle while abroad	41.8	21.1	34.2	2.9
Inform yourself about local disease outbreaks or weather events prior to travel	18.1	15.0	66.5	0.3
Inform yourself of the risks of high altitude	21.6	12.1	55.7	10.5
Observe precautions while swimming	8.6	7.6	80.6	3.2
Pack a comprehensive first aid kit	42.5	14.1	42.2	1.3
Plan a detailed travel itinerary	37.6	17.8	43.6	1.0
Protect your skin from the sun	3.2	2.9	93.3	0.6
Protect yourself against animal bites	15.3	15.3	67.8	1.6
Protect yourself against mosquito bites	7.7	11.3	79.7	1.3
Purchase travel medical insurance	14.4	13.1	71	1.6
Reduce risk of flight-related clots in the leg if you are a female taking the pill	25.3	16.9	23.7	34.
Seek travel health advice from a doctor	47.2	18.6	31.8	2.3
Take practical steps to reduce jet lag	45.3	16.6	37.4	0.6
Wear a bracelet/necklace indicating any serious medical conditions/allergies	23.7	5.4	13.4	57.

*N/A = not applicable

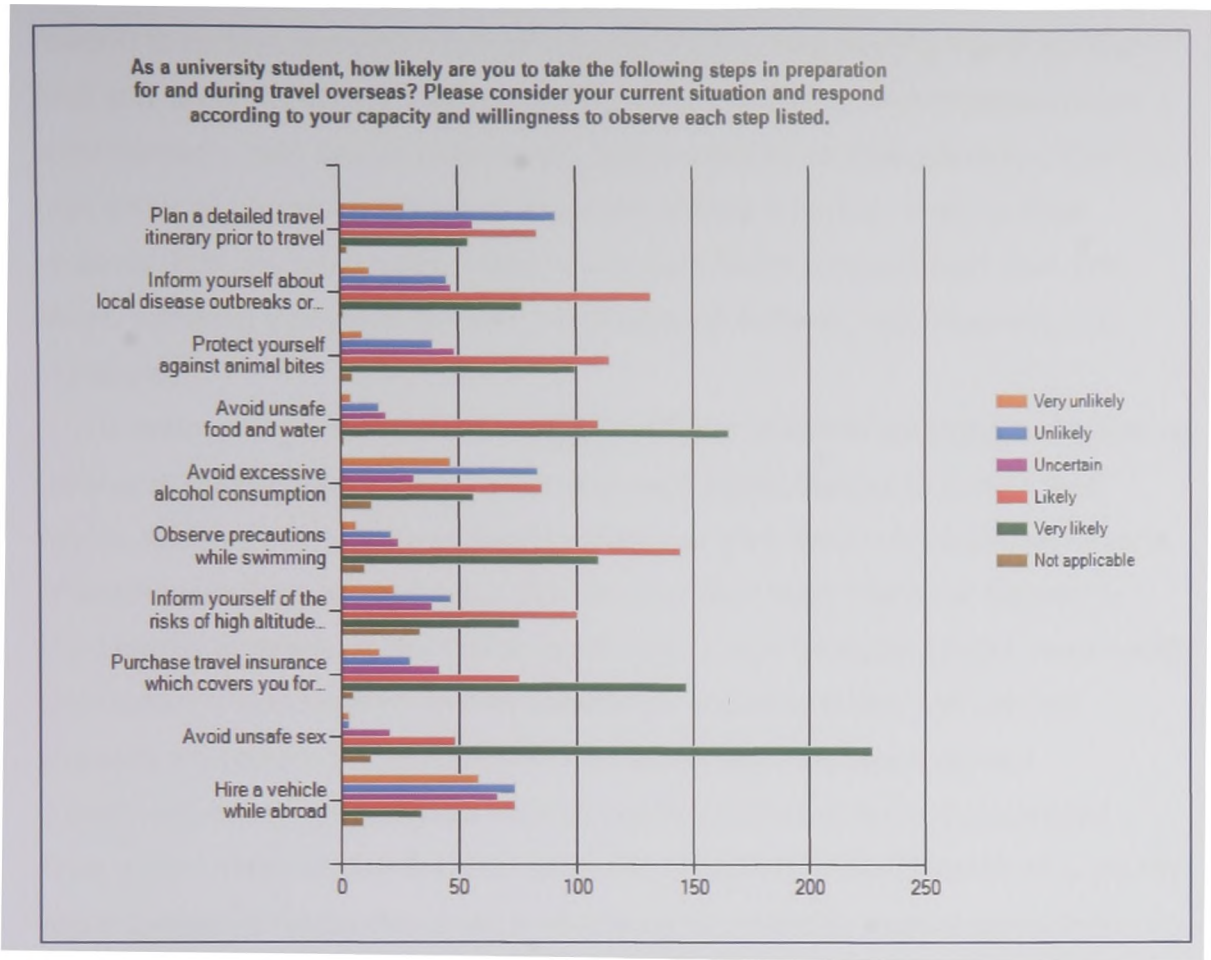

Figure 1.12 Selected travel health precautions observed by students

Discussion

The student population tends to be highly mobile, either by virtue of their course of study, such as is the case for language students, or because they travel overseas during their summer vacation, often to earn enough money to provide at least some financial independence in the following academic year. The limited budget of most students, however, often mandates that they travel by backpacking, which exposes them to a greater level of travel health risk.[12] Student backpackers may not have the luxury of avoiding street hawkers selling inexpensive food. They may also exhibit greater risk-taking behaviour by consuming larger volumes of alcohol, often available more cheaply than they could obtain it in their home country, or engaging in risky sexual behaviours in an unfamiliar environment.

The findings of this cross-sectional survey of students attending a university undergraduate programme in Ireland reveal reassuring attitudes and practices in

relation to certain preventive behaviours associated with healthy travel, such as food and water safety precautions, safety while swimming, skin protection from solar damage, safe sexual behaviours, and avoidance of mosquito bites. Similarly high levels of perceived risk were observed among American study abroad students, with the most highly rated health risks being contaminated food and water, suffering a physical assault, psychological distress, and excessive sun exposure.[9]

It is noteworthy in the current study that 40% of students surveyed had taken no measures during previous international travel beyond Europe to protect their health, such as attend a travel health adviser or seek travel vaccinations, several of which were likely to have been indicated for their trips. The most frequently cited barrier to receiving pre-travel health advice was financial. Useful travel health information is summarised on this university's Students Union website, but students are required to pay for their own travel vaccines which are not subsidised, even for healthcare students completing clinical electives abroad. Over a third of the students in this study did not consider travel health as a priority, and a quarter of respondents were unsure about where to access preventive advice in relation to travel. In the study by Hartjes and colleagues, there was a reliance on travel guidebooks for health information[9], a finding amplified by the current study, which showed that student travellers are more likely to seek travel health advice from family, and are almost as likely to obtain their health information from websites as from their family doctor or student health unit. The authors in the aforementioned study by Hartjes assert that students may respond well to web-based educational materials as they lend themselves to being updated frequently, they are available throughout all phases of travel (pre-, post-, and during travel), and can employ multimedia technology to more actively engage and motivate students to follow healthy behaviours.[9]

This study highlights a lack of awareness of malaria among university students who had not studied it as part of their courses. While most of the students questioned identified the mosquito as the vector of malaria, the majority of them were unfamiliar with the global distribution of the disease, the diurnal feeding habits of the malaria-carrying *Anopheles* mosquito, and what practical steps they should adopt to avoid becoming infected with the parasite. Piyaphanee and colleagues found, in a study of foreign backpackers in Bangkok, Thailand, that

although most backpackers were aware that there was a potential threat of malaria in South East Asia, misperceptions abound and there was poor reported compliance with mosquito bite avoidance and malaria chemoprophylactic regimens.[11]

Particular deficiencies were reported in the attitudes of students in this study towards jet lag prevention, preparation of a first aid kit for travel, wearing a bracelet to identify important medical conditions or allergies, and reducing the risk of deep vein thrombosis. In keeping with the findings of the previous study in Chapter 1.2, just over 40% of respondents expressed a willingness to plan a detailed travel itinerary prior to travel. Since it is a common practice for students to travel abroad in the summer period immediately after they complete their end of year examinations, many of them may travel with limited research into their travel destinations or the health risks they may face while there. Avoidance of excessive alcohol consumption was not a high priority for the students in this study. In a retrospective study of travellers who had attended a travel clinic in Switzerland, 20% of whom were students, the authors found that travellers admitted to doubling their at-risk alcohol consumption during travel.[13] Such behaviour can greatly increase the risk of traumatic injury, including road traffic accidents[14], aggravate pre-existing psychiatric disorders[15], precipitate arrests for public order offences[16], especially in Muslim countries, and promote unprotected casual sexual behaviour.[17]

Conclusion

This study highlights inconsistencies in the approach of university students towards managing personal travel-related health risks. The reluctance of students to seek pre-travel health advice points to the need to develop novel strategies for educating this vulnerable group of travellers.

1.4. Travel health in Asia – the Kuala Lumpur Airport Survey

Introduction

Travel to and from South East Asia has witnessed significant growth in parallel with global tourism trends in recent years. Most Asian international travellers travel within the Asian continent but tourism projections predict that the proportion of outward travellers from Asia to other continents will grow in the near future.[18] Malaysia is a rapidly developing economy which encapsulates many diverse elements of Asian culture and ethnicity, giving rise to the popular tourism slogan "Malaysia - Truly Asia". With its tropical geographical location, Malaysia is endemic for many of the infectious diseases which travel medicine professionals seek to prevent in international travellers.

Seroprevalence rates of Malaysian travellers may confer additional protection against vaccine-preventable infectious diseases, such as hepatitis A. This may serve to minimise the Malaysian traveller's perception of risk and may influence their travel health risk preventive behaviour. Additionally, some travel vaccines, including hepatitis B, already constitute part of the national immunisation schedule in Malaysia.[19] Specialised travel medicine clinical services are not currently well established in Malaysia. A recent editorial highlighted the need for greater research focusing on the specific needs of the Asian traveller.[20] Such evidence is essential to increase awareness of travel health preventive measures in Asian travellers and their medical professionals.

A recently published airport survey conducted at Hong Kong International Airport found a lack of preparedness amongst outbound travellers, only 10% of whom had the recommended travel vaccination coverage. An important finding was the significant proportion of higher risk travellers with pre-existing medical co-morbidities.[21] The current study was designed to investigate the travel trends and preventive attitudes of travellers departing from a major international airport in Malaysia.

Methods

The survey was conducted in Kuala Lumpur International Airport (KLIA) in May and June 2013. Research assistants invited passengers boarding for international flights to various destinations to participate in a survey. The passengers were approached at the departure gates of Kuala Lumpur International Airport (KLIA) and a self-administered, anonymous, 48-item questionnaire was distributed. Upon completion, the data collectors verified whether or not all questions had been answered. On average, the questionnaire was completed in 10 minutes. Only Malaysian passport holders were eligible to participate in this study. Inclusion criteria were that the subjects must be adults of 18 years of age or older with an ability to understand the language in which the questionnaires had been designed. In most cases, these criteria were determined by the data collectors upon distributing the questionnaire. The interviewers supervised the completion of each questionnaire to ensure respondents fully understood the questions.

The questionnaire included a number of personal characteristics such as age, gender, education level, profession and marital status. Questions regarding their trip included destination countries or region, purpose of trip, duration and their knowledge, attitudes and practice relating to their preferred source of travel health information, planned food ingestion habits, perceived risk of specific infectious diseases, status of travel vaccinations, perception and practice of malaria prophylaxis, vaccine-preventable and other travel-related diseases.
Results were tabulated using SPSS 20.0. All tests including descriptive analysis and comparative analysis (using t-test, Kruskal Wallis, ANOVA and chi-square tests) were interpreted at the $p = .05$ significance level.

Results

In total, 498 questionnaires were returned and included in the analysis. In general, the majority of respondents were residents of Malaysia. Overall, 57% of respondents were male and 43% were female (Table 1.3). The 18- to 25-year age group accounted for 34.1% of responses; 31.3% of respondents were between 26 and 35 years of age, 15.9% between 36 and 45 years of age, 12.9% between 46 and 59 years of age, and 5.8% over 60 years of age. 48.2% (n=240) of respondents were single, 50.6% (n=252) were married and 1.2% (n=6) were divorced. Regarding their educational status, more than half of the respondents (60.8%, n=303) had attained at least an undergraduate education, 14.5% (n=72) completed postgraduate studies, and the remainder had graduated from high school (24.7%, n=123). Almost half of the respondents (46.2%, n=230) were working as professionals. Almost one-third of the respondents (28.3%, n= 141) were students, and others, including retired and unemployed individuals and housewives, comprised 16.3% (n=81) of respondents.

A great variety of reasons for travelling were reported (Table 1.3). 78.5% indicated leisure as their purpose for travel. Business travellers accounted for 14.9% of travellers in this study. 96% of respondents planned to remain abroad for less than 1 week, 3% for 1 to 2 weeks, 0.4% for 3 to 4 weeks, and 0.6% for more than 4 weeks.

South East Asia was the most common region visited (47.6%), followed in descending order by the Middle East (17.3%), East Asia (15.9%), Europe (10%), Australia (6.8%), the Americas and other regions including Africa, India and Russia (1.2%). In terms of the average number of international trips taken every year, the respondents reportedly took 2 international trips each year with a minimum of 1 trip and a maximum of 10 trips reported per year. The majority of the respondents (78.3%) were travelling to a single country whereas 21.7% travelled to multiple countries.

Four out of every five respondents were staying at a hotel during the trip, followed by residential (11.3%), and hostel (4.8%) settings. The oldest respondents tended to prefer to travel to the Americas with a median age of 40, followed by Europe (median age 34), Middle East (median age 33.5), South East Asia (median age 29), East Asia (median age 28), and Australia (median age 22.5).

69.2% of the travellers felt informed of local disease outbreaks whereas 17% of them were unlikely to inform themselves about local disease outbreaks. More than half of the respondents (53.4%) did not familiarise themselves with procedures to access medical care in the event of illness during travel. 81% of the interviewed travellers planned to consistently restrict their consumption of all "potentially unsafe food items" listed (for example, ice cream, ice cubes in drinks, tap water, unpeeled or uncooked fruit, salads, and shellfish). 10.4% stated they would not apply any dietary restrictions. The remainder (8.8%) claimed that they would avoid some of the items on some occasions. Those who travelled for the purposes of visiting their relatives and for leisure purposes were more unlikely to avoid unsafe food and water than business travellers.

Approximately 45% of travellers surveyed considered vaccinations essential but only 24% had received vaccines for their current trip. At least 27.8% had one negative opinion regarding vaccination and were not willing to pay for vaccinations. In the intended malaria or dengue endemic destinations, 62.8% of the travellers planned personal protection measures against mosquito bites, such as using insect repellents and wearing long clothes. Approximately 43% of travellers did not have medical insurance or were unsure as to whether or not their insurance policy would cover their medical expenses during the period of travel. Up to 61% were likely to buy travel health insurance if their travel budget allowed this expenditure.

In terms of pre-travel health advice, nearly two-thirds of the respondents (63.2%) had not sought travel health advice prior to the trip. Among the one-third who did seek travel health advice, 67.6% had consulted their general practitioner, 11.8% searched the internet for information, 9.4% obtained advice from family and friends, and 6.5% did so from travel agents. Health advice received from healthcare professionals was perceived to be more reliable than from other sources.

With respect to pre-travel health advice barriers, few were identified which would have prevented the respondents from seeking it (Table 1.4). 22% (n=109) of the respondents were concerned about the potential side effects of vaccines, and 21% (n=104) did not consider themselves to be at risk of acquiring any illness during their travels. Financial constraints and fear of needles were also identified as barriers with 13.3% (n=66) and 11.4% (n=57), respectively, of respondents

citing these barriers. 5.8% (n=29) claimed that they were already immune to tropical diseases, whereas 5.6% (n=28) claimed that there was no specialised travel medicine service offered locally.

Table 1.3 Demographic and travel characteristics of travellers departing from Kuala Lumpur International Airport

	n	%
Gender		
Male	284	57
Female	214	43
Age group		
18-25 years	170	34.1
26-35 years	156	31.3
36-45 years	79	15.9
46-59 years	64	12.9
>60 years	29	5.8
Marital status		
Single	240	48.2
Married	252	50.6
Divorced	6	1.2
Level of education		
High school	123	24.7
Undergraduate	303	60.8
Postgraduate	72	14.5
Occupation		
Professional	230	46.2
Non-professional	46	9.2
Student	141	28.3
Retired/Unemployed/Housewife	81	16.3
Travel frequency		
Once per year	210	42.5
2 to 3 times per year	208	42.1
4 or more times per year	76	15.4
Purpose of travel		
Leisure	346	69.5
Business	30	6.0
Both	122	24.5
Pre-travel health advice obtained		
Yes	183	36.8
No	314	63.2

All participants were asked to estimate the risk for a number of travel-related infectious diseases, from the point of view of a general traveller visiting their proposed destination. Unfamiliarity was highest for dysentery, polio, cholera and typhoid fever, somewhat lower for hepatitis A and B and malaria, and lowest for dengue fever (Figure 1.13). Travellers rated their personal risk of acquiring dengue infection the highest among the infectious diseases presented to them. Nevertheless, this risk was considered to be high by only 38%, and to be low by a further 47.2%. The average scores for other typical travel-related infectious diseases endemic in some destinations visited, such as yellow fever, rabies, tetanus and meningitis varied from 20% to 29% for the "at risk" category. Those who were travelling for leisure purposes (39%) assumed that they were protected against hepatitis A to a greater extent than business travellers (5.4%). In the case of hepatitis B, 47.2% considered that they were protected, 18.1% thought that they might be protected, and 28.5% believed that they had no protection against the disease.

Table 1.4 Reported barriers to seeking pre-travel health advice

Perceived Barriers to Seeking Travel Health Advice	Frequency (n)	%
Concerned about potential side effects	109	21.9
Do not consider themselves at risk	104	20.9
Financial constraints	66	13.3
Fear of needles	57	11.4
Not a priority	43	8.6
Unsure of where to access information	37	7.4
Immune to tropical disease	29	5.8
No specialised service offered locally	28	5.6
Unsure about the effectiveness of advice and vaccinations	25	5.0

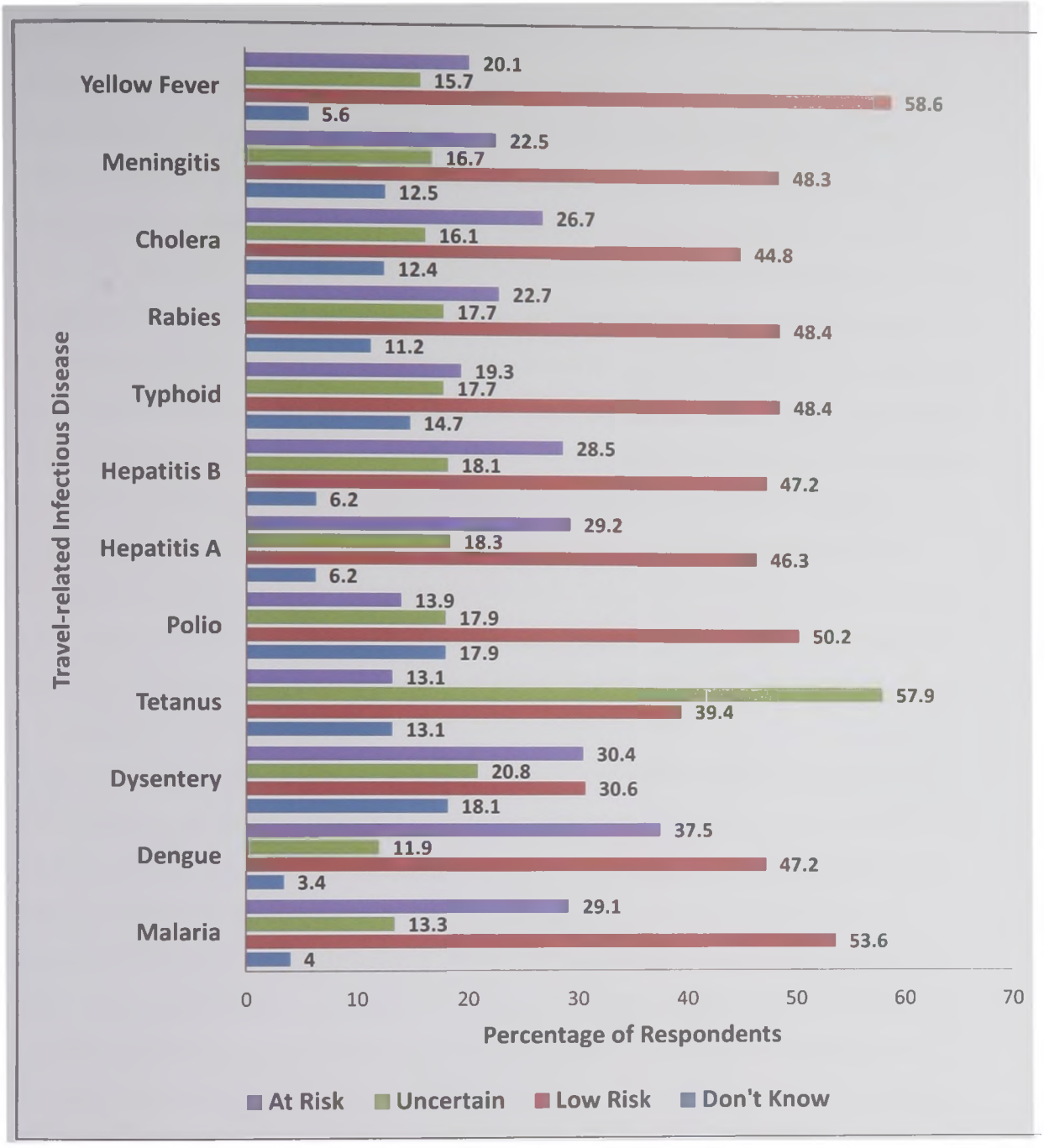

Figure 1.13 Perceived risk of travel-related infectious diseases

Discussion

This cross-sectional airport survey provides valuable insights into the knowledge, attitudes and behaviours of a sample of Malaysian travellers departing from a major international airport, mostly to other Asian countries. In keeping with the demographic profile of the country itself, nearly two-thirds of travellers surveyed were younger than 35 years of age and three-quarters were educated to third level or greater. Leisure travel dominated in this airport survey and the vast majority of trips were of short duration. As disposable income increases throughout Asia, it is likely that travel duration will witness a corresponding increase, with its attendant heightened travel health risks. Of interest is the finding that over a fifth of travellers planned to visit multiple countries during their relatively short trips. This is in keeping with tourist trends observed elsewhere and is an important factor in determining the magnitude of travel health risk. Younger travellers in this study were observed to be more likely to travel within Australasia with older travellers venturing further afield, with trips to North and South America and Europe more represented in this age group.

This study exposes deficiencies in travellers' preparedness for healthy travel, with 43% of participants travelling without travel health insurance and an alarming 63.2% of travellers failing to obtain pre-travel health advice for their current trip. This proportion is consistent with the low rates observed in other airport surveys.[22-26] In a survey carried out at John F. Kennedy International Airport in New York, only 36% of departing travellers had sought travel health advice prior to travel.[27] In airport surveys conducted at Sydney and Bangkok airports, Asian travellers were found to be less likely to seek pre-travel health advice and accept travel vaccines than Australian or other Western travellers.[24] In a multivariate analysis of data collected at Boston Logan International Airport, certain factors predicted a higher likelihood of not seeking travel health information among travellers to low-or low-middle income countries. These included solo travel, travel for less than 2 weeks, and vacation travel.[28] Of those travellers who had sought travel health counselling, over a quarter of them had received this from a source other than a healthcare professional. Internet sources were rated less highly in this survey than in a health survey of travellers conducted in Peru[29], but with the growing internet connectivity in South-east Asia it is reasonable to suggest that

this will become a more important primary source of travel health-related information in the future.

This study highlights some of the traveller-perceived barriers to seeking pre-travel health advice and preventive measures, with vaccine side effects and a low perception of risk being prominent factors among these travellers. Vaccine acceptability levels reported in this study compare well with those published in an airport survey at Munich International Airport.[30] Over half of the travellers in our study admitted that they were unsure about how to access competent medical care were they to become ill during their journeys abroad. While the majority of travellers declared that they would avoid unsafe food and water while travelling, over a third did not intend to use mosquito bite avoidance strategies such as the application of insect repellent. Previous airport surveys in Europe have demonstrated a differential level of awareness of malaria amongst travellers, with an increase in self-protection rates with travel to high-risk destinations for malaria.[31] Almost a quarter of travellers visiting a high-risk malaria area in a large European cohort reported an erroneous risk perception[23], a finding reinforced by the present study.

While this study did not correlate specific destinations with travellers' reported knowledge, attitude and practices, it did reveal a general lack of awareness of the risk of acquiring several common travel-related infectious diseases, including dysentery and typhoid fever. Despite a greater level of risk awareness in relation to dengue infection which is endemic in Malaysia, nearly half of travellers in the study considered themselves to be at low risk of contracting dengue virus. There was a particularly low level of risk awareness towards hepatitis A and B infection but seroprotection from natural immunity (hepatitis A) or childhood immunisation (hepatitis B) may have influenced this perception in this cohort of Malaysian travellers. Since seroprevalence rates for hepatitis A infection are likely to decrease over time[32], it is important that priority be given to protecting travellers against this common vaccine-preventable travel-related disease.[33] In the Dutch Schiphol airport survey, preventive behaviour of European travellers to destinations at risk for hepatitis A increased over a 7 year period, an improvement attributed to the effectiveness of travel health advice.[34]

This study has yielded useful insights into the knowledge, attitudes and practices of Malaysian travellers. Further studies with a larger sample size should

be conducted at other regional airports at various times of the year in an effort to further characterise the typical profile of international travellers departing from Asian countries, including those with pre-existing medical conditions. These data will help to inform the development of specialised travel health services and will help to shape postgraduate educational programmes which will serve the needs of travellers and their healthcare providers.

Conclusion

This study highlights deficiencies in the knowledge, attitudes and preventive behaviour of international Malaysian travellers and raises the need for public awareness campaigns in South East Asia aimed at educating the travelling public about the health risks associated with international travel and the most efficient means of mitigating those risks. The development of specialist travel medicine services throughout Malaysia and other Asian countries should be informed by these important traveller-related factors.

Financial support

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CHAPTER 2

Travel with Pre-existing Medical Conditions

2.1. Profile of Medical Co-Morbidity at a Travel Medicine Clinic

Introduction

There has been a dramatic increase in the number of individuals embarking on international travel in recent years, with over a billion people travelling beyond their country's borders in 2012 alone.[35] With the ease and convenience of modern international transportation, chronic medical conditions no longer present significant barriers to international travel. Patients with complex medical co-morbidities may travel for protracted periods to remote destinations, often with limited access to high quality medical care. The risk of travel-related diseases is 2.3 times greater in travellers with underlying medical conditions when compared with healthy travellers.[36] Travellers taking immunosuppressive drugs report more travel-related skin infections than do their unaffected travelling companions.[37] In some cases, travellers do not protect themselves by obtaining appropriate medical travel insurance. The risk of interactions between travellers' medications and drugs used for malaria chemoprophylaxis and prevention of travellers' diarrhoea must be considered by travel health practitioners.

It is essential that travellers with chronic illnesses are well controlled and that their illness management has been optimised prior to travel.[38] In some cases, patient education with respect to self care during travel should be emphasised, a health plan devised, and a comprehensive travel health kit assembled. The timing of the pre-travel consultation is even more critical for the traveller with an underlying chronic medical condition, to ensure that there is adequate time to respond to vaccinations as some immune-compromising conditions and agents, and even immune-senescence brought on by advancing age may impair the antibody response to vaccinations.[39] It is imperative that there is sufficient time to observe patients for adverse effects from newly introduced medications well in advance of travel as compliance to poorly tolerated medication and medication substitution in another jurisdiction with its attendant language barriers is likely to pose additional difficulties for the international traveller.

Some chronic medical conditions, such as chronic obstructive pulmonary disease and coronary heart disease, may decompensate during commercial air travel and fitness to fly issues may arise, necessitating advance precautions and adherence to published guidelines.[40,41] Patients travelling with complex medical histories, implanted devices and other treatment-related equipment will require a physician's letter on office letterhead stationery and they may even travel with a medical assistance company which will allow them to access their medical information worldwide. Patients taking prescribed medications need to be advised to transport their medications safely and legally and to pack double the normal amount in case of lost baggage.[38] In the case of some medications such as insulin, time zone differences will prompt an alteration in the timing and doses of medication administered. Medications co-prescribed to travellers for the prevention of malaria, travellers' diarrhoea or high altitude illness may interact with their regular prescribed drugs and there may be unanticipated local dietary effects on oral anticoagulants such as warfarin[42], which will need to be factored into the traveller's preparations.

Travel medical insurance is essential for the traveller with pre-existing medical conditions and medical evacuation insurance may be advisable in some instances where local healthcare is inadequate. The difficulties faced by travellers in accessing medical care with or without medical insurance are significant and organisations including the International Association for Medical Assistance to Travellers provide reassuring guidance to travellers and their physicians in such circumstances.[43]

Travellers being managed for potentially fatal medical conditions or with severe anaphylaxis to foods, drugs or venom should be advised to wear medical alert bracelets. Many medical conditions and recent surgery increase the risk for traveller's thrombosis and long haul travellers will need to be carefully counselled regarding the recognition of deep vein thrombosis and pulmonary embolism, and the importance of hydration, wearing loose-fitting clothing and mobilising at frequent intervals during prolonged travel.[44]

In its published recommendations for the practice of travel medicine, which this author co-authored, the Faculty of Travel Medicine at the Royal College of Physicians and Surgeons of Glasgow stipulates that it is a standard of good practice that the travel medicine practitioner "determines the relevance of pre-

existing health problems to the traveller's itinerary/destination and tailors risk assessment and risk management advice accordingly".[45] To achieve this standard of care, the travel health provider, be they doctors, nurses or pharmacists, must have a reasonable working knowledge of the travel health-related issues which may result from specific chronic medical conditions.

The published research literature on this subject is limited, however, and few descriptions are available of the actual chronic illness burden of international travellers which would help to inform priorities in educating travel health information providers dealing with patients with complex medical backgrounds. The present study aimed to characterise the profile of pre-existing medical conditions and current medications among a cohort of travellers seeking pre-travel health advice and medical preparation in a specialised travel medicine clinical setting.

Methods

The pre-travel medical registration cards (Appendix 1) of travellers attending the Tropical Medical Bureau travel medicine clinic in Galway city between 2008 and 2014 were examined and information in a panel relating to the past medical and surgical history of subjects was extracted and entered into an SPSS v21.0 database. This panel lists options to select a range of common medical conditions, including items of particular relevance to travel vaccination, including immuno-compromised state and egg allergies. A separate section of the registration card provides space for travellers to expand on any conditions selected and list additional co-morbidities, either intercurrent or in their past medical history. Data were recorded only where the traveller had a documented medical history and/or was taking prescribed medications. Data pertaining to the travel itinerary and patient demographic information were also documented. No comparison was made between 'healthy' travellers and travellers with pre-existing medical conditions as it was beyond the scope of the research question. Ethics committee approval was obtained for this study from the local clinical research ethics committee.

Results

Of the 4,817 records available, 56% (n=2,702) of travellers had a documented past medical history, and 32% (n=1,525) were taking prescribed medication at the time of travel. Almost a third of eligible subjects (n=863) reported more than one personal medical co-morbidity. The majority of travellers with pre-existing conditions were female (67%, n=1,820). The mean age of the cohort was 31.68 (+/- 12.2) years. The mean period remaining before the planned departure date was 40 (+/- 32) days. The most frequent duration of travel was 2-4 weeks (30%, n=803), with travellers planning travel of widely varying durations, from less than 2 weeks (28%, n=754) to 4 years (0.1%, n=2). The most frequently cited purpose of travel (Figure 2.1) was a holiday (58%, n=1,561). Over a third of travellers with pre-existing conditions were travelling to multiple international regions (Figure 2.2), with South East Asia as the most popular single regional destination (18%, n=477). Hotel accommodation was the most popular single accommodation type in this group, but 35% of travellers expressed an intention to stay in more than one accommodation setting, including hostel, camping, and cruise ship travel (Figure 2.3).

Two hundred distinct medical conditions were declared on their medical registration cards by the travellers in this study. Over 400 travellers with medical conditions were travelling alone (17%, n=404). The most frequently reported medical conditions in this cohort (Table 2.1) were allergies (20%, n=541), insect bite sensitivity (15%, n=415), asthma (11%, n=300), photosensitivity (5%, n=135), psychiatric conditions (4%, n=110), and hypertension (3%, n=78). Of the 30 diabetic travellers, nearly half required insulin (n=14). Seventeen travellers reported being immuno-compromised, while 125 subjects (4.5%) were currently taking immunosuppressant drugs, including corticosteroids (Figure 2.4). Half of the female travellers were taking the oral contraceptive pill at the time of their pre-travel consultation. Other frequently used medications included inhalers (7%, n=186), and blood-thinning medications (1.3%, n=34). Eleven travellers were pregnant at the time of their travel health consultation.

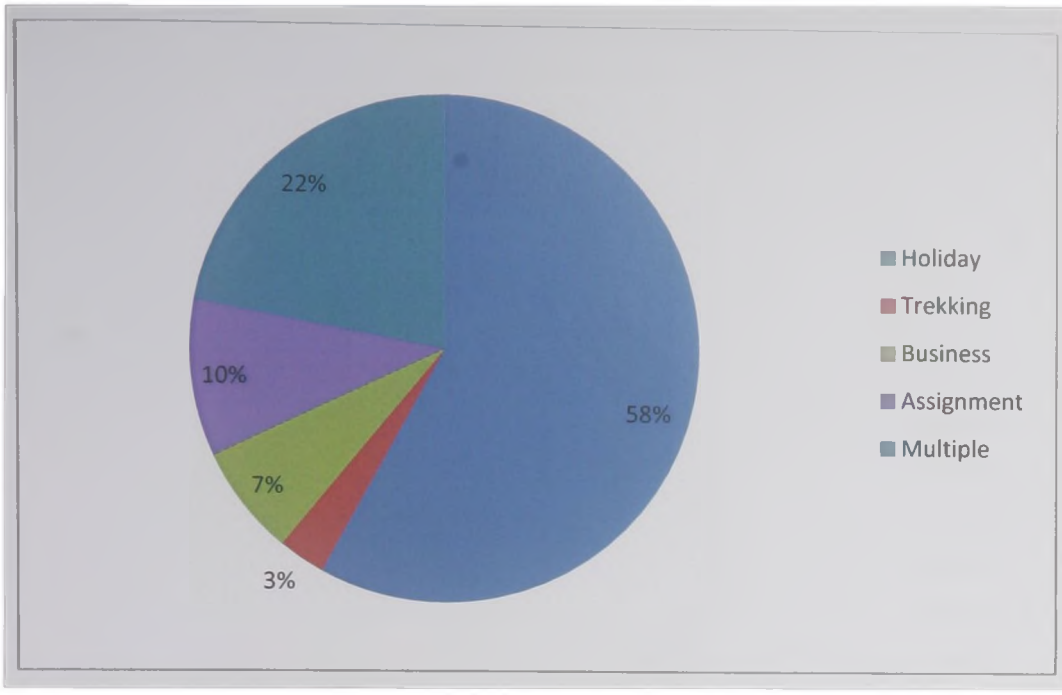


Figure 2.1 Purpose of travel

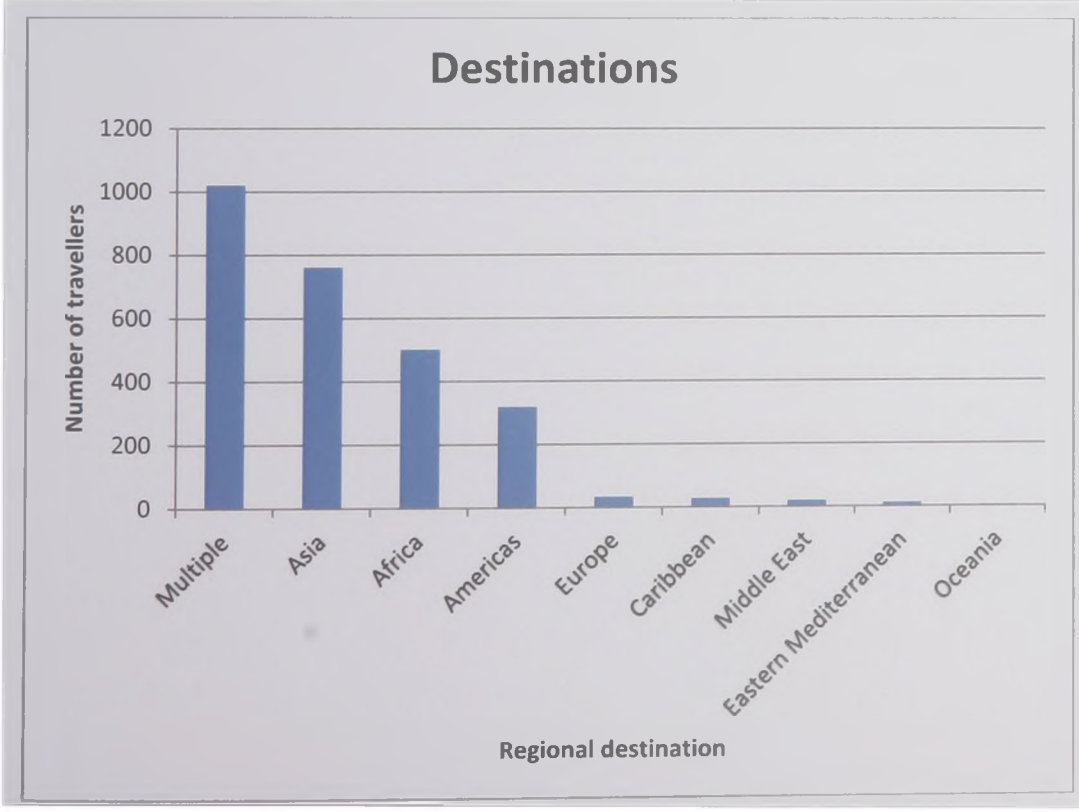


Figure 2.2 Traveller destination profile

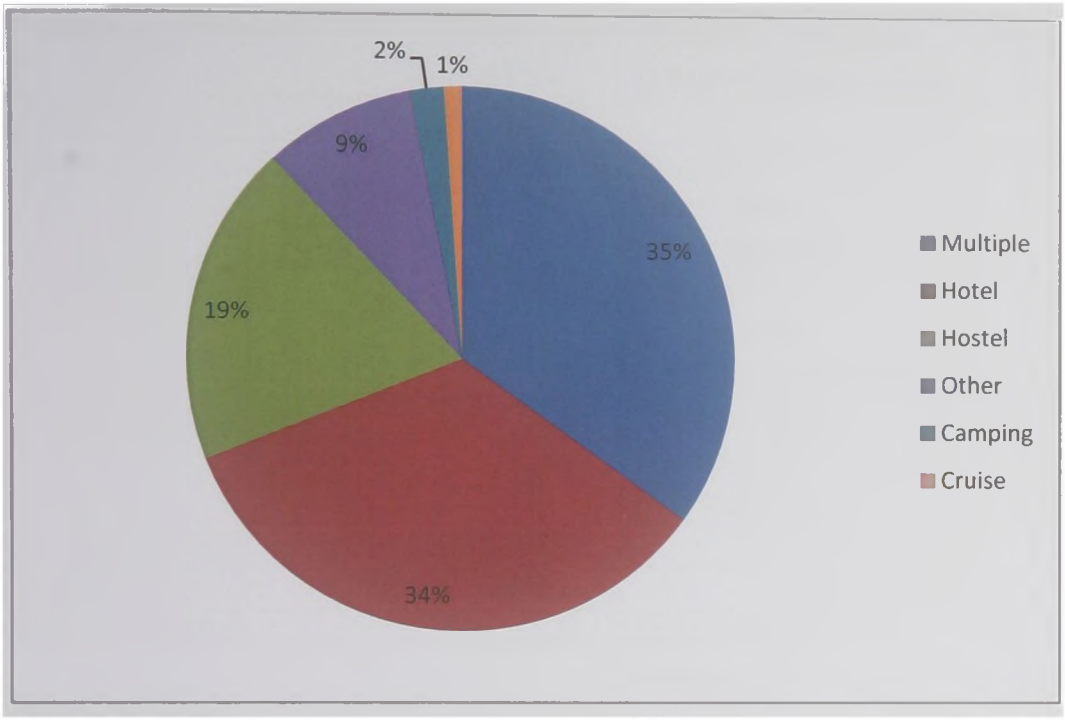


Figure 2.3 Traveller accommodation

Table 2.1 Principal Medical Conditions (Chronic and Intercurrent) among Cohort of Travellers

Disease category	Frequency n (%)	Specific conditions, if reported by patient	Frequency n (%)
Hay fever	637 (23.6)	N/A*	N/A
Allergies	541 (20)	Penicillin	161 (6)
		Other drugs	121 (4.5)
		Environmental	154 (5.7)
Respiratory conditions	525 (19.4)	Asthma	486 (18)
		Pneumonia	11 (0.4)
		Previous tuberculosis	7 (0.3)
Cardiovascular disease	345 (12.8)	Varicose veins	170 (6.3)
		Hypertension	78 (2.9)
		Dyslipidaemia	61 (2.3)
Insect bite sensitivity	415 (15.4)	N/A	N/A
Photosensitivity	135 (5)	N/A	N/A
Psychiatric disorders	110 (4.1)	Depression	74 (2.7)
		Anxiety	22 (0.8)
Previous surgery	73 (2.7)	N/A	N/A
Thyroid disease	59 (2.2)	N/A	N/A
Infectious jaundice	58 (2.1)	N/A	N/A
Musculoskeletal disorders	58 (2.1)	N/A	N/A
Neurological disease	58 (2.1)	Migraine	23 (0.9)
		Epilepsy	22 (0.8)
Skin conditions	51(1.9)	N/A	N/A
Gastrointestinal disease	48 (1.7)	N/A	N/A
Previous tropical infections	48 (1.7)	Malaria	4 (0.1)
Reproductive issues	34 (1.3)	PCOS**	11 (0.4)
		Pregnancy	11 (0.4)
		Endometriosis	6 (0.2)
Diabetes mellitus	30 (1.1)	Type 1	10 (0.4)
		Type 2	5 (0.2)
		Not specified	15 (0.6)
Ear, nose and throat problems	26 (1.0)	N/A	N/A

*N/A = Not applicable, i.e. supplemental information was not provided by travellers

**PCOS = polycystic ovary syndrome

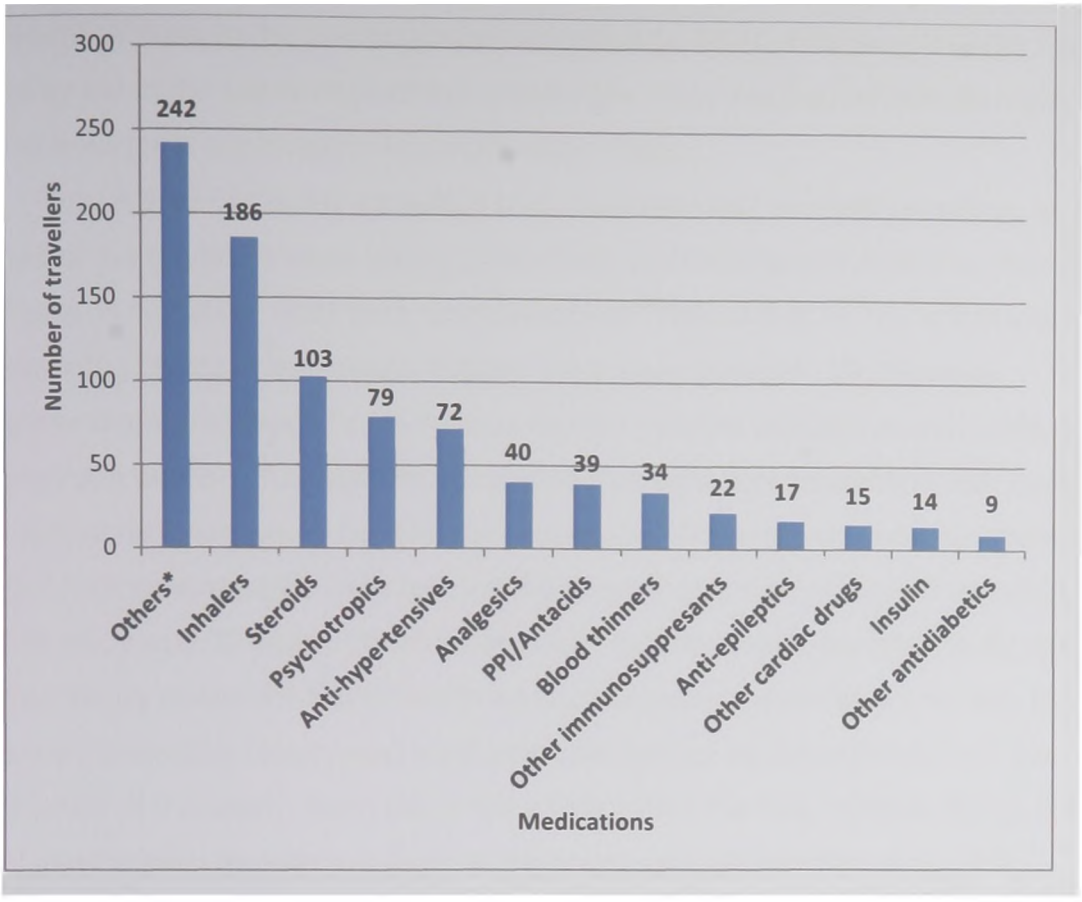


Figure 2.4 Prescribed medications in traveller cohort

*Medications in the "Others" category included a wide range of pharmacotherapies, with the most common drug classes being statins (n=68), L-thyroxine (n=51), antibiotics (n=40), antihistamines (n=23), and hormone replacement therapy (n=12). Inhalers included corticosteroids and bronchodilators. The dose and route of administration of steroids were not provided. Blood thinners included antiplatelet agents (1%, n=27) and the anticoagulant warfarin (0.3%, n=7).

Discussion

This study is the first of its kind in Ireland to examine the medical burden of international travellers in an effort to better prepare travel health advisers for their responsibility of providing specific preventive information to these vulnerable travellers. A majority of travellers who attended the travel medicine clinic during the 6-year period of the study reported at least one pre-existing medical condition on their traveller medical registration card upon arrival at the clinic. The travel medicine physician corroborates this information in the context of a comprehensive travel health consultation and records additional information, if any, on both the registration card and in a specially designed electronic medical

record. Access to the computerised records was beyond the scope of the current study but in the experience of the researcher, most medical information relating to the traveller is captured on the registration cards.

Over a third of eligible travellers had more than one medical condition, and over half of the travellers were taking prescribed medications at the time of their pre-travel consultation. Hochberg and colleagues[46] found that 17.9% of travellers attending clinics in the greater Boston area were high-risk, 23.3% were immunocompromised, 74.3% had co-morbid medical conditions, and 2.5% were pregnant women. The authors concluded that travellers presenting with complex medical histories would benefit from assessment by a travel medicine specialist. Our findings are particularly noteworthy given that the mean age of travellers in this study was 32 years. Whether the older traveller has a preference for attending their family doctor for travel health advice because of their familiarity with the patient's medical history and medication list cannot be determined from the findings of this study, but if this were a factor then the true medical illness burden of international travellers is likely to be underestimated by this study. It is reassuring that the mean length of time remaining before departure was 40 days in this study, which allows the traveller's medical condition to be optimised before travel. Stienlauf and co-workers[47] concluded from a retrospective analysis of travellers to developing countries that the presence of chronic medical illnesses in travellers had little impact on travel itinerary, but a shorter travel duration was observed in travellers taking long-term medications.

Over a third of travellers with pre-existing medical conditions intended to visit multiple global regions on their upcoming trip which increases their exposures to various communicable diseases and other health and safety threats. South East Asia was the most popular single destination in this group and is a region with numerous travel health risks, including vector borne diseases such as dengue and malaria, rabies, travellers' diarrhoea, envenomations, personal safety and security risks, drowning risks, and heat injury. Of particular interest was the finding that nearly 1 in 5 of all travellers with chronic medical illnesses did not have a travelling companion, which may expose them to isolation from prompt medical attention in the event of an emergent illness.

A wide range of medical conditions, of varying severity, was revealed in this retrospective analysis. Allergies were commonly represented with over 1 in 10 of

the travellers being allergic to a drug. Insect bite sensitivity was also frequently reported. This can lead to severe local skin reactions and secondary soft tissue infections but may conceivably promote greater insect bite avoidance behaviour in travellers. It was not surprising to find that 1 in 20 of the travellers were photosensitive given that the majority of clients attending the clinic were Irish-Caucasian. Asthma was particularly common in this cohort but less than 1 in every 2 asthmatics reported use of an inhaler. Asthma symptoms in patients with severe refractory disease may paradoxically improve at altitude[48], but the high levels of environmental air pollution in many developing countries and unacceptably high levels of tobacco smoke in countries without smoking bans in public places may pose a management challenge for the asthmatic[49], especially if their steroid inhaler compliance is poor. A prospective study of asthmatic travellers in the United States concluded that asthma frequently worsens during travel, therapy should be intensified to achieve better control of asthma symptoms, and strenuous trekking activities should be discouraged in the asthmatic traveller.[50]

Psychiatric conditions were disclosed by 4% of travellers but there may be a degree of under-reporting in this instance. Decompensation of psychiatric illness secondary to poor psychotropic drug compliance, culture shock, excessive alcohol use, substance misuse, or traumatic experiences poses a significant challenge for the patient and travelling companions[51], and the availability of competent acute psychiatric care is limited in many developing countries. Difficulty reintegrating into the home environment may be a further risk for the returned traveller with psychiatric disease.

A relatively low number of diabetic travellers were observed in this dataset. This may reflect a true tendency to avoid international travel among diabetics or, more likely, diabetic travellers may prefer to approach their regular GP, diabetologist or diabetic nurse specialist for pre-travel health advice. Whether multidisciplinary diabetes healthcare teams are suitably qualified to provide pre-travel health advice to their patients is the focus of a future study by this author. A study of the travel-related diseases reported by young adults with type 1 diabetes mellitus revealed satisfactory glycaemic control during their travels.[52]

Patients on immuno-suppressant drugs such as corticosteroids were well represented in this study. The travel medicine practitioner must provide accurate specialised advice with regard to the likely immunogenicity of inactivated vaccines,

the potential risks of unchecked viral replication from inadvertent administration of live vaccines, and the potential for acquiring opportunistic infections in this patient population.[53]

One in every 2 female travellers was taking the oral contraceptive pill (OCP) in this cohort, a finding which should focus travel medicine physicians' attention on the need to provide appropriate advice regarding prevention of venous thromboembolism, as well as counselling regarding the oft disputed interactions between doxycycline for malaria chemoprophylaxis and the OCP. A small number of pregnant travellers presented for pre-travel counselling during this 6-year period. Most travel vaccines and all live vaccines are relatively contraindicated in pregnant women and the risks of venous thromboembolism, of developing severe malaria and of antenatal complications resulting from malaria infection make this a particularly vulnerable group of travellers who sometimes should be advised to defer their travel plans until they have delivered.[54]

This study, though it provides a valuable cross-sectional snapshot of the medical burden of international travellers, is limited by the fixed structure of the medical registration card which was developed many years previously by the Medical Director of the travel medicine clinic. Since the traveller completes the card without prompting or guidance, it is possible that inaccurate information may sometimes be recorded owing to recall bias, but this should be corrected during the consultation by the travel medicine physician who will pay particular attention to any listed medical condition or medication which may impact on travel. The section which allows the traveller to expand on the medical history or provide supplemental information is helpful in ensuring that no relevant medical data have been omitted.

Conclusion

This study provides a detailed insight into the medical profile and medication usage of travellers attending a travel health clinic. A diverse range of diseases were reported, which highlights the importance of educating travel medicine physicians about the specific health risks associated with particular conditions. The importance of providing relevant preventive advice to travellers is supported

by the study findings. This is particularly critical in the case of individuals who travel alone or whose conditions and medications present particular challenges during travel.

Acknowledgements

I am grateful to Mr. Calvin Teo Jia Han, a fourth year medical student at NUI Galway, for assisting me with the data collection. Calvin was supported by an unrestricted educational grant received from the Travel Medicine Society of Ireland. I also wish to thank Dr. Graham Fry, Mr. Andrew Lewis and Ms. Laura Nolan of the Tropical Medical Bureau travel medicine clinic in Galway, Ireland for facilitating the project. We should also like to acknowledge the statistical advice provided by Ms. Gloria Avalos of the School of Medicine, National University of Ireland, Galway.

2.2. Stem Cell Tourism[1]

Introduction

Medical tourism is the term commonly used to describe the process that involves patients leaving their country of residence with the intent of accessing medical care.[55] Medical tourism is a global, multi-billion dollar industry that is predicted to grow exponentially in the next five-ten years.[56] This expected growth is being facilitated by increased use of the internet allied with the ubiquitous nature of accessible, low cost air travel. Patients are employing the internet to identify interventions that are not available or are too expensive in their home countries and travelling abroad to access these treatments.[57] Studies utilising different definitions and methods have estimated that there are between 60,000 and 750,000 medical tourists annually from around the world.[58]

Stem cell tourism is a growing subset of medical tourism.[59] Stem cell therapy presents a realm of novel therapeutic possibilities for both patients and clinicians. Currently, stem cells are established as therapeutic agents in the treatment of haematological disorders including graft versus host disease. A number of further uses for stem cells are under investigation. Many of these therapies are awaiting successful completion of approved clinical trials culminating in phase 3 pivotal trials.[60] There are currently 2000 stem cell trials underway globally and while the potential efficacy is enormous the outcome of this rigorously conducted phase is still awaited.

Despite a lack of clinical data or appropriately designed clinical trials, demand for stem cell therapy is growing[61], with many patients travelling to avail of stem cell therapies through clinics represented on the internet.[62] Online clinics describe a vast array of treatments with a diverse range of indications, making them potentially relevant for a substantial portion of the world's population.[62,63] The provision of stem cell therapies in such an unregulated online environment offers a substantial potential risk to the health of stem cell tourists. This practice

[1] Adapted, with the permission of the co-authors and publishers, from: Connolly R, O'Brien T, Flaherty G. Stem cell tourism - A web-based analysis of clinical services available to international travellers. Travel Med Infect Dis. 2014 Oct 7;12(6PB):695-701.

also undermines the credibility of legitimate stem cell research and the continued development of this promising branch of medicine.

Patients are employing the services of online stem cell providers, regardless of the experimental nature of treatments and the lack of accreditation and outcome data provided.[64,65] There is a lack of understanding of the difference between experimental medicine and approved therapeutic products. The services provided by online clinics enable clients to avail of stem cell therapies, thereby facilitating them in their quest to overcome the delay imposed by protracted clinical trials. This represents a fundamental problem and has led to stem cell tourism becoming the object of intense scrutiny in recent years, with rising ethical concerns and reports of baseless claims and adverse events.[63,66,67] Examination of the literature in this field yields evidence of a brain tumour following neural stem cell transplantation[68], and also the development of renal angiomyeloproliferative lesions following autologous stem cell therapy.[69]

In addition to the risk of experimental therapies, many stem cell tourists are travelling to countries with endemic risks of infectious disease transmission. This travel is frequently undertaken without adequate consultation from travel healthcare professionals. In many instances, the patient population seeking stem cell interventions overseas is affected by underlying debilitating conditions and frequently has medical co-morbidities. These patients are placing themselves at the dual risk of receiving an unproven treatment, coupled with the risk of travelling to a new country without receiving the recommended pre-travel health advice or travel vaccinations.

Stem cell therapy represents a developing branch of travel medicine. There is a need to equip travel medicine practitioners with the requisite knowledge and resources to ensure patient safety. The aim of this study was to explore the representation of stem cell therapies available online with a view to making recommendations for travel medicine practitioners.

Materials and methods

This research is based on an analysis of stem cell clinics with an online presence. A web-based search utilising five search terms was employed: stem cell clinic, stem cell cure, stem cell therapy, stem cell treatment, and stem cell centre. The first twenty pages of each search result were further screened. This strategy

yielded 1091 web pages and the homepage of each site was assessed as to whether or not it was a stem cell clinic that administered stem cells to treat human disease.

224 of the 1091 pages represented stem cell clinics. A number of the web pages representing online clinics appeared on multiple occasions within the search process and were analysed only once. Web pages representing the same clinic despite a different uniform resource locator were excluded. In addition, web pages promoting clinics led by the same physician and clinics operating under the same network were also excluded. After the exclusion criteria were applied 68 sites remained.

Over 340 variables were utilised to analyse the websites. The variables employed focused on the description of stem cell therapies offered, the portrayal of the clinics and doctors involved and the marketing approach used to attract potential patients. A sub-section of the analysis examined pre-travel and post-travel advice for patients intending to use their services.

A literature review pertaining to stem cell therapy was also conducted, with particular emphasis on the domains of medical tourism, stem cell tourism, the online representation of stem cell therapy, and regulation surrounding the translation of stem cells into clinical practice.

Results

World Wide Web

A marked geographic spread of online stem cell clinics was noted with 21 countries spanning 5 continents represented. All clinics analysed disclosed their location and are plotted in Figure 2.5. The USA had the highest density of clinics, with American clinics accounting for one quarter of clinics studied. This can be attributed to two factors: a number of the American clinics were based in the USA but provided cross border treatment in Mexico, with an additional number of American clinics advocating the use of minimally modified stem cell treatment regimens. Asia contributed a large portion of the online clinics with China, India and Thailand providing 35% of the clinics analysed. Europe was poorly

represented, providing 11% of the clinics assessed, reflecting the strict regulatory protocols in place within the European Union.

More than half the clinics analysed were based in developing countries such as India, Thailand, Mexico and the Dominican Republic. Despite this, no stem cell clinic discussed infectious disease risks, medical risks pertaining to travel, or food and water precautions involved in travelling to their country. No clinic advised that patients consult with a travel medicine practitioner prior to travel and no clinic discussed or advocated recommended travel vaccines prior to commencing their treatment protocol.

Treatments were often presented as a medical tourism package, where patients combine a treatment with various additional services such as flights, accommodation, adjunctive therapies, supervised shopping trips, and guided tours of the local regions. Costs of treatments were mentioned by 35% of sites, with costs ranging from 5,000 to 50,000 US Dollars.

Stem Cell Clinics and the Internet

The essential element of online stem cell clinics appears to be the creation of user friendly sites, which are easy to navigate and which provide information in the vernacular of the target audience. Over 50% of the clinics employed social media outlets such as Twitter®, Facebook®, YouTube® and Skype® to further enhance and augment the accessibility of their service, highlighted in Figure 2.6. Online advertisement was utilised by 9% of the clinics analysed. A further 88% invited patient contact via online comment boxes. In many instances patients were prompted to initiate contact by the promise of further information following such communication.

Clinic Descriptions

It was observed that many web pages representing stem cell clinics contained much complimentary text. The terms "experienced", "renowned" and "acclaimed" were frequently used to describe both the doctors and the clinics involved. Doctors were named in 62% of cases, while 80% of doctors were described as "specialists". The terms "modern", "advanced", and "state of the art" were commonly used to portray the clinics.

Thirty-four per cent of sites mentioned the number of patients they had treated while one quarter of clinics provided outcome data and had patented their therapies. Twenty-nine per cent of clinics demonstrated an internationally recognised accreditation, with 19% of these accreditations solely laboratory-related and not pertinent to the clinical applications themselves.

Therapy Descriptions

The stem cell therapies were invariably described as safe and effective. Ninety per-cent of clinics advocated the safety of treatment, while 15% stated that there was "no risk" involved. Eighty-eight per cent of clinics claimed treatment effectiveness, with 16% describing the curative potential of therapy. Nine per cent referred to specific research publications to support their outcomes with three per cent referencing original peer reviewed research.

Information on precise treatment protocols was deficient. Over 40% of sites did not specify the number of treatments required, duration of procedure or therapeutic course. A single treatment lasting 1-3 hours as an outpatient was the most common regimen among those mentioned.

Of the sites analysed, 53% requested access to patients' medical records and 12% recommended that patients discuss the proposed therapy with their general practitioner. Almost one quarter of sites referenced contraindications to treatment, with just 41% of sites mentioning follow up patient care.

Clinical Indications

Over 390 conditions spanning a broad spectrum of disease categories were indicated for stem cell therapy in the online clinics studied. The top five indications for stem cell therapy encountered, in descending order, were: multiple sclerosis, anti-aging, Parkinson's disease, stroke and spinal cord injury, with neurologic and musculoskeletal conditions particularly prominent as shown in Table 2.2.

Stem Cell Type

Adult, autologous stem cells were the most commonly utilised stem cell, with 82% of clinics employing them for their therapies. 26% of clinics used culture expanded cells. Stem cell types encountered during the analysis are summarised in Figure 2.7. These stem cells were frequently sourced from bone marrow and adipose

tissue. Additional sources of stem cells can be seen in Figure 2.8, and included peripheral blood, umbilical cords, and blood/marrow donors, with 10% of clinics using foetal stem cells. Stem cells were administered intravenously in 60% of cases with 11 different routes of administration described, as presented in Figure 2.9.

Table 2.2 Top 10 indications for stem cell therapy in descending order of frequency

Rank order	Condition
1	Multiple sclerosis
2	Anti-aging
3	Parkinson's disease
4	Stroke
5	Spinal cord injury
6	Cerebral palsy
7	Autism
8	Amyotrophic lateral sclerosis
9	Alzheimer's disease
10	Arthritis

COUNTRY	% OF CLINICS
1. USA	27
2. China	12
3. India	12
4. Thailand	11
5. Mexico	9
6. Argentina	3
7. Australia	3
8. Austria	3
9. Germany	3
10. Ukraine	3
11. Malaysia	3
12. Colombia	1
13. Dominican Republic	1
14. Israel	1
15. Korea	1
16. Lebanon	1
17. New Zealand	1
18. Panama	1
19. Phillipines	1
20. Russia	1
21. Spain	1

Figure 2.5 Countries represented by online stem cell clinics

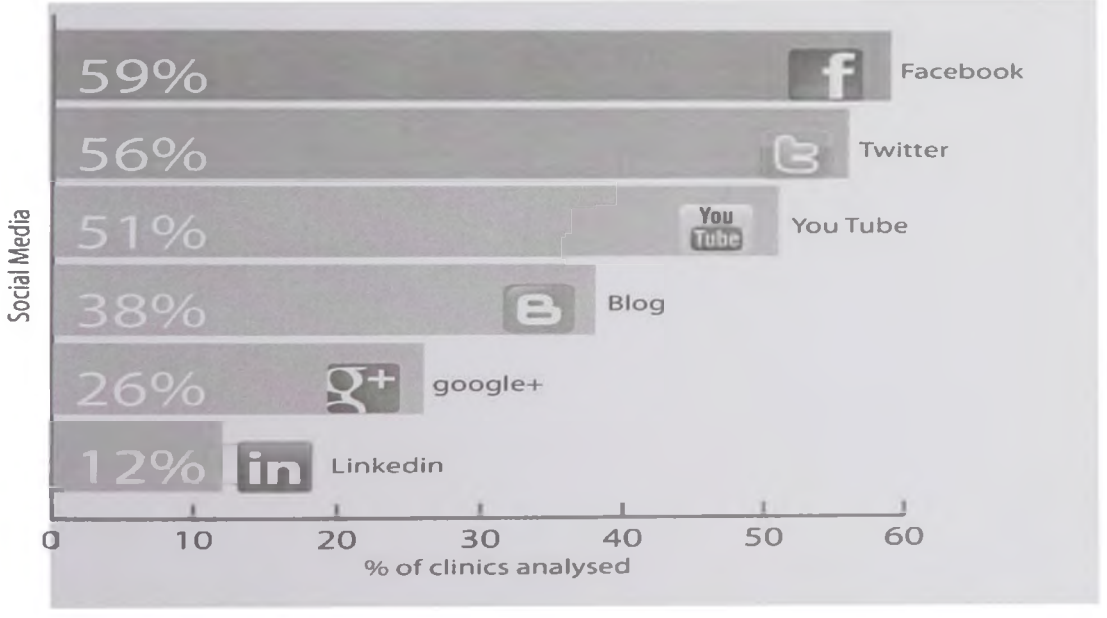
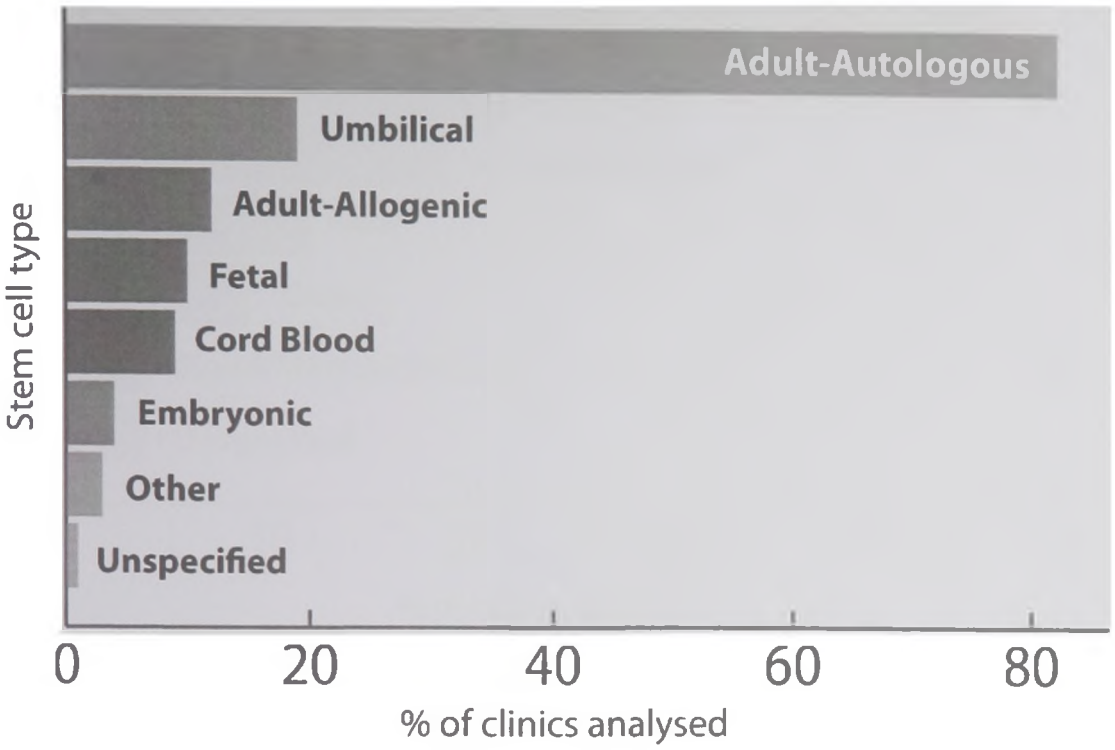
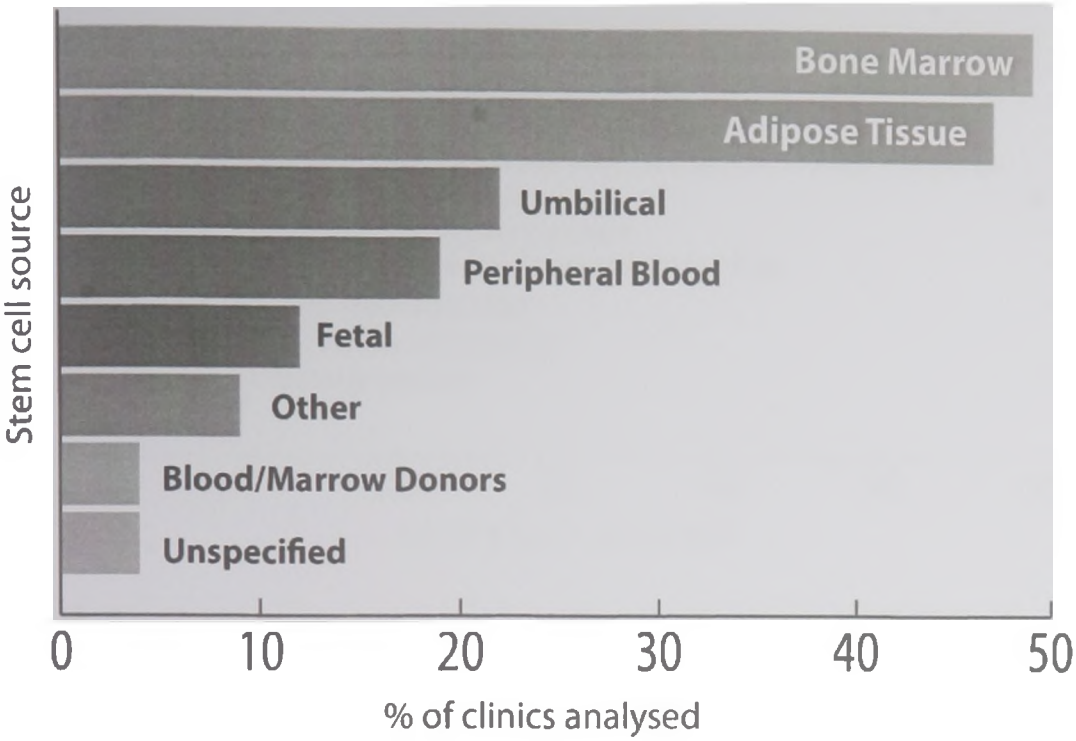


Figure 2.6 Use of social media by clinics analysed



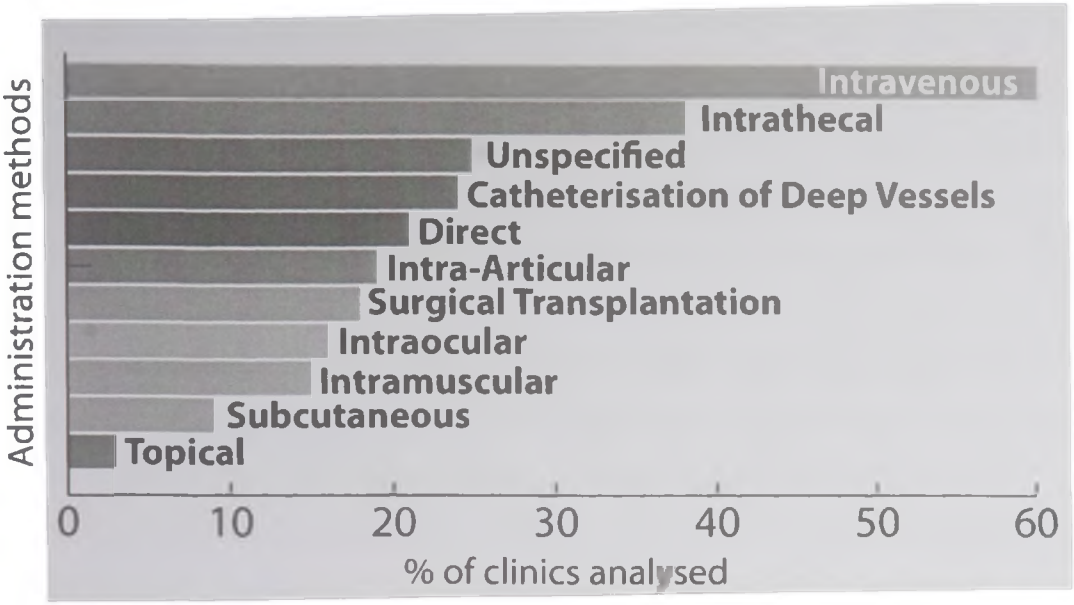
Stem Cell Type	Percentage Of Clinics
Adult-Autologous	82
Umbilical	19
Adult-Allogenic	12
Fetal	10
Cord Blood	9
Embryonic	4
Other	3
Unspecified	1

Figure 2.7 Type of stem cell utilised as reported by clinics



Stem Cell Source	Percentage of Clinics
Bone Marrow	49
Adipose Tissue	47
Umbilical	22
Peripheral Blood	19
Fetal	12
Other	9
Blood/Marrow Donors	4
Unspecified	4

Figure 2.8 Source of stem cells utilised as reported by clinics studied



Administration	Percentage of Clinics
Intravenous	60
Intrathecal	38
Unspecified	25
Catheterisation of Deep Vessels	24
Direct	21
Intra-Articular	19
Surgical Transplantation	18
Intraocular	16
Intramuscular	15
Subcutaneous	9
Topical	3

Figure 2.9 Administration methods of stem cells as reported by clinics

Discussion

The growing popularity of stem cell tourism represents a significant challenge to travel medicine practitioners. A heightened awareness of both the extent of the practice of stem cell tourism and the risks associated with unproven stem cell therapies should be a prerequisite among the travel medicine community in the interest of patient safety.

We identified a number of factors which could potentially concern travel medicine practitioners. Among these considerations were the ease with which patients could obtain information online pertaining to unlicensed stem cell therapies, as well as the possibly unbalanced description of such therapies. Furthermore, the portrayal of many of the procedures as low risk combined with the representation of stem cell therapies as panaceas is an irresistible prospect for many patients and their families. This is compounded by a lack of undergraduate and postgraduate medical teaching in regenerative medicine, as well as a deficit in clinical guidance, conferring a lack of knowledge of the topic on practitioners.

There is a significant shortage of resources available to travel medicine practitioners from which they can obtain reliable information in order to safely guide patients. Frequently, this deficiency places the travel medicine practitioner in the unsatisfactory position of having to resort to extrapolating adequate care pathways from guidelines pertaining to different medical tourism indications.[70-72]

Stem cell clinics represented online neglect to acknowledge the importance of travel medicine, travel vaccinations, and the merits of a pre-travel consultation with a travel medicine practitioner. This places patients at risk of travel-related morbidity while concurrently exposing them to largely experimental therapies.

Online stem cell clinics are employing the internet to directly communicate with patients and to advertise largely unproven stem cell therapies. These clinics are readily accessible online and operate globally. Fifty-nine per cent of the total American population use the internet as a source of health information.[73] With the advent of smart phones and tablets, the internet will undoubtedly gain an even greater influence within the field of patient information and education. As this study reveals, many stem cell clinics have already harnessed the powerful resource of the internet, with therapies described in an exaggerated manner, with often minimal discussion of the potentially detrimental effects of such therapies.

While many clinics have been the subject of intense scrutiny in the past, they continue to function despite a lack of accreditation.[63] This is partly due to the fact that patient demand for stem cell treatments far exceeds that which regenerative medicine is capable of accommodating.[74] This demand has been complicated and exacerbated by long treatment waiting times.[75] One of the principal factors driving demand for these unproven therapies is that of human aspiration.[61,76] Many of the conditions targeted by stem cell therapists have a poor or chronic prognosis under the supervision of conventional medicine. A number of the clinics encountered offer cure and major improvements in the clinical status of patients. The prospect of such an improvement in clinical status promotes patient subscription to these therapies, perhaps without due consideration of the experimental nature of treatment and the risks involved.

No specific documents are available to aid the travel medicine practitioner prior to a consultation regarding travel for stem cell therapy. The International Society for Stem Cell Research (ISSCR) have devised guidelines relating to responsible translation of stem cell research and also provides a very informative patient handbook on stem cell therapies.[60,77] Such documents, however, fail to discuss the pertinent travel medicine issues, such as appropriate pre-travel vaccination and malaria chemoprophylaxis, food and water precautions, as well as pre- and post-travel health advice. Practitioners may refer to general guiding principles in relation to medical tourism[70] or utilise briefing papers, information documents and patient safety checklists devised by other medical tourism sub-specialties to provide an indication of the information that people considering travel for medical care should discuss.[89,90]

Documents such as these provide a framework from which to develop specific stem cell pre-travel consultations; however, no specific pre-stem-cell travel documents are currently available. This places travel medicine practitioners in an unwelcome position of having to consult on a difficult issue without a reliable source to guide them and structure their consultations.

Recommendations

Improving both physician and patient education is essential in terms of overcoming the uncertainty surrounding unlicensed stem cell therapies. Family physicians have a critical role to play in this area. They are a preferential source of information with respect to stem cell therapies and can ensure that patients and their caregivers are making decisions that are as informed as possible and truly in their best interests.[78] This is complicated by a sense within patient groups that family physicians may not be sufficiently knowledgeable to discuss the topic of stem cell therapies in detail.[79] Furthermore, providing advice can be problematic for physicians due to a lack of published guidance.[79]

Developing travel medicine protocols specific to the stem cell tourist would equip physicians with a substantial framework from which to address patient queries and structure consultations. The provision of reliable information would equip patients with the requisite knowledge to make an informed decision. This process would promote patient autonomy and discourage many from crossing international borders to pursue experimental and potentially dangerous treatments.[78]

Rigorous regulation can ensure translation of stem cell science into effective therapies rather than into ineffective market products.[80] A broad agreement exists within the stem cell community, advocating the need for more international regulation and oversight of unproven therapies.[81-83] This would require international agreement, as most regulations currently apply intra-nationally. This was highlighted recently in Italy when an exception was made at parliamentary level for a trial to be pursued outside of previously recognised regulatory boundaries, bringing the field into disrepute and undermining legitimate research ongoing within Italian and European borders.[80]

Unfortunately, a global consensus on a bespoke regulatory pathway for the translation of stem cell therapies is far from being realised. Major changes to regulation of stem cell medicine only occur in response to public pressure after a significant event by which stage it is too late as the life of a patient has already been compromised and the esteem with which the field of stem cell research is held has already been diminished.[84]

Another area of concern pertains to scientific responsibility, whereby scientists provide cell lines exclusively to researchers involved in legitimate

studies adhering to recognised guidelines and policies. Implementation of such a policy would reduce the amount of stem cell material being used by unlicensed clinics.

An example of a centre working within legal parameters is the Centre for Cell Manufacturing Ireland (CCMI) in Galway, Ireland, where patients will receive a good manufacturing practice (GMP)-prepared treatment based on scientific rationale and established pre-clinical data in an appropriately regulated clinical setting with the support of expert clinicians and proven healthcare infrastructure.

Conclusions

It is imperative that the travel medicine community is made aware of the potenital threat posed by unregulated online stem cell clinics. These clinics are harnessing the internet to attract a wide range of patients suffering from a diverse catalogue of conditions to therapies that are described in an attractive but possibly exaggerated manner. A concerted effort from scientists, researchers, doctors, advocacy groups and governments is required to rapidly address the existing legislative deficiencies to prevent these clinics from offering clinically unproven treatments to vulnerable patients.

It remains beyond doubt that improving physician and patient knowledge in tandem with enhanced regulation and scientific responsibility would benefit vulnerable patients and also protect the unquestionably immense potential of stem cells as a therapy for human beings. Stem cell therapy is only in its infancy and needs to regulated and monitored adequately today so that it can change the lives of patients tomorrow.

Acknowledgements

I am very grateful to Dr. Ruairí Connolly for his assistance in retrieving information from relevant websites for the purposes of this study.

2.3. Travelling Safely With Diabetes Mellitus

This section reproduces an original learning resource I developed for use as an OSKE workshop (see Chapter 6.2) at the 2012 Northern European Conference on Travel Medicine hosted by the Travel Medicine Society of Ireland in Dublin. I was Chair of the scientific committee for the conference. I also published articles on the subject in *Modern Medicine*, and in *Emporiatrics*, the newsletter of the Faculty of Travel Medicine at the Royal College of Physicians and Surgeons of Glasgow.

Workshop title: Preparation of Patients with Diabetes for Healthy Travel

Learning outcomes:

By the end of this workshop, the delegate is expected to be able to:

1. List the topics which should be raised with a diabetic traveller in a pre-travel consultation.
2. Understand the predicted effects of travel on glycaemic control.
3. Advise the diabetic traveller on how to safely transport and store insulin.
4. Have an awareness of the most important travel vaccines which are indicated for the diabetic traveller.
5. Offer advice to diabetic travellers on safe air travel, including insulin dose adjustment.
6. Counsel diabetic patients on staying healthy in hot climates.
7. Give basic advice on how to stay healthy at high altitudes.
8. Educate diabetic travellers on how to obtain medical care overseas.

Summary of content:

Earlier generations of diabetic patients may have approached travel with some trepidation and may even have been dissuaded from venturing overseas by their well meaning physicians. Travelling overseas poses unique difficulties for people with diabetes but once these are addressed well in advance of travel it is possible for the patient with diabetes to travel safely on extended trips across multiple time zones to a variety of exotic destinations.

Pre-travel consultation

If time allows the diabetic traveller should be encouraged to schedule a pre-travel visit to his/her doctor, diabetes specialist nurse or GP practice nurse at least four to six weeks before departure.[85] The patient should take along a reliable travelling companion who should be informed about the medical emergencies that may arise and thus be able to render assistance if necessary. Any changes in the patient's medical management should be made well in advance of departure so that the patient is familiar with the changes and any adverse effects of treatment are observed.

International travel is associated with disturbed glycaemic control[86] so it is important to optimise your diabetic patient's glycosylated haemoglobin before travel. You should screen for complications such as diabetic retinopathy, diabetic nephropathy and diabetic neuropathy at the pre-travel consultation. Patients with particularly brittle diabetes or established complications should attend the diabetes clinic before making final travel arrangements as they may be advised to postpone travel until improved glycaemic control is achieved.

The traveller's doctor should provide a covering letter on headed paper detailing the medical history, current medications, and the need to carry insulin pens, syringes, needles, lancets and a glucometer in the hand luggage.[87] The traveller should be advised to contact the airline before booking the flights to check the airline's policy regarding the transport of insulin. Remind your patient to present this letter at airport security stations and international customs. Glucometers can be safely x-rayed if necessary. It is important that the diabetic traveller does not carry insulin in a suitcase stored in the luggage hold as this will reach sub-zero temperatures and destroy the insulin. Double the usual amount of all medications should be taken and divided into two parts, stored in separate bags.

The usual pre-travel vaccinations and malaria preventive advice will apply to the diabetic traveller.[88] It is reasonable to offer influenza and pneumococcal vaccines particularly to the older diabetic as well as hepatitis B vaccine in case medical intervention in hepatitis B endemic countries is required. Those travellers embarking on a cruise should inform the cruise liner company well in advance so that the cruise ship doctor is aware of their condition and any special needs they may have. Cruises are not suitable for diabetics who are very prone to motion

sickness or who have poorly controlled diabetes because of the often prolonged isolation from hospital care.

Precautions during air travel

It is not recommended to contact the airline prior to departure to request a special diabetic diet as these meals may not contain sufficient carbohydrate. Rather, encourage your diabetic patients to self-monitor their capillary blood glucose frequently during travel and at their destination. It is advisable to carry an additional source of sugar, such as small snacks or glucose tablets, in case the meals are delayed due to turbulence. The rapid acting insulin should not be injected until the food is on the tray in front of the passenger.

Insulin dose adjustment

Advise your diabetic patients to leave their watch unadjusted during flight so that it continues to show the time at the point of departure as this will make it easier to judge whether there is an undue delay between meals. For flights crossing more than six time zones the insulin doses should be adjusted. No blanket guidelines should be offered as individual patients will differ and must be guided by their capillary blood glucose values. As a general rule, flying eastward will cause an overlap of two injections as the day is shorter so that a reduction in the rapid acting insulin doses may be necessary, while westward travel may necessitate an extra meal and an extra injection of rapid acting insulin.[89] No adjustments are needed when travelling due north or south. Type 2 diabetics taking oral hypoglycaemic agents should maintain their dosing schedule according to local time.

It may be safer to allow blood sugar levels to run slightly higher than normal rather than run the risk of hypoglycaemia. Those travellers using subcutaneous insulin infusion pumps should continue with their normal basal and bolus insulin doses, but they should carry spare long acting and short acting insulin and spare batteries. The clock on the pump should be changed upon arrival at the destination. The diabetic's travelling companions and the flight attendants should be given a glucagon kit to use in the event of a hypoglycaemic episode on board the flight.

Diabetics on long haul flights may find that their lack of activity during the flight causes hyperglycaemia so they should be advised to move about the cabin as much as possible to utilise glucose. Exercise is also essential in the prevention of deep venous thrombosis. The use of flight stockings is contraindicated in the diabetic with established peripheral arterial disease.

Staying healthy in hot climates

Strongly advise your diabetic patient to wear loose fitting, light-coloured cotton clothing and a wide-brimmed hat and take the shade as much as possible to prevent heat exhaustion or heat stroke. Sunburn should be avoided by wearing a high-sun protection factor sun cream and reapplying it frequently especially after swimming. Hot climates will increase the blood flow through the skin and lead to a more rapid absorption of insulin than usual. Advise your diabetic patient to be wary of hypoglycaemia when sunbathing in particular. The diabetic should carry bottled water during all excursions as dehydration will pose particular problems. Patients with diabetic autonomic neuropathy or on beta-blockers are particularly susceptible to heat injury including heat syncope, heat exhaustion and heat.[90]

The capillary blood glucose should be checked before swimming or other strenuous exercise. If there is ketonuria, physical activity should be avoided in the type 1 diabetic as diabetic ketoacidosis may otherwise ensue. If the blood sugar is teetering on the low side the patient should take some rapidly absorbable carbohydrate to prevent hypoglycaemia. Exercise may give rise to a delayed hypoglycaemia several hours later or even the following day.[91] The diabetic should never swim alone while on holidays and also never after drinking alcohol. It is a good idea to purchase a cool-bag with a cool pack to keep the insulin cool when on the beach. Glucagon can be stored out of a fridge for up to 18 months.

The usual precautions governing food and water safety ('boil it, cook it, peel it or forget it') apply to the diabetic traveller. It is important that the 'sick day rules' are observed and that insulin is not withheld if the diabetic traveller is unable to keep any food down due to prolonged vomiting. Life-threatening diabetic ketoacidosis may occur if the type 1 diabetic omits insulin doses. Provide your patients with electrolyte replacement solutions and with a supply of a suitable antibiotic such as ciprofloxacin should they develop severe diarrhoea with signs of dysentery.

Other health considerations

Sand on the beach and in the sea may contain sharp materials such as stones, sea-urchins, shells and glass and street pavements can reach high temperatures in hot climates. The diabetic traveller should therefore always wear well-fitting sandals and never walk barefoot. Diabetic trekkers should wear hiking boots that are well worn-in and apply blister plasters at the first appearance of a blister. If a blister develops it should not be punctured but rather covered with an antiseptic and relieved of pressure. Any diabetic foot infection, however trivial, mandates prompt medical attention. An antibiotic/antihistamine cream and a course of oral flucloxacillin should be provided to treat insect bites as these may become badly infected.

Diabetics trekking to high altitude should be warned that the symptoms of acute mountain sickness make it difficult to maintain the increased caloric intake required to fuel the increased physical effort involved.[92] In general, people with type 1 diabetes are advised to reduce their daily insulin dose by 20-30% and double their usual carbohydrate intake during the climb.[93] A further problem is caused by the similarity between the symptoms of high-altitude cerebral oedema and hypoglycaemia. Diabetic trekkers should be aware that glucometers may give falsely low readings of up to 40% at very high or extreme altitude, leading to the overdiagnosis of hypoglycaemia.[93,94]

Obtaining medical care overseas

Travel insurance is essential for diabetic travellers who must declare full details of their condition to the insurance provider. All diabetic travellers should wear MedicAlert® bracelets to identify them as diabetic in the event of a personal medical emergency. Encourage your patient to learn and write down some basic phrases in the local language, such as *"I have diabetes; please call for a doctor"*. The names of English-speaking physicians practising in foreign countries may be obtained by contacting the International Association of Medical Assistance to Travelers (www.iamat.org). Other useful sources of practical information include Diabetes UK (www.diabetes.org.uk), manufacturers of insulin and the patient's local pharmacist.

CHAPTER 3

Health Risks of Travel to High Altitude

3.1. Awareness of Health Risks of Travel to High Altitude[2]

Introduction

Each year, some 40 million people travel to altitudes above 2,500m.[95] The increasing interest in outdoor recreational pursuits and adventure travel has exposed a greater number of travellers to the dangers of high altitude. Improved access to high-altitude destinations accounts for a shift in the demographic profile of the travellers visiting them.[96] The mountains and high-altitude ski resorts are no longer the sole domain of travellers with expertise and experience but rather are attracting many young, poorly equipped, and ill-informed travellers who may not be aware of the health risks attendant upon high-altitude travel.

It has been my impression that many of the travellers who attend travel medicine clinics have poor baseline knowledge of the risks of high-altitude travel, have not given due consideration to their travel itinerary, and are not prepared to deal with medical emergencies they may encounter at high altitude. Frequently, such travellers have not been to high altitude before and have overambitious plans to summit high peaks, some of them at extreme altitude, without adequate acclimatisation schedules.

It is against this backdrop that I chose to study the awareness of travellers attending a travel medicine clinic of the health risks of high-altitude travel. I wished to highlight areas where travellers' knowledge may be particularly deficient in an effort to improve the pre-travel health advice provided to them.

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[2] Adapted, with the permission of the co-authors and the British Global and Travel Health Association, from: G Flaherty, T O'Brien and G Fry. Public awareness of the health risks associated with travel to high altitude destinations. British Travel Health Association Journal 2006;8:27-31.

Aims and Objectives

The overall aim of this study was to determine the level of awareness among a sample of travellers attending an Irish travel medicine clinic of the health risks associated with travel to high-altitude destinations. The specific objectives of the project were as follows:

1. To construct a demographic profile of Irish travellers to high altitude.
2. To determine the level of knowledge amongst these travellers of their travel itinerary and ascent profile.
3. To ascertain their degree of awareness of the risks of high-altitude illness.
4. To study their knowledge of other health risks apart from high-altitude illness which they may encounter at high altitude.
5. To issue recommendations based on the findings of the study which will serve to promote safer travel to high altitude.

Literature Review

Background

The chronicle of mankind's attempts to climb ever higher is one of the most exciting in medicine.[95] Human beings travel to high altitude for many reasons. Approximately 140 million people reside permanently at altitudes greater than 2,500m[97], and each year some 40 million people travel to such altitudes.[95] Miners in parts of South America commute each week to altitudes up to 6,000m from their homes at lower altitudes.[98] Increasing numbers of people travel to high altitudes to engage in recreational activities, such as trekking, mountaineering, and skiing. The deployment of soldiers to high-altitude regions in India and Afghanistan has also focused attention on the subject of altitude illness. In travelling from lowland regions of the world to high-altitude destinations, travellers fly in aircrafts with cabin pressures of between 1,525m and 2,000m. These cabin pressures may rarely reach the equivalent of 8,000ft (2,440m).[99]

The designation "high-altitude illness"[†] is a collective term for a group of syndromes that can affect unacclimatised travellers shortly after ascent to high altitude. High-altitude pulmonary oedema and high-altitude cerebral oedema are uncommon but potentially rapidly fatal conditions. The far more common entity of acute mountain sickness can be considered a public health problem because of the millions of visitors to high-altitude locations around the world each year. Acute mountain sickness has economic consequences, especially for the ski industry.[100] High-altitude illness occurs in previously healthy, physically fit young people and it is preventable if it is recognised early, and appropriately managed. Unfortunately, many physicians are still unaware of high-altitude medical problems and may not be able to offer accurate advice to intending travellers.

Categories of high altitude

Four levels of altitude at which medical problems may be encountered are commonly described:

1. Intermediate altitude (1,500m-2,440m) – Significant altitude illness is rare in this altitude range, although mild acute mountain sickness is reported as low as 2,000m.[101] Visitors to Kenya should be advised that the capital city Nairobi is at an elevation of 1,800m.
2. High altitude (2,440m-4,270m) – Most altitude-related medical problems occur at this altitude range, since these are the elevations visited by the greatest number of people.[99] The incidence of acute mountain sickness in new arrivals increases from 25% to 40% as the altitude increases from 2,700m to 3,600m.[102] Visitors to Quito in Ecuador and La Paz in Bolivia are at altitudes of 2,800m and 3,700m, respectively.
3. Very high altitude (4,270m-5,490m) – These altitudes are commonly encountered by trekkers and mountaineers in South America and the Himalayas. Many high-altitude base camps are found at this altitude and climbers may stay at these camps for weeks at a time. It is considered very dangerous to ascend to these altitude levels without proper acclimatisation.

[†] In the current study, the term "altitude sickness" is used for simplicity and because it is more familiar to laypersons. No distinction was made between the different types of high-altitude illness to avoid confusion among the study subjects.

4. Extreme altitude (5,490m-8,848m) – The extreme altitude mountain ranges are only reached by experienced expeditionary mountain climbers. Acute medical problems at these elevations are more frequently related to terrain and weather-related problems such as falls, avalanches, rockfalls and hypothermia, since most climbers at these lofty elevations will have acclimatised slowly. High-altitude pulmonary oedema and high-altitude cerebral oedema may first occur in this altitude range, however, if ascent is too rapid or the work load too great.[99]

High altitude deterioration occurs above about 5,500m and is characterised by weight loss, poor appetite, slow recovery from fatigue, and an increasing apathy.[103] Acclimatisation does not occur at these altitudes. Altitudes above 8,000m in the Himalayas have been called 'the death zone', and for this reason climbers who are establishing routes and camps beyond this elevation return to base camp for several days before ascending rapidly for their summit attempt.

Acclimatisation to altitude

It is remarkable to consider that an unacclimatised subject exposed acutely to an altitude equivalent to the summit of Everest remains conscious for only 2 minutes.[103] Birds can fly higher for long periods, but humans are unable to live permanently above 5,300m, suggesting that this is the upper limit of altitude to which they can acclimatise. The term 'altitude acclimatisation' refers to the physiological processes whereby lowland humans defend themselves against the reduced partial pressure of oxygen in the inspired air at high altitude. The time courses of these responses vary but most of the changes occur in a matter of days to weeks. There is considerable individual variation in the speed and extent to which people acclimatise. Apart from previous acclimatisation there are no reliable predictors of future performance at altitude.[103] The most important physiological effects are an increase in ventilation due to hypoxic stimulation of the peripheral chemoreceptors in the carotid bodies and a gradual loss of bicarbonate from the kidneys which restores the blood pH to normal following the initial respiratory alkalosis caused by hyperventilation. The well-known increase in haemoglobin concentration at high altitude is due to an initial decrease in plasma

volume causing haemoconcentration, followed by a slow increase in the red cell mass secondary to hypoxic stimulation of erythropoietin secretion.

The most important risk factors for the development of high-altitude illness are the rate of ascent, the sleeping altitude, and individual susceptibility. Other risk factors for high-altitude illness include a history of high-altitude illness and physical exertion.[104] Lack of physical fitness is not a risk factor for acute mountain sickness[105] which is contrary to the belief amongst climbers that fit people should be less susceptible to altitude illness. Children and adults appear to be equally affected[106], but people older than 50 years may be less likely to develop acute mountain sickness than younger people.[107] Neck irradiation, by damaging the carotid bodies[108], and respiratory tract infection[109] are potential risk factors for high-altitude illness, but it is unclear if dehydration is an independent risk factor for acute mountain sickness.[98]

Most trekkers and mountaineers accept the axiom of 'climb high, sleep low' and, after a day's climbing, they prefer to return to a lower elevation to sleep. An oft quoted rule of thumb is that above an altitude of 3,000m each night's camp should not be more than 300m above the previous night's one, and that there should be a rest day every 2 or 3 days or after every 1,000m above 3,000m.[110] Climbers frequently take day excursions to higher altitudes during their 'rest days', probably because the greater altitude and exercise promote acclimatisation. The expedition leader should pace the party to accommodate the slowest member of the team or perhaps send that person down to a lower altitude.[102]

For the average trekker who plans to climb and sleep at altitudes between 10,000 feet and 14,000 feet, 2 to 4 days spent trekking at an intermediate altitude, between 6,000 feet and 8,000 feet will be beneficial. If possible, the first camp should be no higher than 2,400m (8,000 feet).[111] For example, trekkers embarking on the Inca trail will benefit from spending a few days at the intermediate altitude of Cuzco (3,326m) before ascending to Machu Picchu. Trekkers planning on reaching very high altitudes of 14,000 feet to 18,000 feet are advised to spend a second stage of 2 to 4 days acclimatising at 12,000 feet to 13,000 feet.

In regions such as the popular Everest trail in the Himalayas, graded ascent is possible, whereby long approach marches allow acclimatisation to occur gradually during the approach to base camp (5,338m). It is popular to fly from Kathmandu (1,300m) to a landing strip in Lukla (2,440m) as this saves

considerable time. However, it does greatly increase the risk of developing altitude illness.[112]

Persons who have only a short period of time to spend on a mountain are reluctant to "waste" time acclimatising[102], and the author is aware of commercial expeditions on Kilimanjaro which rapidly convey inexperienced trekkers to the extreme altitude of the summit at 5,895m in 4 days, without making allowances for rest days.[113] It is not surprising, therefore, that the summit success rate on such expeditions is disappointingly low. Awareness amongst trekkers of the duration of their trek, the maximum altitude they intend to reach, and the number of days taken to reach this altitude is essential if acclimatisation is to be facilitated and high-altitude illness avoided by ascending at a reasonable rate. This is particularly pertinent if trekkers are climbing without professional guidance.

Epidemiology of high-altitude illness

Although it is a source of much morbidity amongst travellers, the risk of dying with high-altitude illness is low.[114] The all cause mortality rate for trekkers to Nepal in one study was 0.014% and from altitude illness 0.0036%.[115] Altitude-related illnesses accounted for 17% of all deaths amongst British climbers attempting peaks over 7,000m.[116] From 1950 to 2001, the world's fourteen 8,000m peaks, all in the Himalayas, had claimed the lives of 604 mountaineers.[117] High-altitude cerebral oedema and high-altitude pulmonary oedema were estimated to contribute 17.4% of the 23 deaths in British expeditions to peaks above 7,000m from 1968 to 1987.[118] It is likely that high-altitude illness was a co-factor in many of the fatalities at extreme altitude attributed to accidents such as falls.

Acute mountain sickness

According to the Lake Louise Consensus Group, acute mountain sickness is defined as the presence of a headache in a previously unacclimatised person who has recently arrived at an altitude greater than 2,500m plus the presence of at least one of the following symptoms: gastrointestinal symptoms such as anorexia, nausea or vomiting, insomnia, dizziness, and lassitude or fatigue.[119] Symptoms typically develop within 6 to 12 hours after ascent, but may appear as early as one hour. The non-specific symptoms of acute mountain sickness may readily be

attributed to other conditions such as dehydration[114], especially by trekkers who do not wish to depart from a prearranged schedule or retard the progress of their group. Symptoms of acute mountain sickness may be quantified by using the Lake Louise scoring system (Appendix 2). Apart from the occasional presence of peripheral oedema, which can occur independently at altitude, there are no physical signs that are diagnostic of acute mountain sickness.

The reported rate of acute mountain sickness varies greatly (Figure 3.1). In the Mount Everest region of Nepal, about 50% of trekkers who walk to altitudes above 4,000m over 5 or more days develop acute mountain sickness[120], while 84% of those who fly directly to 3,860m are affected.[121] Gaillard and co-workers[122] compared the prevalence of acute mountain sickness around the Annapurna mountain range in Nepal in two cohorts of trekkers 12 years apart. The prevalence of acute mountain sickness had decreased from 43% to 29%, an observation attributed by the authors to a slower ascent rate and an improved awareness of altitude illness.

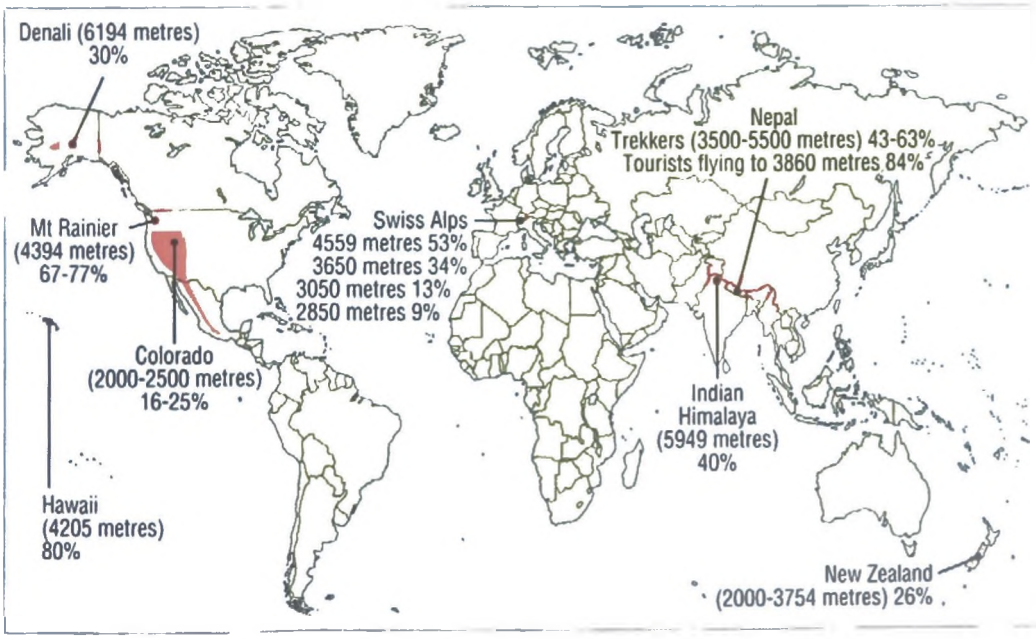

Figure 3.1 Global incidence of acute mountain sickness (reproduced with the kind permission of the authors[21]).

The complex pathophysiology of acute mountain sickness is believed to arise from a combination of a mild increase in brain volume[123], increased sensitivity of pain receptors with hypoxia[124], free-radical mediated damage to the blood-brain barrier[125], and upregulation of the gene for vascular endothelial growth factor[126], a promoter of capillary leakage. According to the model of Roach and Hackett[127], hypoxaemia leads to increased cerebral blood flow, altered permeability of the blood-brain barrier, and cerebral oedema. Acute mountain sickness may occur in people with a lower ratio of cranial cerebrospinal fluid to brain volume since they are unable to buffer the brain swelling by displacing cerebrospinal fluid.

High-altitude cerebral oedema

High-altitude cerebral oedema is widely regarded as the end stage of acute mountain sickness and so therefore should be preventable if the preceding acute mountain sickness is not ignored. It may be defined as the onset of ataxia, altered mental status, or both, in someone with acute mountain sickness or high-altitude pulmonary oedema. In people with concomitant high-altitude pulmonary oedema, severe hypoxaemia can cause rapid progression from acute mountain sickness to high-altitude cerebral oedema.[98] The prodromal symptoms of drowsiness or a change in behaviour may be ignored by patients and their climbing companions. Clinical examination may disclose ataxia, papilloedema, retinal haemorrhages and, occasionally, focal neurologic deficits.[98] The illness may progress over a few hours and lead to coma and death from coning. Many conditions mimic acute mountain sickness and high-altitude cerebral oedema and are listed in table 3.1.

Table 3.1 Differential diagnosis of high-altitude illness

Acute mountain sickness and high-altitude cerebral oedema
Acute psychosis
Arteriovenous malformation
Brain tumour
Carbon monoxide poisoning
Meningitis
Encephalitis
Dehydration
Diabetic ketoacidosis
Exhaustion
Hypoglycaemia
Hyponatraemia
Hypothermia
Ingestion of alcohol or recreational drugs
Migraine
Epilepsy
Stroke
Transient ischaemic attack

Management of acute mountain sickness and high-altitude cerebral oedema

Three axioms guide the management of acute mountain sickness: further ascent should be avoided until the symptoms have resolved; if patients do not respond to medical treatment they should descend to a lower altitude; and at the first sign of high-altitude cerebral oedema, patients should descend to a lower altitude.[100] A descent of as little as 500m to 1,000m usually leads to a resolution of acute mountain sickness while high-altitude cerebral oedema may require further descent.[100] Rest alone may be sufficient in cases of mild acute mountain sickness with judicious use of analgesics such as ibuprofen and anti-emetics. The use of portable hyperbaric chambers may be a useful temporising measure while

preparing for descent in cases of severe acute mountain sickness or high-altitude cerebral oedema. With the use of these chambers at a pressure of 2psi, descent is simulated so that the equivalent altitude is about 2,000m lower than the ambient altitude.[100]

When terrain or weather problems delay descent and supplementary oxygen is not available, medical therapy may be instituted. The carbonic anhydrase inhibitor acetazolamide may be used in severe acute mountain sickness or high-altitude cerebral oedema. It acts by inducing a metabolic acidosis through renal loss of bicarbonate ions, thus stimulating the respiratory centre in the brain stem, causing increased ventilation and improving oxygenation of the blood. Dexamethasone is as effective as or superior to acetazolamide and works within 12 hours.[128] After acute mountain sickness has resolved, further ascent should be undertaken cautiously, perhaps with acetazolamide prophylaxis.[100]

Prevention of acute mountain sickness and high-altitude cerebral oedema

The optimal strategy for preventing acute mountain sickness and high-altitude cerebral oedema is a gradual ascent to promote acclimatisation. Only when the climber has acclimatised to the current altitude should he ascend further. Some authorities recommend acetazolamide as prophylaxis of acute mountain sickness for people such as rescuers who have to make a forced rapid ascent to altitudes above 3,000m and for those with a history of severe acute mountain sickness.

Dexamethasone may be used in people allergic to sulpha drugs but it is important to advise such patients that dexamethasone does not promote acclimatisation and so they should not continue to climb while taking the drug. Acetazolamide may be more effective than dexamethasone[129], and the combination of the two drugs is more effective than either alone.[130] It has been proposed that gingko biloba may act to prevent acute mountain sickness because of its antioxidant effects[131], but in the largest trial to date[132] the combination of gingko and acetazolamide was no more effective than acetazolamide alone.

High-altitude pulmonary oedema

Most deaths from high-altitude illness are due to high-altitude pulmonary oedema.[100] Risk factors include a rapid rate of ascent, individual susceptibility, unilateral absence of a pulmonary artery, exertion, and cold, the latter by

increasing pulmonary artery pressure.[100] High-altitude pulmonary oedema commonly appears on the second night at a new altitude and rarely strikes after more than four days at a given altitude.[100] In one study 50 percent of those with high-altitude pulmonary oedema had acute mountain sickness, and 14 percent had high-altitude cerebral oedema.[123] Symptoms include marked shortness of breath with exercise, progressing to dyspnoea at rest, a dry cough, with later pink or bloody sputum, weakness, and poor exercise tolerance. Tachypnoea, tachycardia and fever are common and there may be crackles in the chest, with a predilection for the right middle lobe.[100] Children, in particular, with a respiratory tract infection may be at increased risk.[134]

High-altitude pulmonary oedema is a non-cardiogenic pulmonary oedema characterised by increased pulmonary capillary pressures leading to patchy vascular leakage and stress failure of endothelium. Some patients who are susceptible to high-altitude pulmonary oedema may have an exaggerated hypoxic pulmonary vascular response.[135] Other studies implicate a defect in nitric oxide synthesis[136], possibly due to reduced activity of nitric oxide synthase. In a double-blind, randomised, placebo-controlled study of mountaineers susceptible to high-altitude pulmonary oedema, prophylactic inhalation of the beta-adrenergic agonist salmeterol reduced the incidence of high-altitude pulmonary oedema by 50%[137], possibly by increasing the clearance of alveolar fluid.

Prevention and treatment of high-altitude pulmonary oedema

Gradual ascent to allow sufficient time for acclimatisation is also the best way to prevent high-altitude pulmonary oedema. In people who have had high-altitude pulmonary oedema previously, nifedipine may be used as prophylaxis.[138] With early recognition of high-altitude pulmonary oedema, immediate descent and supplementary oxygen, if available, are the mainstays of treatment. If descent is impossible, treatment in a portable hyperbaric chamber with the head tilted upward to 30 degrees may be lifesaving. Nifedipine may be used as an adjunct to descent and oxygen.[139]

Other health risks at high altitude

Other non-altitude illness health risks encountered on treks to high altitude include travellers' diarrhoea, malaria, rabies, sunburn, dehydration, blisters, disturbed

sleep, hypothermia and frostbite. Although malaria transmission does not occur at altitudes above 2,000-2,500m, travellers often pass through malarious areas en route to or from high-altitude destinations.[140] Trekkers to Kilimanjaro, for example, will have passed through malarious regions before starting their trek, and will be taking anti-malarial prophylactic drugs on the mountain. Of the anti-malarials, mefloquine may be best avoided in mountaineers because the drug may cause dizziness and its neuropsychiatric side effects may mimic high-altitude cerebral oedema. Of the alternative drugs, atovaquone-proguanil is perhaps the most acceptable since the regimen finishes a week after leaving the malarious area. The photosensitivity associated with doxycycline should be highlighted to the traveller since the risk of sunburn at high altitude is already increased.[141]

Many of the popular high-altitude destinations are endemic for the rabies virus and are located in remote areas, at a considerable distance from competent medical assistance. Trekkers are generally recommended, therefore, to receive pre-exposure rabies prophylaxis as rabies immunoglobulin may be difficult to acquire and may not be adequately screened for blood-borne viruses.

Travellers should similarly be advised to take food and water precautions and in some cases to disinfect drinking water with iodine as many of the high-altitude regions of the world are found in countries with a high risk of acute diarrhoeal illness in travellers.[140]

Sleep is very commonly impaired at high altitude and trekkers often complain that they wake frequently, have unpleasant dreams and feel unrefreshed in the morning.[142] Periodic breathing occurs at high altitude and causes apnoeic periods, during which profound arterial hypoxaemia occurs. Acetazolamide reduces the time spent in periodic breathing and improves the arterial oxygen saturation thus improving the quality of sleep.[143]

The importance of protecting their extremities against the cold, maintaining an adequate intake of fluids, wearing boots that are well worn in and treating blisters as soon as they become apparent should all be highlighted to the traveller.

Public awareness of high-altitude illness

The foregoing information on high-altitude illness underscores the need for public awareness of this potentially fatal, yet largely preventable condition. The focus of the present study is an assessment of the level of awareness of altitude-related

sleep, hypothermia and frostbite. Although malaria transmission does not occur at altitudes above 2,000-2,500m, travellers often pass through malarious areas en route to or from high-altitude destinations.[140] Trekkers to Kilimanjaro, for example, will have passed through malarious regions before starting their trek, and will be taking anti-malarial prophylactic drugs on the mountain. Of the anti-malarials, mefloquine may be best avoided in mountaineers because the drug may cause dizziness and its neuropsychiatric side effects may mimic high-altitude cerebral oedema. Of the alternative drugs, atovaquone-proguanil is perhaps the most acceptable since the regimen finishes a week after leaving the malarious area. The photosensitivity associated with doxycycline should be highlighted to the traveller since the risk of sunburn at high altitude is already increased.[141]

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Methods

A descriptive cross-sectional observational study was conducted to assess the level of current awareness of the health risks of high-altitude exposure in a group of trekkers. Ethics committee approval was not deemed necessary by the local ethics committee. A consecutive sample of travellers attending the Galway and Dublin clinics of the Tropical Medical Bureau for pre-travel health advice and travel vaccinations were invited to participate in the study. Subjects were recruited for the purposes of this study over a 5-month period. Travellers attending the Tropical Medical Bureau were greeted by the clinic manager at the reception desk and asked to complete a pre-travel health card. The destinations of the travellers were already known to the clinic staff, having been recorded on the appointment list at the time of booking. All travellers were asked if they planned on visiting destinations at altitude and if they responded positively they were asked to fill out a one-page questionnaire, "to help us improve the advice we give to people going to high altitude". Participants were excluded from the study if they refused to take part or if they had difficulties understanding written English. Where travellers who did not appear to be travelling to regions of high altitude subsequently indicated to the travel medicine physician during their medical consultation that they planned on reaching altitude, they were not asked to participate in the study as they may have increased their knowledge of altitude-related health risks by reading the available literature in the waiting room.

A written survey instrument comprising a combination of 18 multiple-choice and open questions was administered to eligible subjects (Appendix 3). The questionnaire was preceded by a half-page explanatory document outlining the background to the project and subjects were informed that the questionnaire would take 5-10 minutes to complete. Participants were assured that their responses would be treated confidentially. Subjects were instructed to complete the questionnaire without consultation and without reference to any source of information. Where doubt existed as to the interpretation of a question, clarification was provided by the clinic manager. Where multiple choices were offered, a "don't know" option was also provided. Numerical values were expressed in ranges to facilitate subsequent analysis. The questionnaire was piloted on two travellers and subsequently refined to eliminate ambiguity based on the feedback received.

The initial part of the survey identified demographic data such as gender and age. Data regarding nationality or educational level were not recorded. Knowledge of the travel itinerary was assessed by asking the respondents to indicate how many weeks remained until they planned to depart, their proposed high-altitude destination, the duration of their trip, and the number of people in their group. Subjects were asked if their trek was a guided one and if they had purchased travel insurance for the trip. The maximum altitude, if known, was recorded in feet and where the respondent indicated the response in metres, the altitude was converted to feet and assigned to one of four categories. In order to determine the ascent profile, data were collected on the number of days it would take to reach the maximum proposed altitude. Knowledge of the particular trek involved was further established by enquiring whether or not the expedition would involve technical climbing.

The subjects' previous altitude experience was examined and those travellers who had been to high altitude previously were asked if they suffered from high-altitude illness during that visit. The maximum previous altitude reached, where known, was recorded. Open questions were used to identify the level of knowledge amongst participants of symptoms of altitude illness and of methods of preventing altitude illness. Respondents were asked if lack of physical fitness increased the risk of altitude sickness. A scenario was presented in which one of the respondent's travelling companions developed "severe altitude sickness" and subjects were asked to choose from a list of emergency treatment approaches. Travellers were asked to identify their main information resources in learning about the health risks of high-altitude travel.

Travellers' perceptions of the non-altitude illness-related health risks presented by a visit to a high-altitude destination were explored by asking them if their trek carried a risk of diarrhoea, rabies, malaria, sunburn, frostbite, dehydration, blisters, or disturbed sleep.

Data were entered into a Microsoft Access database, collated and analysed. Specific queries were run as follows:

1. Proportions of male and female subjects.
2. Proportions of subjects in each age group.
3. Number of weeks until departure.
4. Destinations.

5. Group sizes.
6. Whether the trek was guided.
7. Whether travel insurance was obtained.
8. Maximum proposed altitude.
9. Number of weeks taken to reach maximum altitude.
10. Whether technical climbing was involved.
11. The level of previous altitude exposure.
12. Whether altitude sickness was experienced previously.
13. Whether the subjects knew of ways to reduce the risk of altitude illness.
14. Whether they identified the symptoms of altitude illness.
15. Whether they thought that fitness protected against altitude illness.
16. What advice they would give to a companion suffering from severe altitude sickness.
17. The sources of information they would consult on the topic of altitude-related health risks.
18. Whether their high-altitude trek carried a risk of diarrhoea, rabies, malaria, sunburn, frostbite, dehydration, blisters, or disturbed sleep.

Statistical analysis

Results were collated and analysed by SPSS 12.0 software (SPSS Inc.). *P* values were calculated by a Chi-square test to determine associations between factors. Results with a *p* value less than .05 were considered to be significant.

Results

Study participation

Seventy-seven subjects were recruited consecutively in the study over a 5-month period. Twenty-two subjects were recruited from the Galway Tropical Medical Bureau clinic and 55 from the Dublin clinics. The results from both centres were pooled and not compared as the populations in the two centres were considered to be demographically comparable.

Subject characteristics

Forty-four (57%) male and thirty-three (43%) female travellers participated in the study. Thirty-six percent of the travellers (n=28) belonged to the 26-30 year age group. No traveller under the age of 20 years was surveyed. Six trekkers over the age of 40 years responded to the questionnaire (Figure 3.2).

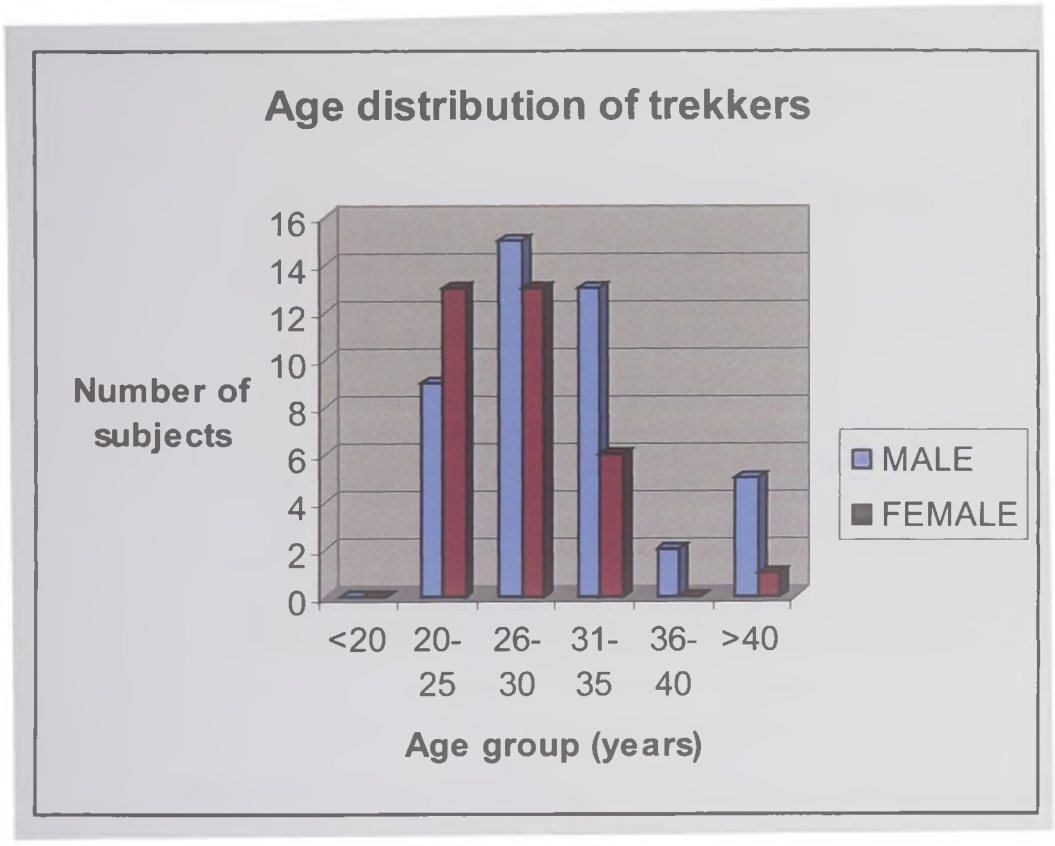

Figure 3.2 Age distribution of trekkers

Awareness of travel itinerary

The majority (62%) of trekkers in this study attended the travel medicine clinic with at least 3 weeks remaining before their intended travel date. A significant minority (10%) had less than one week left before their departure (Figure 3.3). These travellers were more likely to be aged over 31 years ($\chi^2 = 17.364$, $p = .008$).

The most popular high-altitude destination in this study (Figure 3.4) was the Inca trail in Peru (65%), followed by the Himalayas (15%). Two participants planned to trek in both the Andes and the Himalayas during a single trip. Both

were male and aged between 20 and 30 years. One of these individuals had not been exposed to high altitude previously. The Inca trail was the most popular destination for the 20-25 year and 26-30 year age groups ($\chi^2 = 14.538$, $p = .024$), with Kilimanjaro and the Himalayas more popular amongst older trekkers.

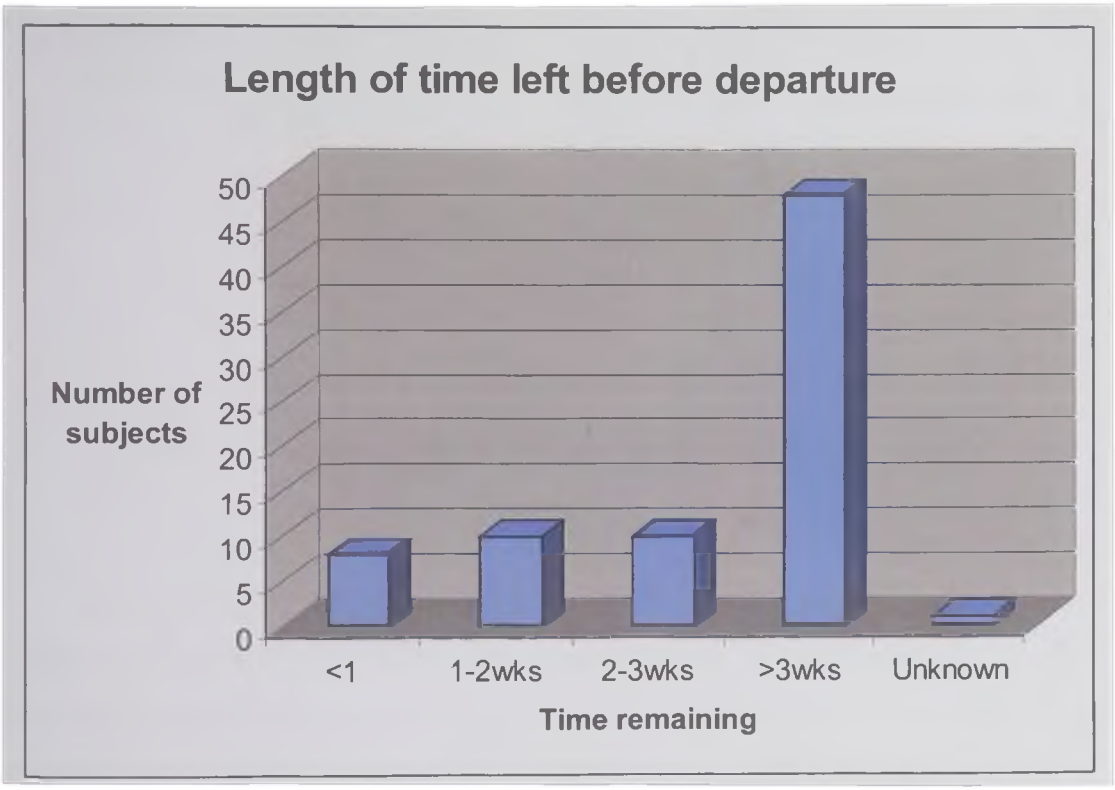

Figure 3.3 Amount of time remaining before departure

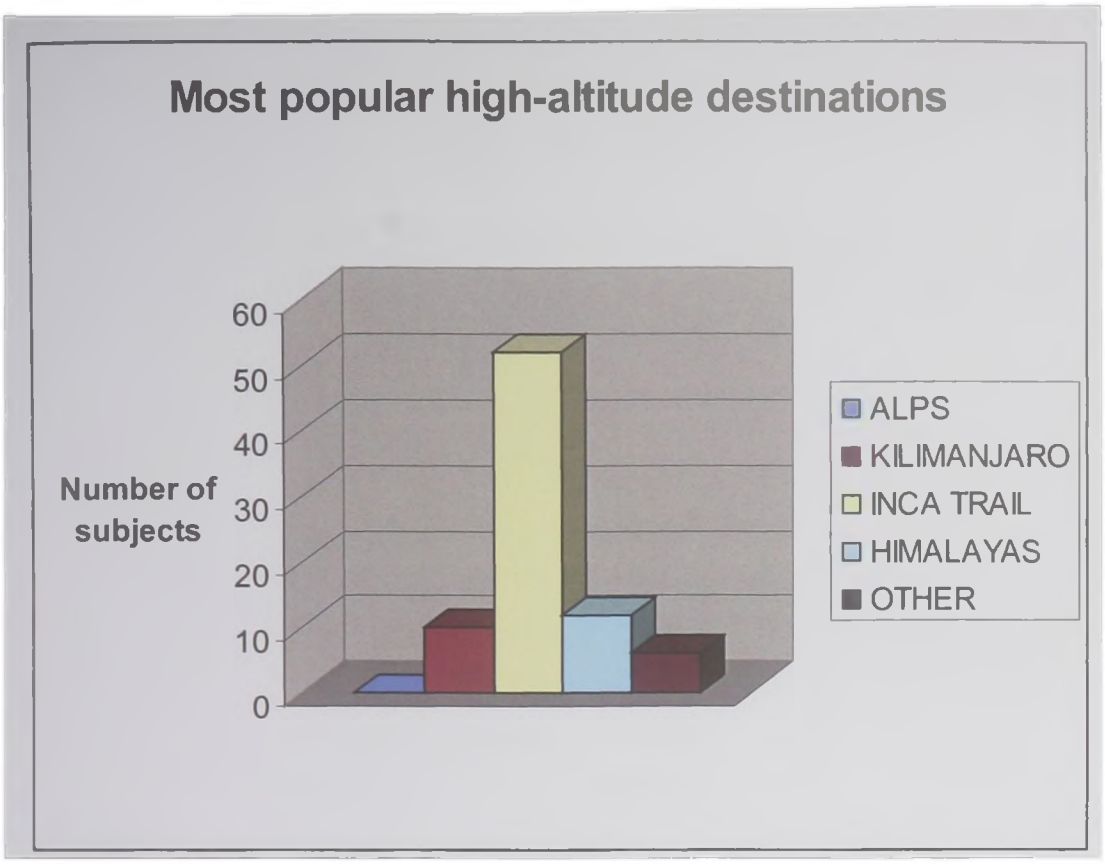

Figure 3.4 Most popular high-altitude destinations visited

Most trekkers (57%) planned on spending over 4 weeks at their high-altitude destination (Figure 3.5). A significant minority of trekkers (10%) planned on spending less than 2 weeks on their trip. These individuals were more likely to have had no prior altitude experience. The question asked subjects about the duration of their trip and not their trek so it is possible that some respondents either over- or underestimated the length of time they would spend at altitude.

Most of the travellers (78%) surveyed reported being part of a group of fewer than 5 people. Four percent of the trekkers (n=3) were members of a group of over 15 people (Figure 3.6). Approximately 8% of respondents were unsure of the size of their trekking party.

The majority (61%) of respondents reported that their trek would be guided (Figure 3.7). Of the 15 subjects who stated that their trek would not be guided, 10 were planning a trek to the Inca trail. Ninety percent of the trekkers had travel insurance at the time of their pre-travel consultation.

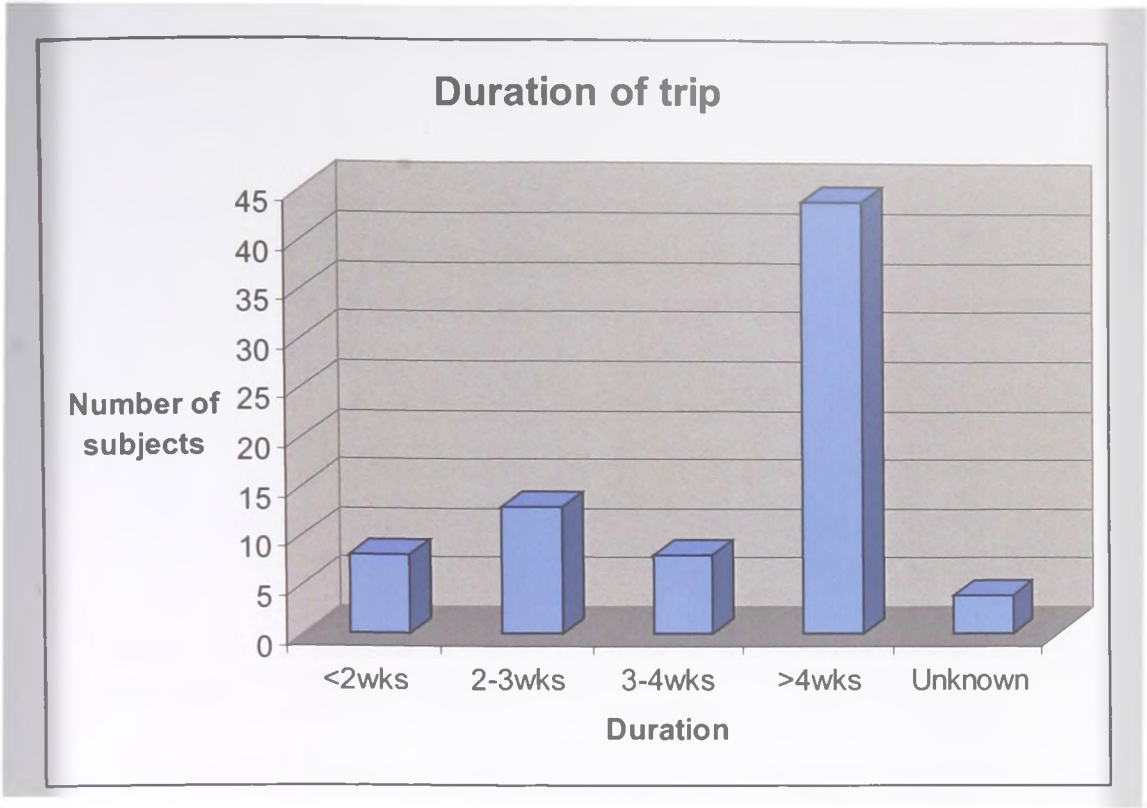

Figure 3.5 Planned duration of trips to high altitude

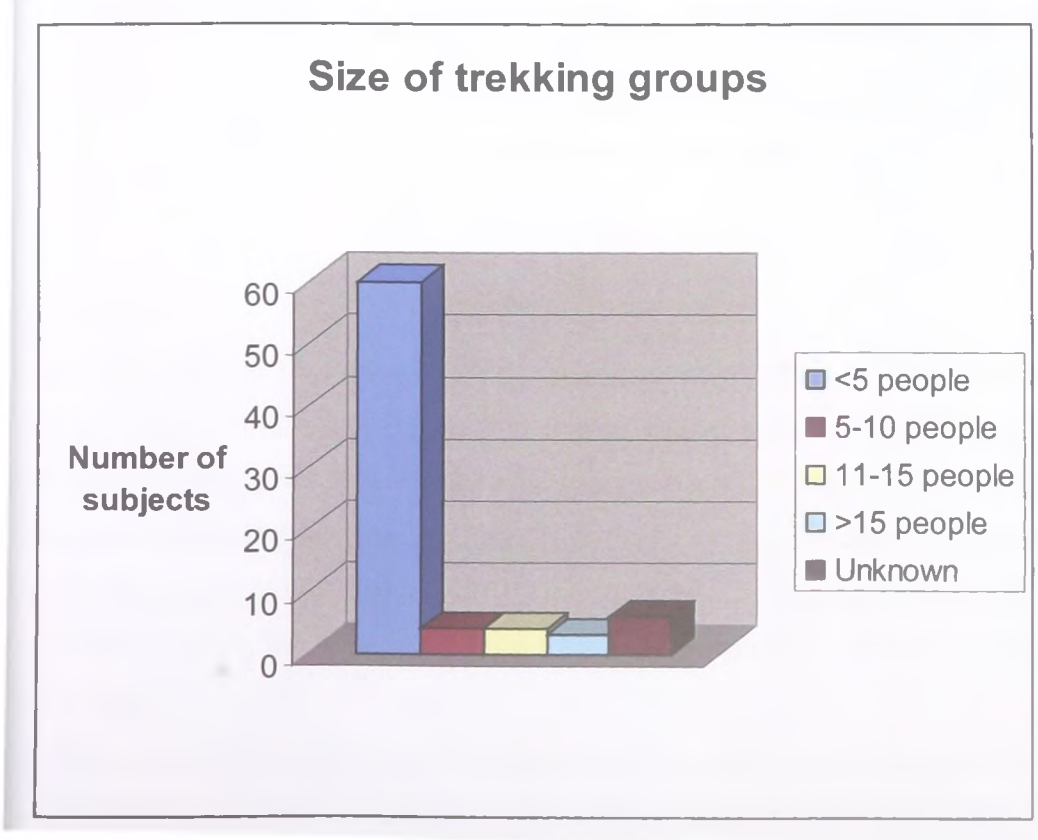

Figure 3.6 Reported size of trekking groups

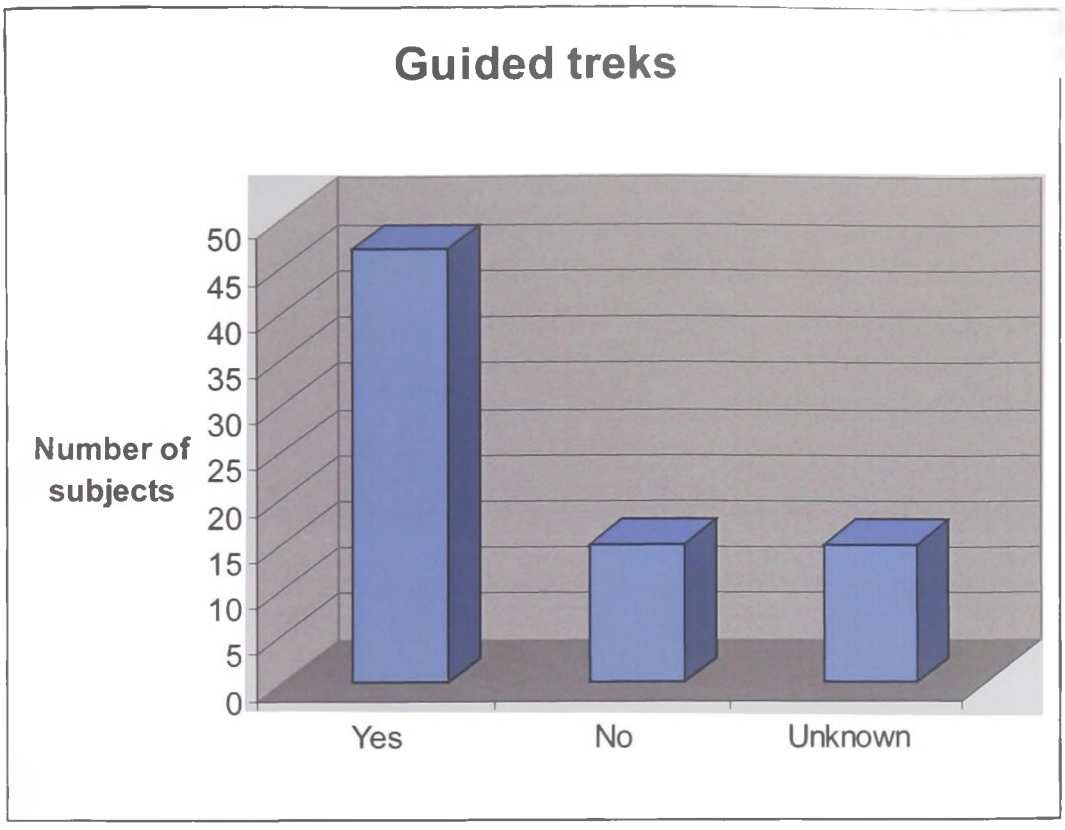

Figure 3.7 Proportion of guided treks

Ascent profile

Forty-four percent (n=34) of the study participants were unaware of the maximum altitude involved in their trek (Figure 3.8). These trekkers were more likely to be female ($\chi^2 = 15.488$, $p = .004$). Twenty-two percent (n=17) of the trekkers reported a maximum anticipated altitude of 15,000-20,000ft. Twelve percent of trekkers (n=9) did not expect to exceed an altitude of 10,000ft. Of these trekkers, two planned to trek along the Inca trail and a further two travellers planned to trek in the Himalayas.

Twenty-seven percent (n=21) of respondents stated that it would take 2-4 days to reach their maximum altitude; 26% of travellers (n=20) were unable to estimate the length of time this would take, while 14% of adventurers (n=11)

planned to take less than 2 days to reach their maximum altitude (Figure 3.9). Of the latter trekkers, one was planning to reach an altitude of 15,000-20,000ft in less than 2 days, a second traveller planned to trek to over 20,000ft in less than 2 days, while two further travellers planned to reach an unknown maximum altitude in less than 2 days.

Eighty-three percent (n=64) of those surveyed did not believe that their expedition involved technical climbing (e.g. fixed ropes, belays, ice axes, crampons); 14% of trekkers (n=11) did not know if there were technical aspects to their ascent (Figure 3.10).

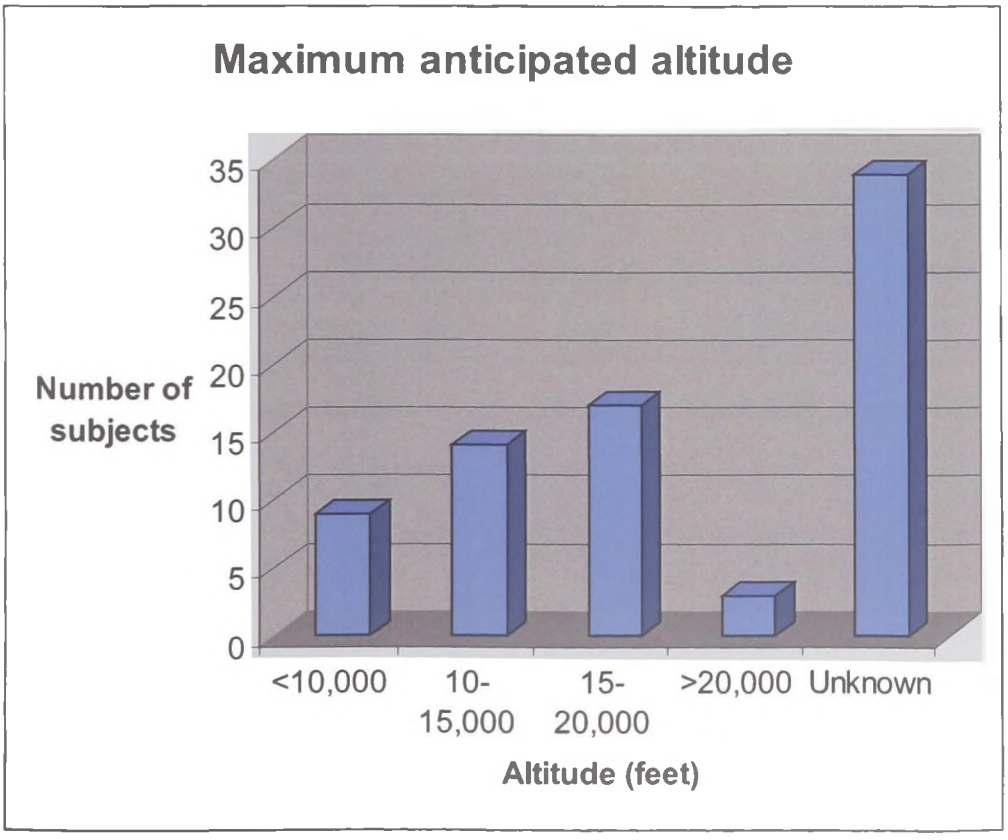

Figure 3.8 Maximum trekker-anticipated altitudes

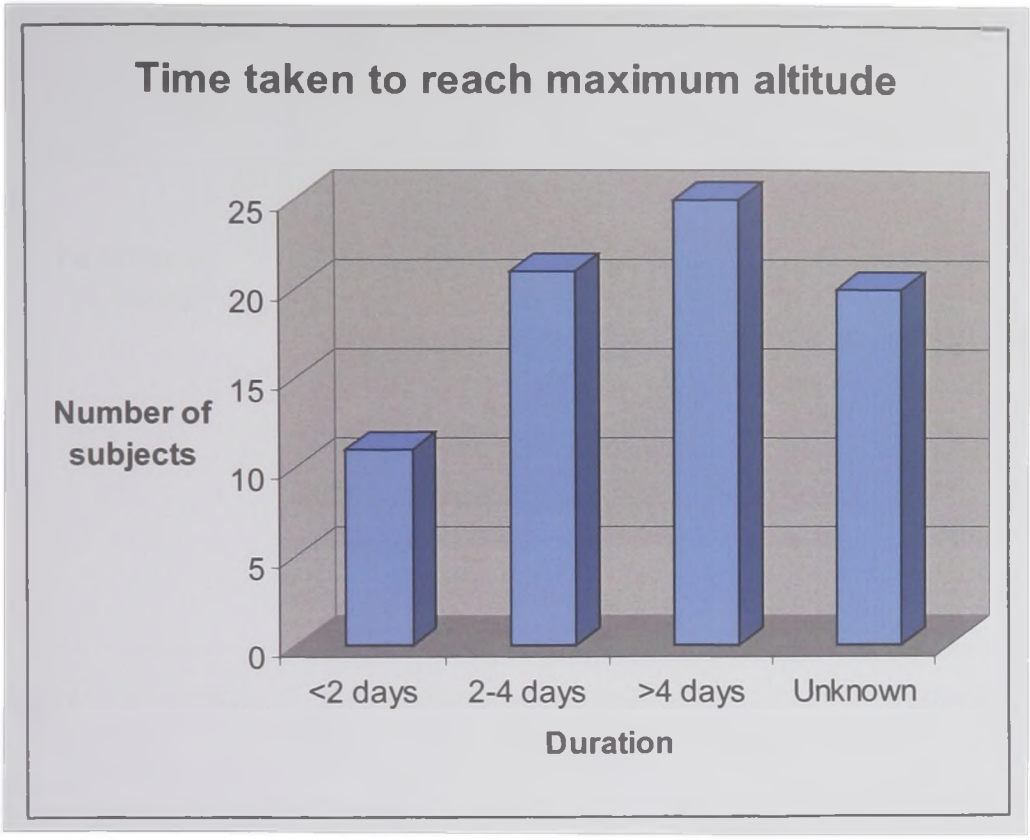

Figure 3.9 Anticipated length of time taken to reach maximum altitude

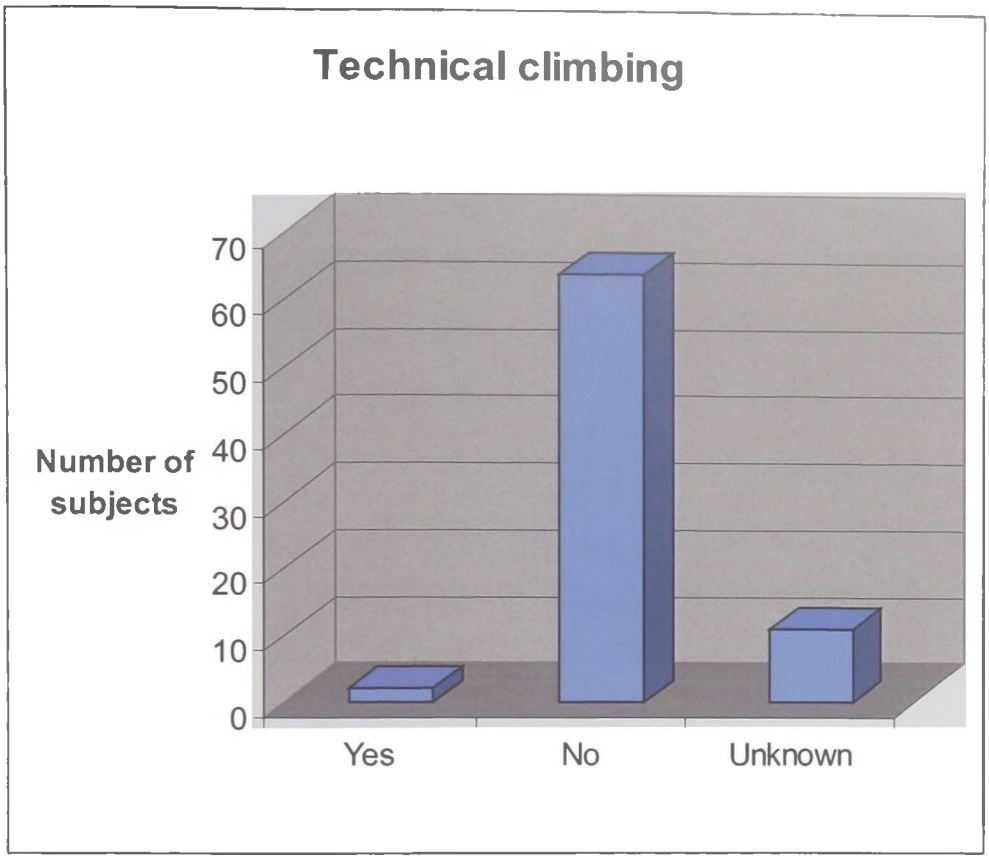

Figure 3.10 Trekkers' perceptions of the technical nature of expedition

Previous altitude experience

Sixty-two percent (n=48) of those travellers surveyed had no previous experier of high altitude (Figure 3.11). Of these trekkers, 67% (n=32) were aged betwee 20 and 30 years.

Thirteen percent (n=10) of respondents in this survey reported a previou maximum altitude of 15,000-20,000ft (Figure 3.12). Of the 12 trekkers who had previously passed 15,000 feet, 10 were male and 2 were female. Of these 12 trekkers, 8 planned to return to an altitude >15,000ft on this occasion.

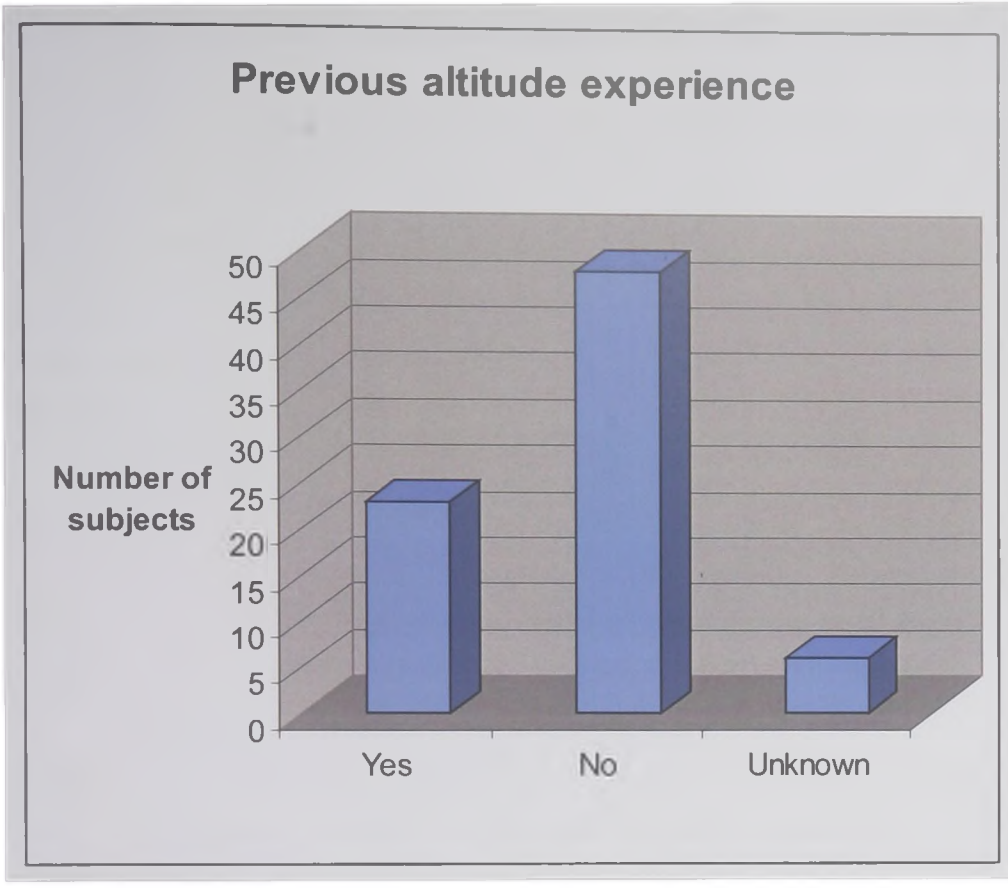

Figure 3.11 Previous altitude experience of trekkers in this study

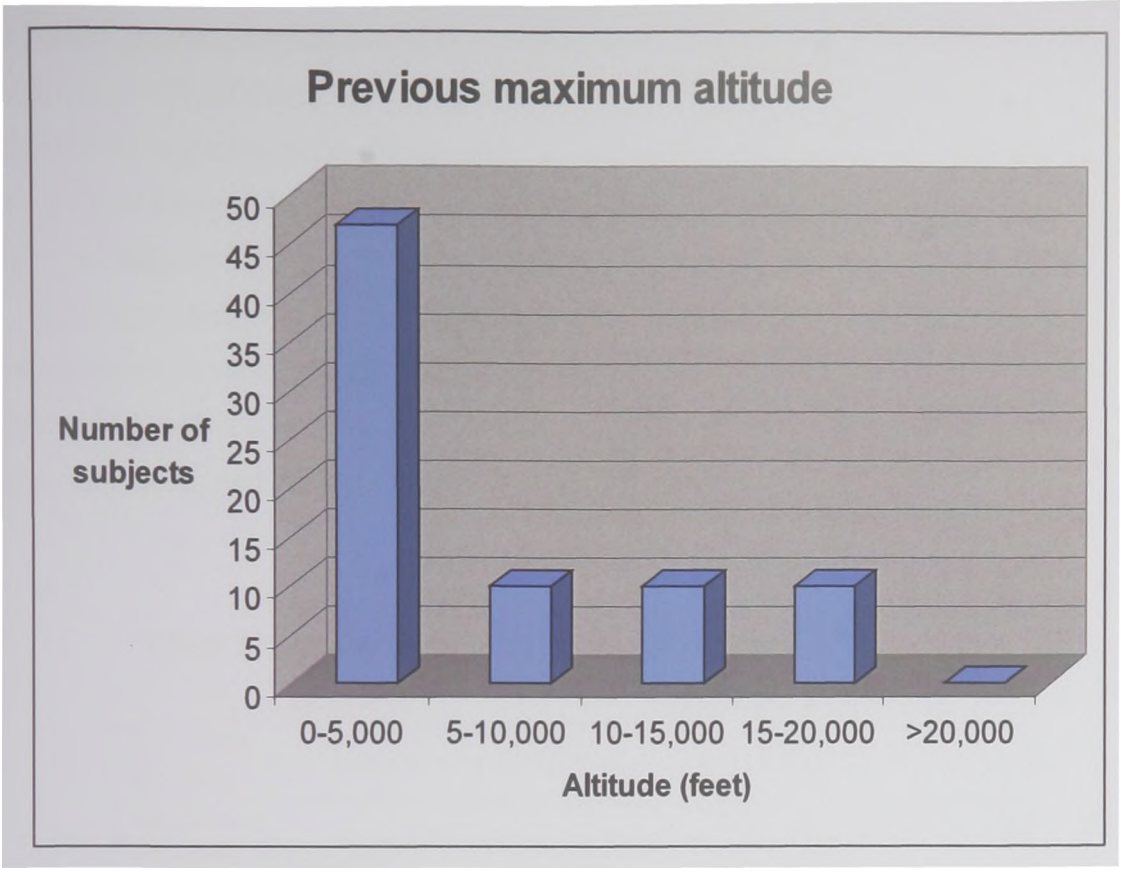

Figure 3.12 Maximum reported previous altitude

Knowledge of altitude illness

Thirty-five percent (n=8) of those trekkers who had previously been exposed to high altitude reported high-altitude sickness on that occasion. A further 35% of subjects were unsure if they had experienced high-altitude illness during their previous visit to high altitude. Seventy percent (n=54) of respondents reported awareness of the symptoms of altitude illness (Table 3.2). Forty-four percent (n=34) correctly recalled more than one symptom of altitude illness (Figure 3.13). Of the 23 subjects who could not recall any symptoms of high-altitude illness, 19 (83%) had not travelled to high altitude previously and 11 (48%) were aged 20-25 years ($\chi^2 = 6.225$, $p = .044$). The most commonly reported symptoms were dizziness (43%), nausea (41%), headache (39%), and shortness of breath (28%). 4 subjects believed that diarrhoea was a symptom of high-altitude illness.

Thirty-two percent (n=25) of trekkers were unaware of any means of preventing altitude illness (Table 3.3). The most commonly reported preventive measures were gradual ascent (46%), hydration (33%) and medications (19%),

including acetazolamide (recorded in the questionnaires as Diamox®). Thirty-nine percent (n=30) of those surveyed believed that physical fitness is protective against the development of high-altitude illness (Figure 3.14). These travellers were more likely to be female ($\chi^2 = 6.388$, $p = .041$) and aged less than 30 years ($\chi^2 = 14.209$, $p = .007$).

When presented with a scenario where one of their climbing companions experienced severe altitude sickness, 61% of subjects advised descent, 43% advocated rest at the same altitude, 25% recommended helicopter evacuation, and 19% endorsed the use of medication (Figure 3.15).

Table 3.2 Knowledge of symptoms of high-altitude illness

Symptom	Number of subjects
Dizziness	23
Nausea	22
Headache	21
Shortness of breath	15
Fatigue	10
Vomiting	11
Insomnia	5
Disorientation	5
Diarrhoea	4
Oedema	2
Loss of appetite	2
Weakness	2
Dehydration	2
Wheezing	2
Cyanosis	1
Dehydration	2
Hallucinations	1
Drowsiness	1
Rapid breathing	1
Confusion	1
Fever	1
Cough	1
Fast heart rate	1
Tunnel vision	1

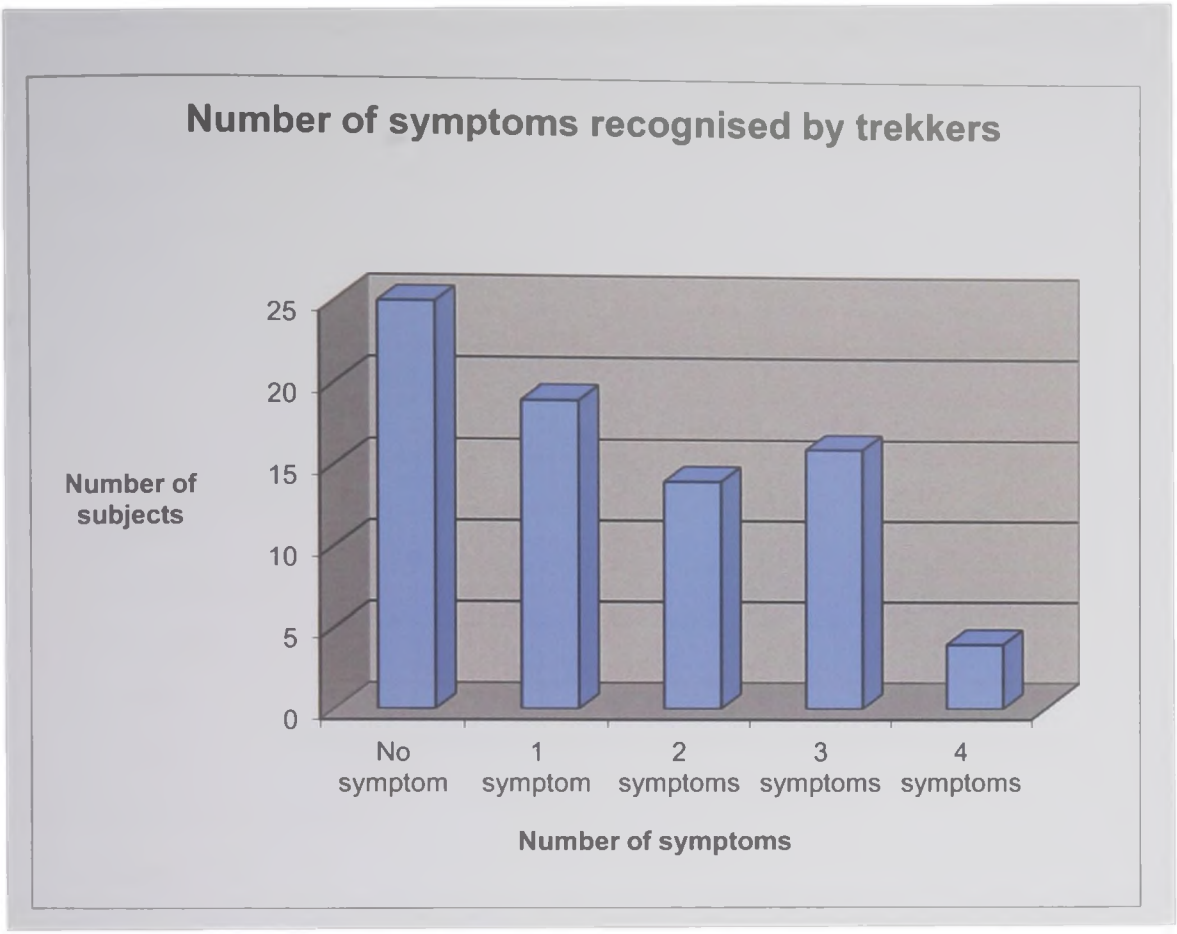

Figure 3.13 Number of symptoms of altitude illness recognised

Table 3.3 Knowledge of ways to reduce the risk of high-altitude illness

Preventive measure	Number of subjects
Gradual ascent	24
Hydration	18
Medication	10
Coca leaves	5
Rest	3
Nutrition	3
Climb high, sleep low	3
Walk slowly	3
Alcohol avoidance	2
Breathe deeply	1
Keep warm	1
Acupuncture	1
Descend before camping	1
Salt replacement	1
Garlic	1
Aspirin	1

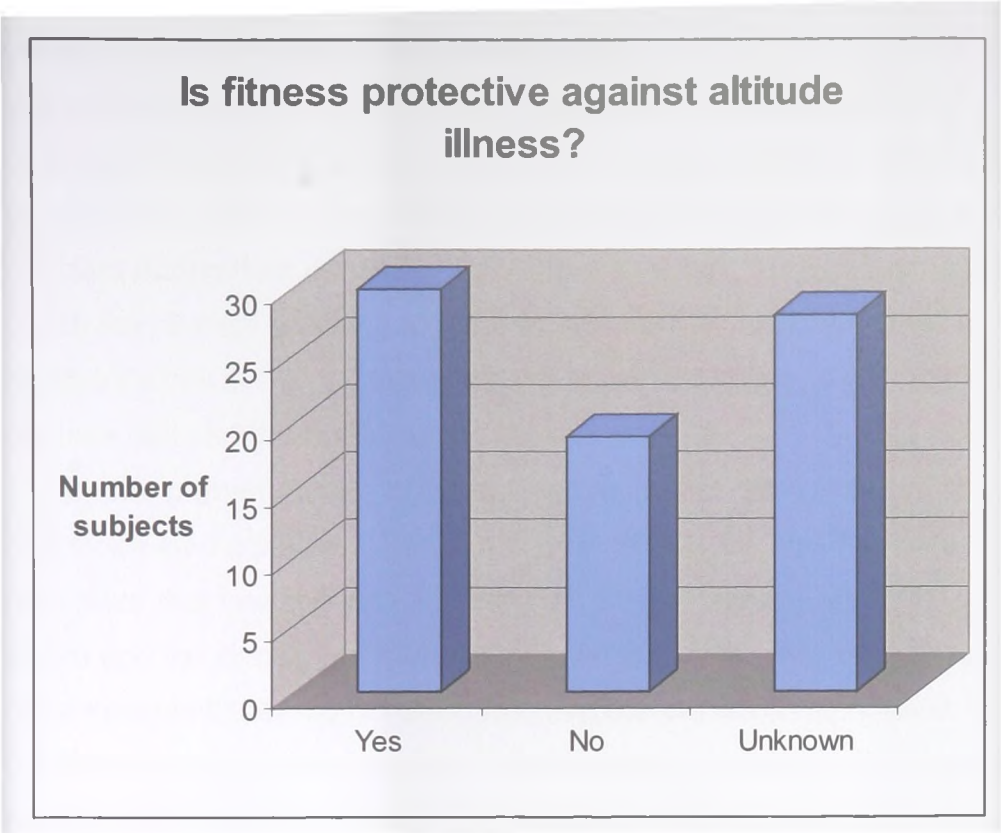

Figure 3.14 Is physical fitness protective against developing altitude illness?

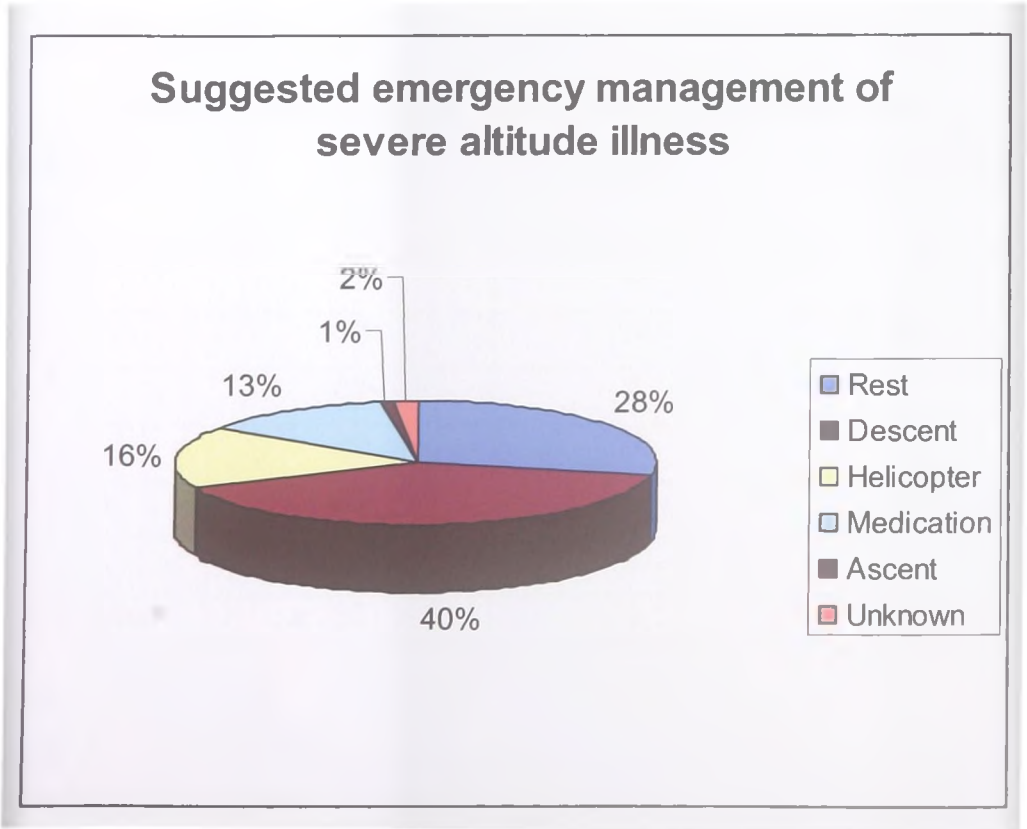

Figure 3.15 Advice offered by subjects to their ill climbing companions

Awareness of non-altitude illness health risks

Subjects were asked if their current trek posed a risk of developing health problems other than high-altitude illness. The results are displayed in table 3.4. Fifty-six percent (n=43) of respondents believed that malaria was a potential health hazard during their upcoming trek. Of those subjects who reported malaria as a health risk, 8 were planning to climb Mt. Kilimanjaro in Tanzania, 27 were visiting the Inca trail in Peru, 3 were trekking in the Himalayas, and 1 was visiting both the Inca trail and the Himalayas.

Fifty-two percent (n=40) of those surveyed either did not believe or were unsure if rabies was a potential health risk on their trek. Of the 27 subjects (35%) who suggested that frostbite was a health risk, 3 each were travelling to Kilimanjaro and the Himalayas while 18 planned to visit the Inca trail. Seventeen percent of trekkers either did not anticipate that blisters would be a health hazard during their expedition or were unsure. Seventy-one percent (n=55) of travellers to high altitude expressed awareness that disturbed sleep would be a potential feature of their trek.

Table 3.4 Awareness of non-altitude illness health risks

Health risk	Yes (n)	No (n)	Unknown (n)
Diarrhoea	63	4	10
Rabies	37	11	29
Malaria	43	14	20
Sunburn	67	3	7
Frostbite	27	28	22
Dehydration	63	4	10
Blisters	64	1	12
Disturbed sleep	55	4	18

Sources of information

When asked about their preferred source of information on the health risks of high-altitude travel, books were reported as the most popular source (26%), followed by the Internet (23%). Twenty percent of trekkers stated that they would consult a travel medicine clinic, while only 14% would attend their general practitioner for specialised advice (Figure 3.16). Fifty-three percent of trekkers (n=41) stated that they would consult just one information source (Figure 3.17). Of those who cited a single source of information, 50% (n=39) would use the Internet and none would approach their general practitioner for advice (Figure 3.18).

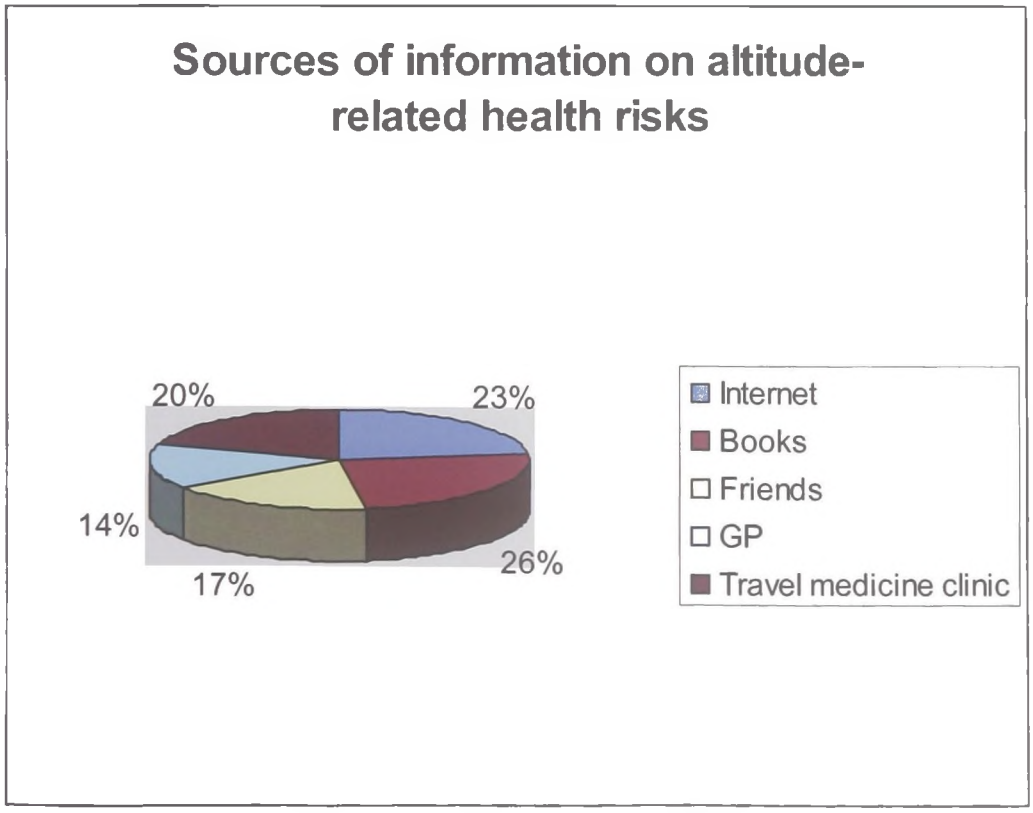

Figure 3.16 Preferred sources of information on altitude-related health risks

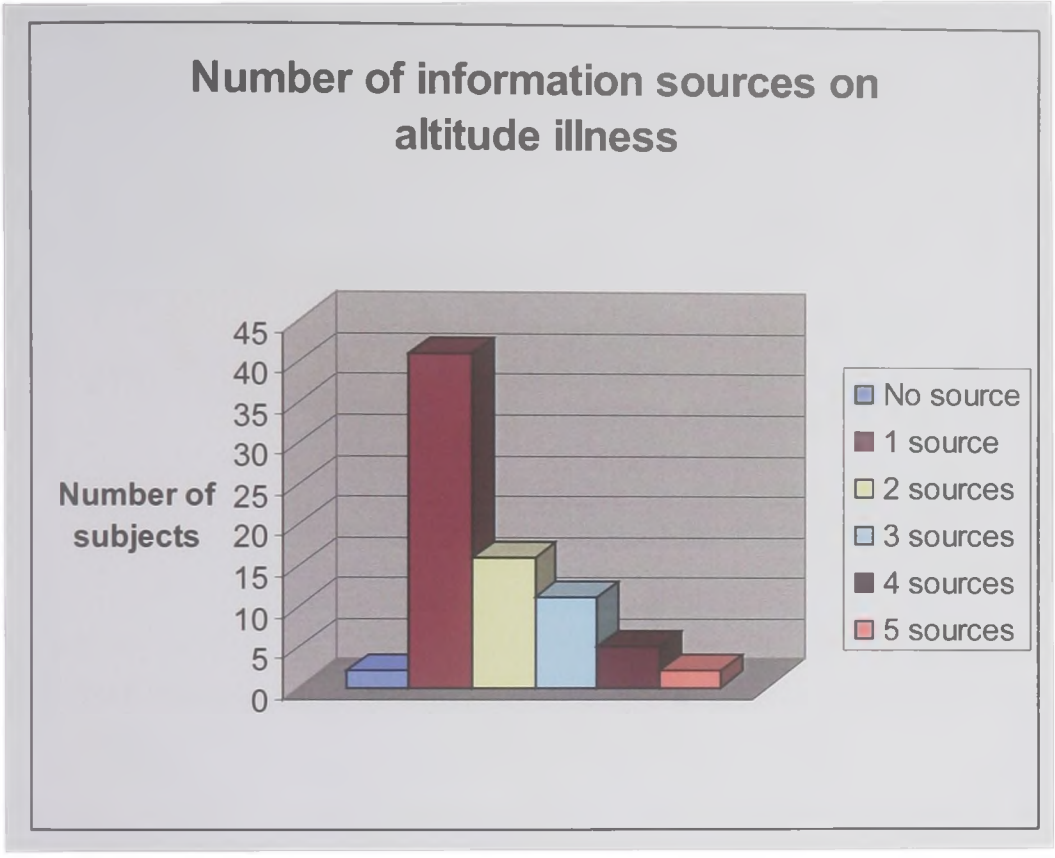

Figure 3.17 Number of information sources consulted by the subjects

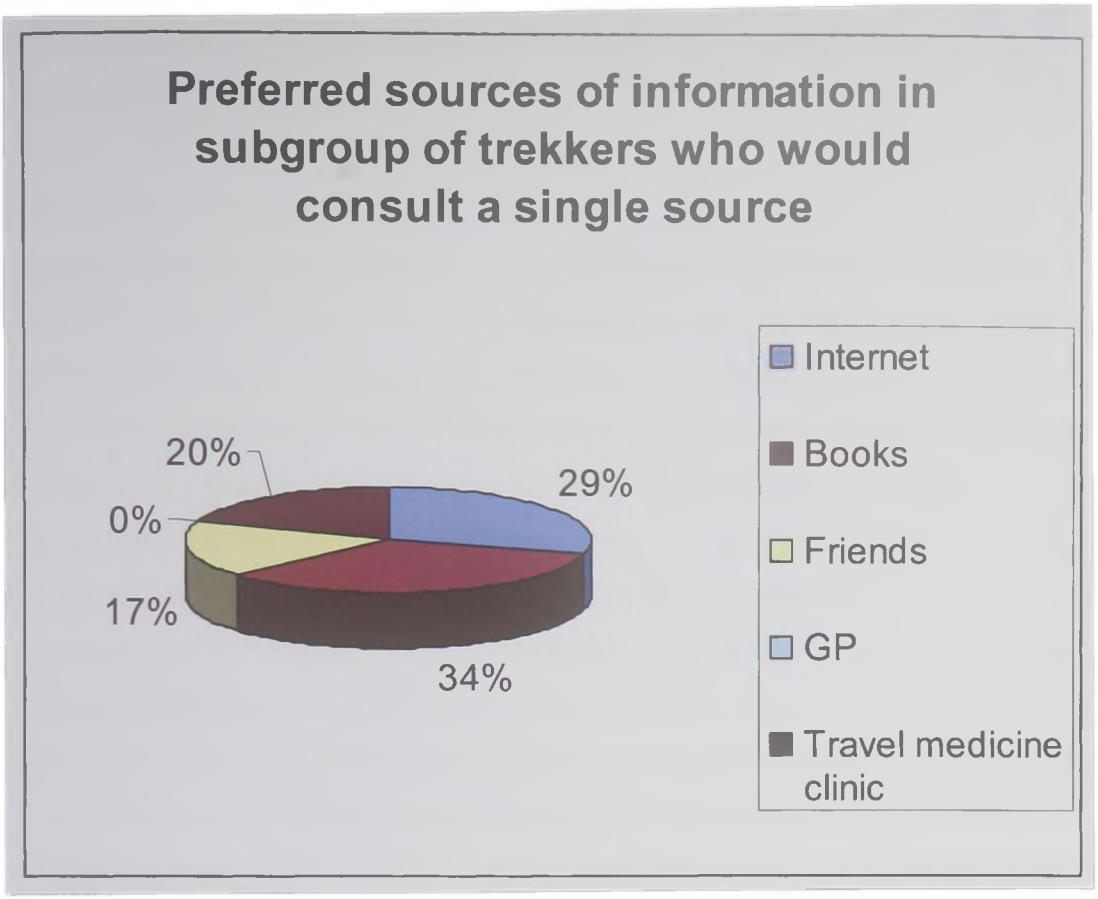

Figure 3.18 Sources of information consulted by trekkers choosing a single source

Discussion

The worldwide popularity of outdoor recreational activities has exposed increasing numbers of persons to the risk of high-altitude illness. Although the dangers conferred by altitude exposure are well described in the literature[98], few of the laypersons who make up the majority of trekkers may have benefited from this information.[96] It is believed that many participants in high-altitude activities, including trekkers, mountaineers, and skiers, may be naïve to the health risks to which they expose themselves.[148] This descriptive study, based on a small sample of trekkers attending a travel medicine clinic in Ireland, attempted to assess their level of awareness of altitude-related health risks. While there are many studies describing the incidence of acute mountain sickness in travellers to various high-

altitude destinations, there is a paucity of published literature examining the subject of traveller awareness.

Demographic profile of travellers

The majority (57%) of trekkers in our sample were male and 40% were aged between 26 and 30 years. It has previously been reported that most travellers to developing countries are young.[149] It has been suggested that there is an inverse relationship between age and the incidence of acute mountain sickness[122]; thus the majority of trekkers in our sample belong to the highest risk group for development of acute mountain sickness. They should, therefore, be particularly well advised of the health risks involved and how to avoid them.

The Inca trail in Peru was the most frequently visited destination in our study and it was particularly popular in the 20-30 year age group. This 50 km long trail commences at an altitude of 2,750 metres and includes three passes, the highest at 4,200 metres, leading to the famous ruins of Machu Picchu. The Inca trail is usually completed in 3 to 5 days. The trail itself features a well-maintained path but there are irregular steps, rocks, steep ascents and descents that require due attention.[150] Cabada et al.[151] assessed the extent of pre-travel health advice received by travellers visiting Cuzco in Peru and found that the majority of travellers were under 40 years of age. Travelling provides young people with an opportunity to seek new experiences, which can increase the health risks to which they may be exposed.[152] Interestingly, the two travellers who planned on visiting both the Andes and the Himalayas during the same trip were both aged in their twenties and one of them had no experience of high altitude. Travellers such as this are at greatly increased risk of developing travel-related health problems and they should be very carefully advised about ways of minimising their risk. Once informed of the health risks they face, many such travellers may revise their itinerary in an effort to reduce their risk.

It is not surprising that Kilimanjaro and the Himalayas attracted an older subset of trekkers in our study as these mountains are located at greater altitude and are generally the domain of more experienced trekkers and mountaineers. There were no visitors to the Alps in this study and it has been my experience that travellers to mainland Europe, with the exception of those visiting Eastern

European countries, rarely seek pre-travel health advice from a travel medicine clinic.

It is reassuring that 57% of participants in this study sought pre-travel health advice, including travel vaccinations, with at least 3 weeks remaining before their intended departure date. It is worrying that 17% of subjects attended the clinic with less than 1 week left before departure. Ninety-three percent of travellers had purchased travel insurance before they attended the travel medicine clinic. This is particularly relevant in the context of high-altitude adventure travel where helicopter rescues and local healthcare may be prohibitively expensive without travel health insurance. It may be useful to advise intending visitors to high altitude to contact their insurance provider before departure to confirm the altitude to which they are covered and to determine if the company will pay medical bills up front.

Knowledge of travel itinerary

Knowledge of travel itinerary may reflect the traveller's general level of preparation for the trip in hand. Knowledge of the ascent profile is of paramount importance to the high-altitude traveller. Basnyat[98] comments that we as health professionals need to improve our ability to advise travellers about their individual risk of acute mountain sickness and the optimal ascent rates necessary to prevent this disorder.

In this study travellers were asked to indicate the duration of their trip. It would have been more appropriate to ask subjects how long they intended to spend at altitude during their trip since it is reasonable to expect that many of them would also be engaged in lowland activities during their vacation. Forty-three percent of those surveyed indicated that they would be spending over 4 weeks in the high-altitude destination. If all of this time were to be spent at altitude, it would allow a reasonable period of time for acclimatisation to occur. It is interesting that the 17% of travellers who intended to spend less than two weeks abroad were all aged between 20 and 25 years and all had no prior experience at altitude. The small sample size does not permit any definitive conclusions to be drawn from this finding but it suggests at the very least that the younger, more inexperienced traveller to high altitude may be less aware of the need for acclimatisation in preventing high-altitude illness.

A third of the sample surveyed was unaware of the maximum altitude to which they would possibly be exposed during their trek. Thirty percent of trekkers planned on reaching the categories of very high to extreme altitude (15,000-20,000ft). Of note, the ascent rates reported in this study are well in excess of those recommended in the literature[9]. Forty percent of participants planned on taking just 2 to 4 days to reach their maximum altitude after arriving in the country in question. An alarming 10% of trekkers planned on reaching their maximum altitude, in one case at over 20,000 feet, in less than 2 days. This reveals a potentially dangerous lack of awareness of the physical demands imposed by a high-altitude trek and of the necessity for adequate acclimatisation. For this group of amateur trekkers it is worrying that 20% of them were part of an unguided group or were unaware if the group was guided or not. High-altitude guides are usually experienced professional mountaineers who are well aware of the need for careful acclimatisation. Whether commercial pressures may influence the ascent profile of guided treks such as these is speculative and deserving of further study.

Group size may be an important determinant of the incidence of high-altitude illness. It has been hypothesised that group members may ignore the symptoms of acute mountain sickness and continue to climb as a result of pressure exerted by the group.[122] It has previously been reported that, although the incidence of high-altitude cerebral oedema is comparable in large groups of trekkers and smaller parties of elite mountaineers, the mortality rate is higher in the larger group.[95] Sixty-seven percent of respondents in our survey reported membership of a group of fewer than 5 people. A minority (7%) belonged to large groups of over 15 people. The degree to which individual group members can be observed for signs of high-altitude illness is influenced by the guide to trekker ratio which varies between commercial trekking groups. The average group size in a study of trekkers in Nepal[122] was 6.5.

Although most trekkers in this study suggested that their proposed trek did not involve climbing of a technical nature, 20% of those surveyed were unsure if technical climbing was involved. This is of concern since technical mountaineering is unlikely in the destinations visited by these trekkers with the exception of higher, snow-covered peaks in the Himalayas which are rarely the province of anyone other than elite mountaineers.

Knowledge of high-altitude illness

For 60% of the travellers in this study, this was their first visit to a high-altitude destination. Seventy-two percent of those without previous altitude exposure were aged between 20 and 30 years. The travel medicine practitioner should counsel the young inexperienced traveller to high altitude carefully about the health risks involved. Fifty percent of trekkers reported previous high-altitude illness which, if we assume this to represent their incidence of acute mountain sickness, is in accord with previous studies in the literature.[102]

Eighty percent of respondents in this study were aware of the symptoms of altitude illness, with 50% of subjects correctly reporting more than one symptom. This is lower than the awareness level reported by Gaillard et al.[102] In their study 95.1% of trekkers could mention at least two symptoms. Of the 6 trekkers who were unable to list any symptom of high-altitude illness, 4 had not previously been exposed to high altitude. It is interesting that the most commonly reported symptom was dizziness which is uncommon in patients with acute mountain sickness and only occasionally noted in patients with high-altitude cerebral oedema. Four subjects erroneously believed that diarrhoea was a symptom of high-altitude illness.

Subjects were asked to suggest measures that would reduce their risk of developing altitude sickness. Twenty-three percent of trekkers were unable to mention even one practical step they would take to reduce their risk. The most commonly reported preventive step was gradual ascent (70%). Seventy-seven percent of trekkers in the study by Gaillard et al.[102] recalled at least two remedies, including descent. Seventy-three percent of the trekkers in this study correctly suggested that their climbing companion should descend if suffering from severe altitude illness. The fact that a third of respondents advocated helicopter evacuation suggests that they may not be aware of the difficulty in arranging such a rescue in the remote high-altitude destinations represented in this study.

Thirty-three percent of subjects in this study believed physical fitness to be protective against the development of altitude illness. Milledge et al.[153] concluded that physical fitness does not protect against high-altitude illness. This is an important finding since the young, physically fit trekker, often male, is apt to ascend at a dangerous rate and may feel impervious to the effects of altitude and thus continue to climb with symptoms of acute mountain sickness. Such

individuals need to be cautioned that the occurrence of high-altitude illness does not correlate with fitness levels.

Respondents in this survey cited books as their preferred source of information on the health risks of travel to high altitude. The main source of awareness of acute mountain sickness in the studies by Gaillard et al.[122] and Cabada et al.[151] was from trekking guidebooks. The most popular single source of information in the present study was the Internet with 43% responding that they would use their computers to educate themselves on high-altitude illness. Thirty percent of trekkers to Nepal in the study by Glazer et al.[96] listed the Internet as their primary source of information. Only 27% in their study said they would ask a doctor or other healthcare professional for advice. About 23% of travellers in the study by Cabada et al.[151] said they would consult their general practitioner while only 3% reported doing so in the study by Gaillard et al.[122] In the present study 13% of travellers listed their general practitioner as a reliable source of information on altitude-related problems. It is surprising that no subject in this study would consult their general practitioner as their single source of information. Forty percent said they would consult their travel medicine clinic so it may be reasonable to suggest that the remaining 60% did not expect to receive advice on altitude-related health risks from their travel medicine clinic. It is accepted that the best pre-travel health advice is given by travel medicine professionals.[154] High-altitude illness receives sparse coverage in the undergraduate medical curriculum so perhaps awareness campaigns should be directed at general practitioners so that they are better equipped to provide preventive health advice to patients travelling to high altitude.

Awareness of other health risks

Sixty percent of travellers in this study listed malaria as a potential health risk during their trip. Fifty percent of these travellers were visiting the Inca trail in Peru. Those flying to Lima and onward to Cuzco do not require anti-malarial chemoprophylaxis but those visiting the Amazonian jungle regions of North-eastern and Eastern Peru would be exposed to malaria. This study was not designed to establish the precise malaria risk of each traveller. Trekkers visiting the Himalayas are unlikely to be at risk of malaria unless they plan on spending time in the Southern Terai district of Nepal. It is a source of concern that nearly

half of this group of trekkers did not recognise rabies as a health risk even though the rabies virus is endemic in each of the destinations visited. The mean incidence of frostbite in one study of mountaineers was 366/1000 population per year.[155] The reported awareness rate of 30% in the present study is difficult to interpret but, considering that two-thirds of those concerned about frostbite were visiting the Inca trail and Kilimanjaro, it is probably an overestimate. Seventy percent of subjects anticipated disturbed sleep during their high-altitude trek but the questionnaire did not identify if they were aware of periodic breathing as a cause of sleep disruption at high altitude.

Limitations of study

The ability to extrapolate the findings of this study to the trekking population in general is limited by its small size (n=77). There may be a degree of selection bias in this study since a sample of travellers who seek pre-travel health advice before embarking on a high-altitude trek may not be representative of the trekking population. Subjects were not asked to indicate their level of educational attainment which may influence their level of knowledge. No effort was made to identify respondents with medical training which would be a further confounding factor. The questionnaire was not designed to assess travellers' awareness or knowledge of the different categories of high-altitude illness and the term "altitude sickness" was used throughout to avoid confusion. It would be preferable in a questionnaire of this kind to indicate altitude in both feet and metres but respondents had been assured that they could record elevations using their preferred measurement unit and this did not interfere with data analysis. In future studies of this kind it would be reasonable to list sexually transmitted diseases as a possible health risk since Cabada et al.[156] have previously reported that some travellers to Cuzco along the Inca trail engage in casual sexual activities that place them at risk of acquiring and transmitting sexually transmitted infections.

Implications of study

Arising from this study, I believe that advice on the health risks associated with travel to high altitude should be targeted especially at the young, inexperienced traveller. General practitioners should receive training in high-altitude illness and should be proactive in attempting to reduce their patients' risk. Travel agents should be made aware of the risks of high-altitude travel and should be encouraged to refer travellers early for their pre-travel health consultation. Knowledge of the ascent profile of a trek is of the utmost importance and travel medicine specialists should be able to advise travellers on the importance of a safe ascent rate. Written information on travel to altitude should be made available to travellers with information on early recognition, management and prevention of altitude illness. The risk of rabies amongst trekkers in endemic countries should be highlighted and rabies vaccination advised. A list of reputable websites and books should be provided to trekkers (Appendix 4) since this study identified these resources as the most popular sources of information to the high-altitude traveller.

Conclusions

This study has revealed a considerable lack of awareness of the health risks associated with high-altitude travel amongst a sample of trekkers attending a travel medicine clinic. In particular, there is a lack of appreciation of the importance of a safe ascent profile in allowing time for altitude acclimatisation to occur. Specific information should be delivered to young, inexperienced travellers who may be at greatest risk. This information should include advice on avoiding rabies infection in a wilderness setting. Health professionals dealing with travellers to high altitude should be well informed on the recognition, management and prevention of health problems at high altitude.

3.2. Travelling to Altitude With Pre-Existing Medical Conditions (Major Review)[3]

Search strategy and selection criteria

A literature review was completed using Ovid/Medline (1950-Present) and Pubmed databases. The following search terms were employed: pre-existing medical conditions and altitude; each individual condition and altitude; air travel and pre-existing medical conditions, and high altitude medicine. Published articles were used as a source of further references not yielded by the primary search. Textbooks written by recognised experts in the field of high altitude medicine were consulted to source information not available elsewhere.

Introduction

The demographics of adventure travel are shifting. Expanding road, rail, and air networks as well as mechanised mountain lifts have rendered it increasingly possible for people of varying levels of health and fitness to reach remote high altitude destinations (Table 3.5).[157] High altitude cities and employment sites also attract holidaymakers, workers and business travellers.[158] Passive ascent to altitude by airplane, automobile, train, hot air balloon or cable car may result in sudden exposure to altitude without adequate time for acclimatisation.

The environmental conditions at altitude and the associated hypobaric hypoxia pose a significant physiologic challenge to the human body (Figure 3.19). Furthermore, many high altitude sojourns include strenuous physical activities such as skiing, hiking, and climbing. Emergencies in remote locations demand that the sick or injured rely on their companions or on their own compromised abilities

[3] Adapted, with the permission of the co-authors and the publishers, from: Mieske K, Flaherty G, O'Brien T. Journeys to high altitude - risks and recommendations for travelers with pre-existing medical conditions. J Travel Med. 2010; 17(1):48-62.

in order to access the medical help they need. The conscientious traveller will take steps to gain the knowledge and skills necessary to minimise personal risk. However, many at-risk travellers remain naïve to the health risks of high altitude travel.[159,160] Similarly, physicians should prepare themselves with the knowledge required to advise their patients on safe travel to altitude (Table 3.6). The need for knowledge and preparedness is especially critical in the case of individuals with pre-existing medical conditions. These patients may be at increased risk for developing altitude related illness or decompensation of their underlying disease with altitude related changes in physiology.

This article reviews the effects of altitude in relation to a selection of common medical conditions and gives recommendations for how people with these disorders can protect their health at altitude.

Table 3.5 Altitude Definitions[157]

	Metres	Feet
Intermediate Altitude	1500-2500	4921-8202
High Altitude	2500-3500	8202-11483
Very High Altitude	3500-5800	11483-19029
Extreme Altitude	>5800	>19029

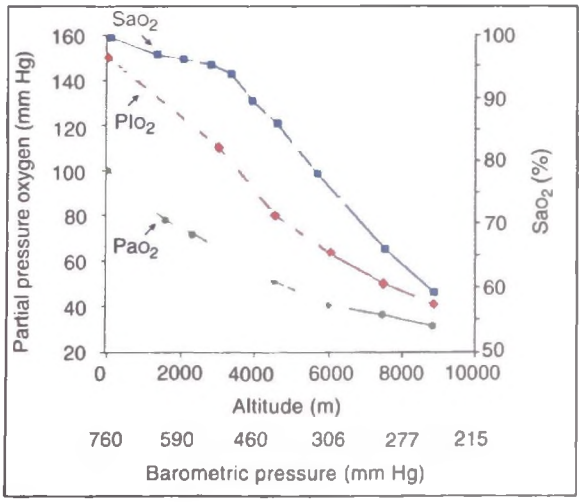

Figure 3.19 Increasing altitude results in a decrease in inspired PO_2 (PIO_2), arterial PO_2 (PaO_2), and arterial oxygen saturation (SaO_2). (Adapted with permission from Hackett and Roach, 2007).[158]

Table 3.6 Review articles on altitude travel with pre-existing medical conditions

Medical Condition	Review Article
Cardiovascular Diseases	Hultgren, 1992[161]
Hypertension	Luks, 2009[180]
Respiratory Diseases	Cogo, Fischer, and Schoene, 2004[162] Luks, Swenson, 2007[209]
Kidney Disease	Luks, Johnson, Swenson, 2008[224]
Diabetes	Brubaker, 2005[163] Leal, 2005[164]
Neurological Conditions	Baumgartner, Siegel, Hackett, 2007[165]
Elderly Travellers	Cooper, 2006[166]
Women and Pregnancy	Jean, Leal, Kriemler, Meijer, and Moore, 2005[167] Niermeyer, 1999[168]
Ocular Conditions	Mader and Tabin, 2003[169]
Medication Considerations	Luks and Swenson, 2008[170] Küpper, Schraut, Burkhard, et al., 2006[171]
Air Travel	Gendreau and DeJohn, 2002[298] Silverman and Gendreau, 2009[299]

Cardiovascular disease

Hypertension

There is a significant amount of individual variability in the effects of altitude on blood pressure. In the majority of people there is a small alpha-adrenergic-mediated increase in blood pressure proportional to elevation gain[172], the effect of which is not clinically significant until above 3000m.[158,173,174] However, in some people, there is a pathological reaction to high altitude which results in large blood pressure increases.[161,173] Work by Häsler and colleagues[175] suggests racial differences in the blood pressure response to altitude. Black mountaineers experienced a progressive decrease in systolic blood pressure (SBP) with increasing altitude while the matched white subjects experienced increasing SBP. Furthermore, bilanders who divide their time between sea level and high altitude residences experience significantly higher mean arterial pressure at their high altitude dwelling compared to sea level.[173] In all people, the extent of pressure change depends on the degree of hypoxic stress, cold, diet, exercise, and genetics.[173] Over-reactive sympathetic responses during sleep may cause periodic breathing which increases the risk of exacerbating hypertension and causing cardiac arrhythmias.[161] Hypertension is also an independent risk factor for sudden cardiac death (SCD) during mountain sports.[177]

Despite these risks, well controlled hypertension is not a contraindication to high altitude travel[178] or physical activity performed at altitude.[174] Aneroid sphygmomanometers have been validated for use at high altitude (4370m).[179] Patients with poorly controlled blood pressure should monitor their blood pressure while at altitude[180] and be made aware of the potential for sudden, large fluctuations in blood pressure.[158,183] A plan for medication adjustments should be prepared in advance and should include increasing the dose of the patient's usual antihypertensives as a first line strategy for uncontrolled hypertension. Alpha-adrenergic blockers and nifedipine are the drugs of choice if hypertension remains severe.[158,161] The development of hypotension may necessitate a later medication reduction with acclimatisation to altitude.[180] Patients taking diuretics should exercise caution in avoiding dehydration and electrolyte depletion. Furthermore, beta-blockers limit the heart rate response to increased activity and interfere with thermoregulation in response to heat or cold.[181]

Coronary Artery Disease

There is no evidence to date linking coronary artery disease (CAD) to either a higher incidence or severity of altitude illness.[182,183] There are also no data to suggest that exposure to altitudes up to 2500m increases the incidence of SCD[177,184] or myocardial infarction (MI) in patients with CAD.[158,161,182,185] However, a theoretical potential for increased risk exists in that both myocardial oxygen delivery and requirements are altered with exposure to high altitude. CAD is associated with an increased risk of SCD during skiing and hiking in the mountains.[177,186]

Acute hypoxia[187], physical activity, dehydration, and cold cause sympathetic activation at altitude[188], the results of which include vasoconstriction and an increase in heart rate, blood pressure and cardiac output.[161,188] This increase in cardiac workload and oxygen demands is most notable in the first three days of altitude exposure.[158,188-192] People with CAD have significantly reduced capacity to compensate for the increased demands on the heart, even at moderate altitude.[192] Diseased arteries have impaired endothelial vasomotor control, and thus alkalosis, cold and unopposed sympathetic activity may cause constriction of the coronary arteries and reduced myocardial perfusion.[188] Levine et al. noted a 5% decrease in the angina threshold for people with CAD in the pre-acclimatisation period at 2500m.[190] Wyss et al. demonstrated an 18% decline in exercise-induced coronary flow reserve in patients with stable obstructive CAD at 2500m.[192] Additionally, at altitude, myocardial oxygenation in areas supplied by stenotic arteries is significantly reduced relative to areas supplied by healthy vessels.[192] Patients with CAD may be at significant risk of life-threatening ventricular arrhythmias at altitude due to the combined effects of pulmonary hypertension and myocardial ischaemia.[193,201]

Patients with exertional angina at their resident altitude will likely experience a worsening of their symptoms at higher altitude. Thus, travel to high altitude is not recommended and exercise at altitude generally contraindicated in this cohort.[161,183,194] However, Morgan et al. proposed that patients are safe to exert themselves at altitudes up to a target heart rate which is 70-80% of their low altitude ischaemic endpoint.[195] Patients with well controlled CAD who participate in

unrestricted physical activity at sea level are probably safe to travel up to 2500m.[183,188,190,192] However, it is recommended that physical exertion be avoided for the duration of a 3-5 day acclimatisation period.[177,178,182] Adequate nutrition and hydration should be maintained at all times in order to minimise the risk of adverse events.[177] Wyss et al.[192] recommend further caution, recommending that people with CAD should avoid physical exertion even at moderate altitudes.[192] Travel to high altitude is contraindicated for 6 months following a MI. Beyond 6 months, a normal exercise stress test should be a prerequisite to travel.[191,194] Non-MI patients who have undergone coronary artery bypass grafting or coronary angioplasty may be limited in their exercise potential at high altitude but there is no evidence to suggest that altitude exposure increases the risk of graft closure or stent restenosis.[194]

Heart Failure

People with congestive cardiac failure tend to quickly decompensate with high altitude exposure due to the effects of acute mountain sickness (AMS)-related fluid retention.[158,173,178,181]High altitude travel is therefore contraindicated in people with diagnosed heart failure.[178] However, should they decide to travel to altitude, patients should expect a decrease in work capacity proportional to the altitude gained and their sea level exercise capacity.[196] Acetazolamide prophylaxis or an increase in the dose of the patient's regular diuretic should be considered.[158,178] Furthermore, particular attention must be paid to fluid balance. Patients should be monitored closely for signs of fluid retention while avoiding dehydration due to exertion and use of diuretics.[173,178,181]

Cardiac arrhythmias

A number of studies have documented electrocardiographic (ECG) changes in healthy subjects at real and simulated altitudes up to 8848m but there are no data on patients with existing arrhythmias. Benign sinus arrhythmia is common with altitude exposure but appears to be self limiting. Heart rate increases progressively with elevation gain at rest and during exertion.[193,196-199] At extreme

altitude, ECG changes are consistent with pulmonary hypertension and resolve with descent to low altitude.[198,199] A single case report documented an age-related increase in left ventricular ectopy and tachycardia at altitude.[197] This sympathetically mediated effect may provide an explanation for sudden unexplained deaths at altitude.[193,197,200] Another case report describes resolution of recurrent paroxysmal atrial fibrillation in a patient who took up residence in a new home at 2750m.[201] The improvement in his condition was attributed to decreased left atrial wall tension secondary to an altitude-associated decrease in venous return. Given the paucity of research evidence in this specific area, it is recommended that patients with cardiac arrhythmias should consult their cardiologist for individualised risk assessment and advice prior to pursuing high altitude travel.

Congenital Heart Disease (CHD)

Exposure to hypobaric hypoxia results in pulmonary vasoconstriction, excessive amounts of which result in HAPE.[158] Patients with CHD including tetralogy of Fallot, ventricular septal defect, atrial septal defect, patent ductus arteriosus, or absence of a pulmonary artery have an exaggerated pulmonary arteriolar vasoconstrictor response to hypoxia which makes them more susceptible to the development of pulmonary hypertension and HAPE.[158,161,202] The extent of this risk is not well understood or easily predicted. Some individuals have demonstrated the ability to function well at high altitude while others suffer the consequences of increased pulmonary hypertension, HAPE, or right heart failure even at moderate altitudes.[202-208] Symptoms with ascent may include dyspnoea, weakness on exertion, and syncope.[161]

For people with symptomatic pulmonary hypertension at sea level, altitude exposure is contraindicated.[158] Asymptomatic patients with CHD should be warned of the potential for developing HAPE and take nifedipine prophylactically to reduce their risk. Travellers with a brisk hypoxic pulmonary vasoconstrictor response may be identified in the clinic by observing their response to inhalation

of a low oxygen mixture.[161] These recommendations equally apply to patients with primary or secondary pulmonary hypertension.[161]

Respiratory conditions

Chronic Obstructive Pulmonary Disease (COPD)

People with COPD may be hypoxaemic at sea level and thus may develop altitude related symptoms at lower elevations than healthy people (Figure 3.20).[158,178,209] Blunted carotid body response due to chronic hypercapnia may reduce their ability to produce a hypoxic ventilatory response, thus further exacerbating the hypoxia.[162] Breathing cold air results in pulmonary vasoconstriction and increased pulmonary artery pressure.[209,210] Elevated levels of carboxyhaemoglobin due to smoking may further compromise oxygen carrying capacity in this cohort.[211] Depending on baseline oxygen saturation and the pathological condition of the lungs, risks associated with altitude exposure include profound hypoxaemia, pulmonary hypertension, disordered ventilatory control, impaired respiratory muscle function and sleep-disordered breathing.[158]

No studies have been conducted on patients with COPD at high altitude. However, studies of patients with mild to moderate COPD at 1920m concluded that it is safe for such patients to travel to intermediate altitude.[185,211] Altitude exposure is contraindicated for patients with severe COPD who have dyspnoea at rest or on mild exertion at sea level. Patients with moderate disease should undergo individualised risk assessment and ascend with caution.[158,162] Hypoxic challenge, spirometry testing, and the British Thoracic Society's (BTS)[212] guidelines for respiratory patients planning air travel may provide useful guidance for physicians.[158,162,178] In order to minimise the risk of adverse effects, patients with COPD should avoid strenuous exercise at altitude and ensure optimal health prior to ascent.[178] Maintenance of hydration at altitude is important in order to avoid problems associated with thickened mucosal secretions.[213]

Bronchial asthma

Altitude can influence bronchial hyperresponsiveness, and thus, the likelihood of an acute asthma attack. Possible aggravating factors at altitude include physical exertion, hypoxia, cold air, decreased air density, and decreased humidity.[162,178,209] Furthermore, bronchoconstriction at low barometric pressure exacerbates hypoxia and thus, theoretically predisposes asthmatics to HAPE and AMS.[158] At altitudes up to 2000m, asthmatic travellers receive the benefits of decreased airborne allergens and reduced resistance to airflow.[162,178,209,214] At altitudes above 2500m, conditions may be more conducive to inducing an asthma attack due to the cold dry air.[214] Travellers at highest risk are those who use inhaled bronchodilators more than three times per week at their living altitude and those who participate in strenuous aerobic activity at altitude.[214,215] Between 3500m and 5000m, it has been shown that asthmatics have a reduced risk of suffering an asthma attack. While the cold, dry air provides a stimulus for an asthma attack, changes in physiologic mediators that occur with acclimatisation are thought to exert a modulatory effect over airway hyperresponsiveness.[162,214,216]

While at altitude, use of volumetric spacers is recommended for metered dose inhalers and the mouth should be protected against cold and wind.[209,214] It is notable that high altitude natives routinely use silk scarves to protect their airways from exposure to cold air. Exertion at altitude should be moderate to avoid excessive hyperventilation and passive ascent to high altitude should be avoided as sudden exposure to hypoxia can increase airway irritability.[214,217] Peak expiratory flow rate is a practical method of monitoring asthmatic status at altitude.[209]

Obstructive Sleep Apnoea (OSA)

Hypobaric hypoxia associated with high altitude is likely to exacerbate the effects of OSA. Richalet et al. suggest that individuals with Down Syndrome and OSA have significantly impaired chemoreceptor sensitivity to hypoxia and are thus at increased risk of HAPE with exposure to even moderate altitudes.[218] Thus, high altitude travel is contraindicated for people with OSA who demonstrate arterial

oxygen desaturation at sea level.[183] It is of interest that acetazolamide has been shown to reduce the apnoea-hypopnoea index in patients with OSA.[219] Should a patient with OSA choose to travel to altitude, it is reasonable to prescribe acetazolamide prophylaxis in an effort to improve the symptoms of OSA and reduce the risk of developing AMS. Patients who travel with their continuous positive airway pressure (CPAP) machine may need to adjust the pressure setting to accommodate for the decrease in barometric pressure at altitude.[209]

Pleural and interstitial lung disease (ILD)

No baseline data exist to help the physician predict which patients with ILD are most likely to suffer a deterioration in their respiratory status at high altitude. It is recommended that patients with ILD in whom the presence of pulmonary hypertension has not been confirmed should undergo echocardiography before travelling to high altitude. Symptomatic pulmonary hypertension is a contraindication to high altitude travel. If patients with secondary pulmonary hypertension wish to travel to high altitude they should use supplemental oxygen and nifedipine for HAPE prophylaxis.[209] According to the Aerospace Medical Association, patients should wait a minimum of 2 weeks following resolution of a pneumothorax before high altitude ascent, including commercial air travel.[220]

Gastrointestinal disorders

High altitude exposure is associated with a risk of gastrointestinal (GI) bleeding that increases with altitude and is thought to be related to hypoxia and cold.[221] Wu et al. report that bleeding generally appears within 3 weeks of altitude exposure and includes haematemesis, melaena, or haematochezia. Endoscopic examination of affected patients revealed a number of pathologies including haemorrhagic gastritis, gastric ulcer, duodenal ulcer and gastric erosion. A history of peptic ulcer disease, high altitude polycythaemia, alcohol consumption, use of non-steroidal anti-inflammatories (NSAIDs) and dexamethasone increase the risk of high altitude GI bleeding.[222] Travel to high altitude is contraindicated for patients with active peptic ulcer disease. Patients with a history of peptic ulcer disease should avoid alcohol, NSAIDs, smoking and caffeine at altitude. Dexamethasone

should only be used in cases of high altitude cerebral oedema or HAPE. Should gastrointestinal bleeding develop at altitude, the treatment of choice is twice the normal dose of omeprazole twice daily. The patient should be evacuated as quickly as possible.[223] Patients with active inflammatory bowel disease should avoid remote travel during active phases of the disease and avoid long term wilderness travel even in a quiescent stage.[194]

Chronic kidney disease (CKD)

Depending on the extent of the kidney disease, impaired renal function could alter an individual's ability to maintain fluid, electrolyte, pH and blood pressure homeostasis at high altitude.[224] Furthermore, Quick and colleagues demonstrated that patients with renal anaemia do not compensate for hypobaric hypoxia by increasing erythropoietin secretion which could limit their acclimatisation and increase susceptibility to AMS.[224,225] The mild metabolic acidosis associated with chronic renal insufficiency is theoretically protective against AMS due to increased ventilatory drive. However, the metabolic acidosis also causes pulmonary vasoconstriction and thus may increase susceptibility to HAPE. Impaired fluid regulation could further contribute to the development of pulmonary oedema and exacerbate hypoxaemia. Chronic hypoxia may accelerate the progression of CKD in patients who remain at high altitude for extended periods.[224]

The limited available evidence suggests that people with CKD are able to safely tolerate short trips to high altitude, albeit with caution. In the excellent review by Luks, Johnson and Swenson[224], a number of helpful recommendations are made for patients with CKD planning a trip to high altitude. Patients on diuretics should monitor their weight daily and adjust their medication dose if fluid retention develops. Non-steroidal anti-inflammatory medications should be avoided as they have the potential to exacerbate renal hypoxia by inhibiting renal vasodilatation and increasing renal oxygen consumption. Angiotensin-converting enzyme inhibitors should be prescribed in order to minimise altitude related proteinuria. Doses of some medications for AMS treatment and prophylaxis may need to be adjusted for patients with CKD (Table 3.7).[224]

Diabetes mellitus

A single case control study concluded that diabetes represents a risk factor for SCD during mountain hiking.[186] Type 1 diabetics acclimatise well and there is no evidence to date indicating that they are at increased risk of developing altitude illness.[227-230] Altitude exposure, including intensive exercise, is not contraindicated for diabetics with good glycaemic control and no vascular complications.[163,164,194,228,231] However, the unpredictable high altitude environment is far from the ideal milieu for maintaining effective glycaemic control.

Diabetic mountaineers report a reduction in metabolic control with increasing altitude[164,229], as demonstrated by elevated HbA_{1c}, insulin requirements and capillary blood glucose.[230,231] Reduced insulin sensitivity, altered carbohydrate intake and exercise are thought to be the major factors contributing to these effects.[163,164,232,233] Nutrition and exertion while trekking or mountaineering are variable and at times unpredictable (e.g., the need to wait out or outrun bad weather). Furthermore, illness, cold, stormy weather, stress, fear, fatigue and altitude related cognitive impairment may present major challenges to diabetes self management.[163,164]

Strenuous physical activity, hypothermia and gastrointestinal symptoms of AMS predispose diabetic mountaineers to hypoglycaemia, requiring adjustments in insulin dose.[163,164] Physically fit diabetics appear to have improved glycaemic control at altitude when compared to less fit diabetics.[164] Early recognition of poor glycaemic control is difficult at altitude, as symptoms of hypoglycaemia may be confused with AMS or paraesthesiae associated with acetazolamide prophylaxis. HAPE has also been reported as a trigger for diabetic ketoacidosis in a previously undiagnosed diabetic.[234] Furthermore, inappropriate insulin dose reduction, decreased caloric intake and absorption, metabolic acids produced during exercise and acetazolamide prophylaxis may result in the development of ketoacidosis.[231] Dexamethasone also rapidly increases insulin resistance and is only recommended for emergency use in diabetics.[163,164,235]

In order to maximise glycaemic control, precise tracking of energy intake and expenditure, frequent blood glucose monitoring and flexible insulin dosing are

imperative.[163,194,228] However, some blood glucose monitors are unreliable at moderate to high altitude due to the combined effects of elevation, temperature and humidity.[231,236,237] Exogenous insulin may be sensitive to heat and cold and thus should be stored carefully in an inside pocket to prevent it from freezing.[163,164,171]

Diabetic retinopathy is a relative contraindication for travel to high altitude, as hypoxaemia frequently causes retinal haemorrhage in healthy mountaineers above 5500m.[158,164,169] Travel to altitude could have more severe consequences for diabetic patients with complications or poor metabolic control and they should be evaluated and counselled accordingly. All diabetic patients should be carefully screened for complications that could increase their risk associated with exercise or exposure to altitude.[164] The website www.mountain-mad.org is an excellent resource for people with diabetes who are interested in mountain pursuits.[238]

Obesity

Ri-Li et al. found that obese people had worse AMS scores than non-obese counterparts at a simulated altitude of 3658m.[239] This effect is attributed to nocturnal desaturation associated with periodic, apnoeic breathing.[239,240] Furthermore, excess abdominal weight increases the likelihood of obstructive sleep apnoea and obesity-hypoventilation syndrome.[209] These factors can both exacerbate hypoxaemia and pulmonary hypertension which may increase an individual's risk for developing HAPE.[194,209] Excess body weight may also complicate or preclude stretcher rescue from remote locations. Obesity-hypoventilation syndrome is a contraindication to high altitude travel. If such travel is necessary, supplemental oxygen and prophylactic acetazolamide are recommended.[209]

Neurological disorders

Epilepsy

The effect of altitude on the seizure threshold has not been studied in depth. However, many well-controlled epileptics safely travel to altitude and are at no

known increased risk for development of altitude related illness or seizures.[194,241]There have been multiple case reports of seizures occurring in non-epileptic individuals at altitude, including one fatal case. [165,241-245] Daleau et al. reported a case where previously undiagnosed hyperventilation-induced seizures were unmasked in a patient with a positive family history for epilepsy.[246] Basnyat also reported a single case of grand mal seizures at high altitude in a well controlled epileptic patient on anticonvulsant medications.[241]

Seizures at high altitude are believed to be provoked by a number of potential factors including respiratory alkalosis, hypocapnia, hypoxia, or sleep deprivation.[165,241] Fluoroquinolone antibiotics prescribed for gastroenteritis have also been implicated in two case reports[241,242], due to their potential for lowering the seizure threshold.[247] Lastly, although the potential for having a seizure may not be greatly elevated at altitude, consideration must be given to the additional potential for harm should a seizure occur in a remote location or while performing high risk technical mountaineering manoeuvres.

Cerebrovascular Disease

The risk of stroke at altitude may be increased due to hyperviscosity secondary to polycythaemia, dehydration, cold exposure, and forced inactivity. Ischaemic stroke and cerebral artery thrombosis are potential complications of high altitude cerebral oedema.[165] Jha et al. document 30 cases of stroke in young (<48 years) individuals working at high altitude for a number of months. Ischaemic strokes were the most common type and altitude related polycythaemia was identified as the most significant risk factor.[248] Travel to high altitude is contraindicated for a 90 day period post stroke or transient ischaemic attack. Following this period, decisions about the safety of high altitude exposure and/or necessary treatment at altitude must be made based on each individual's clinical situation and the physician's estimation of stroke risk.[165]

Migraine

Migraine sufferers do not appear to be at increased risk of developing altitude sickness.[93] However, altitude exposure is a clinically recognised trigger for migraines and the severity of headaches may increase at altitude.[165,173,249,250] Furthermore, Murdoch described a migraine sufferer whose migraine presentation changed drastically at altitude to include focal neurological deficits.[250] Migraine sufferers can safely travel to high altitude, albeit with the caution that migraine frequency, severity and character may be altered.

Haematological conditions

Iron Deficiency Anaemia

There is little information available on the effects of anaemia at altitude and the risk of altitude related illness in this cohort has not been established. Hackett states that patients with iron deficiency anaemia appear to acclimatise well to high altitude.[173] Pollard and Murdoch report that haemoglobin concentrations of 14-18 g/dL are optimal for high altitude acclimatisation.[183] Patients with anaemia can expect to have reduced exercise capacity at altitude. Anaemia should be corrected prior to high altitude travel[194] and pre-menopausal women may benefit from iron supplementation while at altitude if their ferritin stores are low.[251]

Sickle Cell Anaemia

Exposure to altitudes above 2000m has been associated with a high incidence of vaso-occlusive sickle cell crisis or splenic infarcts in patients with sickle cell disease (HbSS or HbSC) or sickle cell trait (HbAS).[157,173,252] Travel to altitude is contraindicated for people with sickle cell disease.[173,183,252] Splenic crisis is the most frequent risk associated with exposure to hypobaric hypoxia in people with sickle cell trait.[253,254] Furthermore, severe exertion has been associated with sickle cell crisis and sudden death in this patient cohort.[255,256] Thiriet and colleagues suggest that while individuals with sickle cell trait are capable of intense exercise at high altitude, their performance is diminished.[257]

While some experts do not recommend absolute activity or altitude restrictions in patients with sickle cell trait[158], others[157] have advised that altitude should be avoided. Should they decide to travel to altitude, people with sickle cell trait should be informed of the risks and instructed to avoid over-exertion, to maintain adequate hydration and to minimise heat stress.[256,258,259] Individuals who are deconditioned should be exceptionally cautious in exerting themselves at altitude.[256] Patients may be unaware of their sickle cell status prior to travelling.[254] Should sickle cell crisis develop, appropriate treatment includes immediate descent, oxygen, fluids and analgesics.[158,254]

Psychiatric conditions

It is well documented that high altitude expeditions may elicit alterations in both emotional and cognitive functioning. These changes are likely due to the cumulative effects of hypoxia, high altitude deterioration, physical exhaustion, fluid and electrolyte disturbances and pre-existing psychological morbidity.[260,261] Cultural and interpersonal challenges are additional stressors likely to be encountered on a high altitude sojourn. Ryn documented profound psychological changes in a large portion of a cohort of healthy Polish mountaineers travelling in the Andes. With increasing altitude, the symptoms progressed from neurasthenic syndrome to cyclothymic disorder to acute psychotic disturbances.[260] New onset anxiety disorders or exacerbations of diagnosed anxiety are also common at altitude and are thought to predispose people to AMS.[260-263]

Safety, positive group interactions and success at mountain travel demand a high degree of skill, cognitive flexibility and emotional control. While at altitude, dramatic changes in a traveller's psychiatric status should be considered a medical emergency and supervised descent should follow without delay.[259] Patients with pre-existing psychiatric disorders should undergo careful psychiatric assessment prior to embarking on a high altitude sojourn. Patients taking psychotropic drugs should ensure that they are compliant with their prescribed medication at high altitude.

Pregnancy

Pregnant women are not believed to be at increased risk of altitude related illness. However, hypoxic conditions have the potential to compromise the uteroplacental circulation and cause placental hypoxia.[266,267] The foetal circulation is further compromised when the mother exerts herself and skeletal muscle competition for blood supply increases.[168] Susceptibility to dehydration increases as a result of the additive effects of pregnancy and altitude related hyperventilation.[167] Women staying at altitudes over 2500m for weeks to months have an increased rate of antenatal complications including bleeding[16], hypertension[268,269], pre-eclampsia[267,268,270], abruptio placentae[167,271], preterm labour[272], intrauterine mortality[270,271], and intrauterine growth retardation.[267-271, 173-175] Isolation from medical care and the potential for physical trauma inherent in many outdoor pursuits present additional challenges. Pregnant women are also more prone to serious complications of certain travel related infections and may be limited in their treatment options.[167]

According to a recent consensus statement, travel to high altitude is contraindicated in the first trimester of pregnancy in women at increased risk of spontaneous abortion. Beyond the first trimester, low risk pregnant women can safely enjoy short sojourns up to 2500m. Moderate physical exertion at these altitudes is acceptable following 2 to 3 days of acclimatisation. Strenuous exercise should be avoided at altitude. Contraindications to altitude exposure beyond 20 weeks gestation include co-existing hypertension, pre-eclampsia, intrauterine growth restriction, anaemia and maternal smoking. Acetazolamide is also contraindicated in pregnant women.[247] Should an extended stay at altitude be necessary for a pregnant woman, extra vigilance in the form of frequent pre-natal checks is necessary to promptly identify problems that may arise.[167]

Miscellaneous conditions

Raynaud's Phenomemon (RP)

Little is known about the specific effects of altitude on patients with RP. However, it is well known that patients with RP are at increased risk of cold injury. Because the high altitude environment may include extremes of cold, these patients should

travel to altitude during warmer months or to high altitude destinations with less severe climates. However, should they travel in winter climates, these individuals should take extra precautions to maintain the warmth of their extremities. High quality boots and mittens are essential; disposable chemical handwarmers are also recommended.[275] Calcium channel blockers (e.g., nifedipine) are the drugs of choice for the treatment of RP and should be considered in patients with RP who wish to participate in cold weather recreation at altitude.[276-278]

Ophthalmologic conditions

Patients who have undergone radial keratotomy to correct their myopia are at risk of significant visual deterioration at high altitude. The incisions made during this procedure weaken the cornea and cause it to deform with exposure to hypoxic conditions.[279] Progressive hyperopic shift with deterioration in both near and far vision has been reported in a number of mountaineers at high altitude.[279-281] Patients who have undergone radial keratotomy should travel to altitude with multiple pairs of corrective spectacles with varying degrees of correction for hyperopia.[282]

Some people who have undergone myopic laser in situ keratomileusis (LASIK) also experience significant visual changes with high altitude exposure.[283-285] The visual changes correct with descent to low altitude or with prolonged altitude exposure[286] but can persist for a number of weeks following descent. It is recommended that patients allow a minimum of 6 months following LASIK before travelling to altitude. Patients who have undergone myopic LASIK should carry spectacles with myopic corrective power while at altitude.[283]

Damage to the carotid bodies

The carotid bodies provide the stimulus for the hypoxic ventilatory response to hypoxia and thus their function is key to high altitude acclimatisation and prevention of AMS.[286,287] Neck irradiation or surgery involving one or both of the carotid arteries can potentially damage or ablate the carotid bodies, and thus alter or eliminate their function. Roeggla et al. [287] analysed blood gas samples taken at

moderate altitude from 4 patients before and after unilateral carotid endarterectomy. Following endarterectomy, the patients had a suboptimal ventilatory response and thus, significantly decreased P_aO_2. Patients with a history of neck surgery should be warned of their potentially limited capacity to acclimatise and should ascend with caution.[161,287]

Medication

The drugs most commonly used to treat or prevent altitude related illness are acetazolamide[288,289], nifedipine[288-291], and dexamethasone.[288,289,292] Salmeterol[288,293], sildenafil[294,295], and tadalafil[293] are occasionally used in the treatment and prevention of HAPE. Patients with pre-existing medical conditions or who are taking other medications may have fewer medication options or elevated risk of experiencing adverse drug reactions. Luks and Swenson provide an excellent review of these issues, the main points of which are summarised in table 3.7.[170]

Table 3.7 Cautions and contraindications in the use of medications to treat high altitude illness in patients with pre-existing medical conditions[170]

Medication	Contraindications	Cautions
Acetazolamide	Hepatic insufficiency Patients on long term high doses of aspirin Ventilatory compromise (FEV < 25%) GFR < 10mL/min Metabolic acidosis Hypercalcaemia Hyperphosphataemia Recurrent nephrolithiasis First trimester and beyond 36 weeks of pregnancy[167]	Renal failure Sulpha allergy Concurrent use of topiramate, potassium-wasting diuretics and ophthalmic carbonic anyhdrase inhibitors Diabetics
Dexamethasone	None	Diabetics Peptic ulcer disease or upper GI bleeding Patients at risk of amoebiasis or strongyloidiasis
Nifedipine	None	Hepatic insufficiency Concurrent use of antihypertensive agents Patients at risk of GI bleeding or gastroesophageal reflux Patients taking medications metabolised by the Cyt P450 3A4 and 1A2 pathways
Salmeterol	Hepatic insufficiency (no data) Patients on beta-blockers Patients on monoamine oxidase inhibitors or tricyclic antidepressants	Coronary artery disease prone to arrhythmia
Sildenafil	Patients taking nitrates or alpha-blockers Oeosphageal or gastric varices	Hepatic insufficiency GFR < 30 mL/min Increased risk of gastroesophageal reflux Patients taking medications metabolised by the Cyt P450 3A4 pathway
Tadalafil	Patients taking nitrates or alpha-blockers	GFR < 50 mL/min Hepatic insufficiency Increased risk of gastroesophageal reflux Patients taking medications metabolised by the Cyt P450 3A4 pathway

Tissot et al. found that patients taking warfarin were 2.7 times more likely to have a subtherapeutic international normalised ratio (INR) following ascent to altitude greater than 2400m. This risk is doubled in patients with atrial fibrillation. Thus, INR should be monitored closely following altitude travel in order to facilitate early detection and compensation for subtherapeutic INR values. In patients with atrial fibrillation, it would be prudent to measure INR after arrival at altitude if this is practicable.[296] Warfarin dosing and monitoring may be hindered by extended periods of remote travel, alterations in eating habits, travel-related illness and physical exertion. Although it comes with the added inconvenience of carrying and disposing of injection paraphernalia, low molecular weight heparin should be considered in patients where adherence to a warfarin regime is not practical but stable anticoagulation is critical. An additional, albeit expensive, option is a portable INR monitor which a suitably trained patient could use in conjunction with a nomogram for adjusting warfarin doses.[276]

Cortisol demands will increase in response to the hypobaric hypoxia at altitude. Patients taking glucocorticosteroids should adjust their dose accordingly. It is recommended that the maintenance dose be doubled at altitudes above 3000m and tripled above 4000m. Supplemental injectible corticosteroids should also be available for administration in case of unexplained deterioration.[297] Medications with a narrow therapeutic index which require toxicity monitoring (e.g., lithium and certain anticonvulsant drugs) pose an additional limitation to prolonged remote travel at altitude.

Medical issues on commercial flights

Passive ascent to altitude may result in sudden exposure to altitude without adequate time for acclimatisation. This rapid change poses an additional physiologic challenge to people with compromised health and affects the safety of some medical devices. Cabin pressure in commercial aircraft is regulated at barometric pressures equivalent to altitudes between 1500m and 2500m. In patients with reduced partial pressure of arterial oxygen at sea level, blood oxygen saturation can fall drastically at normal cabin pressures.[298] Even healthy passengers may be uncomfortable in these conditions[299] and symptoms of

subacute mountain sickness have been reported in flight.[300] Physicians should refer to the British Thoracic Society guidelines for recommendations on predicting and preventing respiratory decompensation during air travel.[210]

Since gas expands with decreasing barometric pressure, pneumatic splints are disallowed on most flights and plaster casts should be bivalved if applied within the previous 48 hours to avoid circulatory compromise.[298] Patients who have recently undergone surgery are at risk of wound dehiscence and should not fly within a 10-14 day post-operative period.[300] Air within feeding tubes, urinary catheters, and cuffed endotracheal or tracheostomy tubes should be replaced with water prior to air travel. Expansion of emphysematous bullae and abdominal gases may further compromise respiration in patients with COPD.[210]

Recommendations for clinical practice

All people travelling to altitude should know the precise details of their planned trip, train for physical demands, be familiar with standard ascent and acclimatisation protocols, and recognise the symptoms of altitude related illness. For people with pre-existing medical conditions, the risks of altitude exposure and removal from potential medical support are significant and must be taken seriously (Table 3.8). On the other hand, with proper planning and precautions, many people with pre-existing medical conditions can safely take part in outdoor adventures at high altitude (Table 3.9). Ultimately, avoidance of potential risk must be carefully weighed against an individual's desire to achieve personal goals. Physician and patient must work together to plan a rational and informed approach.

Table 3.8 Summary of recommendations for travel to altitude

Medical condition	Recommendations regarding altitude exposure	Source of evidence
Hypertension	Ascend with caution	
Heart failure	Contraindicated	
Coronary artery disease • Unstable angina • Exertional angina • Myocardial infarction • CABG, angioplasty	 Contraindicated Ascend with caution Contraindicated for 6 months after MI No contraindication if asymptomatic at sea level	
Cardiac arrhythmia	Individual cardiology risk assessment needed	
Congenital heart disease	Ascend with caution Contraindicated if symptomatic pulmonary hypertension	
Chronic obstructive pulmonary disease Mild Moderate Severe	 Ascend with precautions Ascend with caution, individual risk assessment needed Contraindicated	 Case series Expert opinion Expert opinion
Bronchial asthma	Ascend with specific precautions	
Obstructive sleep apnoea	Contraindicated if oxygen desaturation occurs at sea level	
Pleural and interstitial lung disease Secondary pulmonary hypertension Pneumothorax	Ascend with caution Contraindicated if symptomatic Contraindicated for 3 weeks post resolution	
Peptic ulcer disease	Contraindicated in active PUD	

	Specific precautions if history of PUD	
Inflammatory bowel disease	Contraindicated in active disease; travel with limitations in quiescent disease	Expert opinion
Chronic kidney disease	Ascend with specific precautions	
Diabetes mellitus	Ascend with precautions Relatively contraindicated if poor glycaemic control or retinopathy	Multiple small case control studies
Obesity	Contraindicated in obesity-hypoventilation syndrome	
Epilepsy	Ascend with caution	
Cerebrovascular disease	Contraindicated for 90 days post CVA/TIA Individual risk assessment needed	
Migraine	Ascend with caution	
Iron deficiency anaemia	Correct prior to ascent	
Sickle cell anaemia • Sickle cell disease • Sickle cell trait	 Contraindicated Ascend within limitations	
Psychiatric conditions	Ascend with caution	
Pregnancy	Contraindicated in first trimester if high risk of spontaneous abortion Contraindicated beyond first trimester in presence of certain co-morbidities	
Raynaud's phenomenon	Ascend with specific precautions	
Radial keratotomy Laser in situ keratomileusis LASIK	Ascend with precautions Ascend with precautions Contraindicated for 6 months after LASIK	
Damage to carotid bodies	Ascend with caution	Case series

Table 3.9 Checklist of recommendations for people travelling to altitude with pre-existing medical conditions

- ❑ Seek medical advice before booking the trip.
- ❑ Avoid travel if a medical condition is not stable.
- ❑ Purchase travel insurance including coverage for remote evacuation.[164]
- ❑ Ensure optimal physical fitness prior to travel.
- ❑ Understand airline restrictions and requirements for travel with medication or medical devices. Request necessary documentation from a physician.
- ❑ Consult a physician and/or pharmacist in relation to regular medications as follows:
  - Potential interactions with medications commonly used to treat altitude-related illness[170]
  - Potential respiratory depressant effects[194]
  - Medications that can affect exercise tolerance, thermoregulation, acclimatisation or cognition
  - Considerations for transport and storage of medications (i.e., temperature and ultraviolet sensitivity)[171]
    Understand the effect of time zone changes on medication schedules.[164]
- ❑ Continue with regular treatments unless otherwise instructed by a physician.
- ❑ Bring extra doses of regular medications.[162,301]
- ❑ Carry emergency supplies of medications separate from the main supply.[162,301]
- ❑ Travel with a partner or group.
- ❑ Inform and educate team leaders or travel companions about relevant medical conditions. If necessary, provide verbal and/or written instructions[177] with regards to:
  - The nature of existing medical conditions
  - How to recognise symptoms
  - How to intervene in the case of an emergency
  - The location of key items (e.g., medication, syringes, blood glucose monitor, etc).
- ❑ Wear Medic Alert® identification (e.g., bracelet) at all times.
- ❑ Maintain nutrition and hydration.[177]
- ❑ Allow extra time for acclimatisation (e.g., an extra night around 2000m) and restrict activity during this period.[183]
- ❑ Descend to lower altitude immediately with the onset of symptoms.[183]

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3.3. Pathogenesis of High Altitude Illness (Major Review)

Introduction

High-altitude illness is an umbrella term for a group of conditions that afflict individuals who ascend to high altitude faster than their bodies can acclimatise to its effects. It encompasses three main clinical entities: acute mountain sickness, high-altitude cerebral oedema and high-altitude pulmonary oedema. It also includes two conditions – subacute mountain sickness and chronic mountain sickness – which occur in people who reside permanently at high altitude. Trekking in high-altitude environments has become an increasingly popular recreational activity. It is estimated that about 140 million people live at altitudes above 2500m worldwide and some 40 million lowland dwellers travel to high altitude each year to ski, trek or work.[302] With the large numbers of previously healthy and often young travellers visiting high-altitude destinations, high-altitude illness may be regarded globally as a significant public health problem.

The lack of awareness of the health risks of high-altitude travel and acclimatisation issues in a sample of travellers attending an Irish travel medicine clinic was highlighted in a recent study.[303] There is a need for public health awareness campaigns to reduce the burden of high-altitude illness and to promote safer, more responsible high-altitude travel in the amateur mountaineering community. In order to provide credible and detailed preventive health advice it is necessary to understand the physiologic effects of altitude and the scientific basis of altitude acclimatisation. Misconceptions abound, even in the elite mountaineering community, about the correct approach to acclimatisation at high altitude.[304] Furthermore, despite decades of intensive laboratory and field-based research, considerable uncertainties still exist in the medical scientific community with respect to the mechanisms underlying the development of high-altitude illness. It is only by achieving a greater understanding of the pathophysiologic basis of high-altitude illness that we can hope to design effective therapies both to prevent and to treat this potentially rapidly fatal condition.

Physiologic changes at high altitude

It was not until 1644 that Torricelli announced that the atmosphere above us exerts a pressure:

"We live submerged at the bottom of an ocean of the element air, which by unquestioned experiments is known to have weight".[305]

The most significant physiologic effect of high altitude is a decrease in the partial pressure of oxygen in the circulating blood, such that as barometric pressure decreases, the partial pressure of oxygen also declines. At a skiing altitude of 3000m, the inspired partial pressure of oxygen is only about 70% of the sea level value, while at an altitude of 5000m, considered to be the highest habitable elevation, the inspired PO_2 is about half that at sea level. The partial pressure of inspired air at the summit of Mount Everest (8850m) is less than 30% of its value at sea level, emphasising the magnitude of the hypoxic insult presented by high-altitude environments.[304] While adverse environmental factors such as extreme cold, strong winds and intense ultraviolet radiation may to some extent be mitigated by appropriate protection, hypoxia is an inevitable consequence at altitude unless the subject is breathing supplementary oxygen.

The body partially defends itself against hypoxia by increasing the rate and particularly the depth of pulmonary ventilation via the carotid body peripheral chemoreceptors and the central medullary chemoreceptors.[306] This results in a low partial pressure of carbon dioxide in the blood. The hypoxic ventilatory response (HVR) decreases with advancing age[307] and is lower in men than in women. A low HVR has been implicated in the development of acute mountain sickness[308] and high-altitude pulmonary oedema.[309] The kidneys respond to this respiratory alkalosis over a period of days by reabsorbing hydrogen ions and excreting bicarbonate ions in the urine in an effort to restore the blood pH to normal values. It would seem to be advantageous for a mountaineer or high-altitude resident to be endowed with a brisk HVR in order to maintain a better oxygen supply to the brain and working muscles[310] but the finding of a blunted HVR in high-altitude natives argues against this necessity and elite climbers may not possess a particularly brisk HVR.[311]

Although the work of breathing is reduced by the lower air density at altitude, the high volume of air and the rapid respiratory rate combine to cause fatigue of the diaphragm and other respiratory muscles, thus limiting the maximal

oxygen consumption that may be achieved.[312] On the summit of Mount Everest, the maximal oxygen consumption is only approximately 20% of the value at sea level. This reduced maximal oxygen consumption may result from the reduction in mitochondrial PO_2, which impairs the function of the electron transport chain used to generate cellular ATP.[304] Some sources believe that there is a central inhibitory effect at play in the brain.[313]

Sleep is impaired at high altitude and may be even more disturbed in those with a brisk HVR. People who sleep at high altitude report frequent nocturnal awakenings, unpleasant dreams, and unrefreshed sleep. Periodic breathing, characterised by alternating apnoeic and hyperpnoeic phases, occurs in most people at altitudes above 4000m.[314] It is thought to result from instability in the brainstem control system which balances the effects of the hypoxic drive to ventilation[315] and the response to carbon dioxide.[316] It would seem reasonable to suggest that the marked hypoxaemia occurring in periodic breathers would increase the likelihood of developing acute mountain sickness but studies have not confirmed this and indeed AMS may be reduced in subjects with increased periodicity.[317] The oft-quoted mountaineering axiom of "climb high, sleep low" is based on this phenomenon of periodic breathing.

The effects of high-altitude exposure on mental performance have received much attention from frequent sojourners to high altitude. There are measurable differences in attention span, mental fatigue, visual sensitivity, short-term memory, arithmetic ability, and decision making capacity at altitude[318], and these may be co-factors in some of the high-altitude deaths in mountaineers which are attributed to accidents such as falls.

The major effects of high altitude on the lowlander's heart include an increase in heart rate due to increased sympathetic activity, a minor increase in blood pressure, and preservation of myocardial contractility. The blood pressure of high-altitude residents is lower than that occurring in their sea-level counterparts.[306] Maximal heart rate is not achieved at high altitude such that the heart rate of one climber on the summit of Everest was 110/min at rest and 120/min during exercise, compared to sea-level values of 58/min at rest and 190/min during maximal exercise.[319] Although the cardiac output increases for the first few days after arrival at high altitude because of increased sympathetic activity, the maximal cardiac output attainable at altitude is lower than the

corresponding sea-level value.[320] Less coronary artery blood flow is required at high altitude due to the reduced cardiac output and the increased oxygen-carrying capacity of the blood caused by the leftward shift in the oxyhaemoglobin dissociation curve and the increased haemoglobin.[306] At high altitudes it appears that blood is preferentially shifted from the peripheral cutaneous, splanchnic and renal vascular beds to the lungs.[321] Whether this phenomenon explains the increased pulmonary artery pressure which sometimes leads to the development of high-altitude pulmonary oedema is uncertain. As I will discuss later in the review, it is the pulmonary arteriolar constriction which is thought to contribute most to the pulmonary hypertension which occurs at high altitude.

Plasma volume decreases with ascent to high altitude[322], resulting in a raised haematocrit secondary to the dehydration caused by the increased loss of water vapour with faster breathing rates. A true increase in red cell production resulting from the release of erythropoietin by the kidneys takes weeks to develop[323] and, although this effect is exploited by athletes in an effort to gain a training advantage, it is unlikely to be of much significance to the short-term traveller who spends a week or so at high altitude.

There is evidence that hypobaric hypoxia stimulates the adrenal cortex to release cortisol by increasing pituitary release of ACTH.[306] Increased sympathetic activity is accompanied by an increased release of epinephrine[324] and norepinephrine[325] from the adrenal medulla. After several weeks at high altitude these effects are downregulated. Exercise in recent arrivals to high altitude destinations leads to an increase in renin, aldosterone, antidiuretic hormone and atrial natriuretic factor production which is more marked in individuals who subsequently develop acute mountain sickness.[326] These maladaptive responses will be discussed later when considering the pathogenesis of acute mountain sickness in greater detail.

Acclimatisation to altitude

The response of the body to hypoxia depends not only on the extent of the oxygen deficit but on the rate at which that hypoxia develops. To appreciate the crucial importance of altitude acclimatisation one needs only to consider the fate that

awaits a pilot whose oxygen supply in an unpressurised aircraft at the height of the summit of Mount Everest suddenly fails. The pilot would probably become unconscious within a few minutes, whereas the acclimatised mountaineer, though breathing very rapidly, would not only remain conscious but will also be able to work out his route and climb slowly.[310] The term 'altitude acclimatisation' refers to the physiologic responses whereby lowland humans respond to the reduced partial pressure of oxygen in the inspired air at high altitude. Later in this review, I will consider the maladaptive changes which occasionally produce serious illness at high altitude.

The most important aspect of acclimatisation is the increase in the rate and depth of breathing, resulting in an increase in alveolar ventilation. It is believed that the carotid bodies become more sensitive to hypoxia during prolonged exposure to high altitude.[327] Hyperventilation reduces the alveolar partial pressure of carbon dioxide and increases that of oxygen. On the summit of Mount Everest, the alveolar ventilation is increased by a factor of 5, reducing the alveolar PCO_2 to one fifth of its normal sea level value. The alveolar PO_2 is thus maintained at a level near 35mmHg which, although extremely low, is just enough to keep the climber alive.[328] It is of interest that the summit of Everest is at the upper limits of human survival without supplementary oxygen; were the mountain located at the more northerly latitude of Mount McKinley in Alaska where the equatorial bulge in the troposphere is not at play, it would not be possible to climb it without the aid of bottled oxygen.[310]

The respiratory alkalosis resulting from the hyperventilation mentioned above increases the pH of the cerebrospinal fluid (CSF) and arterial blood. Within a day or so, movement of bicarbonate out of the CSF normalises its pH, and after another day or two the pH of the arterial blood approaches normal values through renal excretion of bicarbonate ions.[304] Later in this review I will discuss the use of the drug acetazolamide, a carbonic anhydrase inhibitor, which accelerates the normal process of acclimatisation by causing a bicarbonate diuresis.

It is a commonly held misconception that the process of acclimatisation returns the body to its sea level condition. Astronomers working at the radio telescope station in Mauna Kea in Hawaii, for example, never fully acclimatise and exhibit a degree of arterial hypoxaemia which, if caused by chronic obstructive airways disease, would entitle them to continuous oxygen therapy. A similar

situation pertains to miners in the Andes who commute from sea level to working altitudes of 4500m and sleeping altitudes of 3800m. Such workers may benefit from oxygen enrichment of room air which has been shown to increase work productivity, reducing fatigue, and improving the quality of sleep.[329]

There is great individual variation in the rate and extent of altitude acclimatisation. How often have we observed a climber who struggles to acclimatise at a moderate altitude only to perform well subsequently at extreme altitude? Apart from past experience, there are no reliable predictors of effective acclimatisation and the discovery of predictive tools which could be used at sea level to anticipate an individual's acclimatisation profile is one of the greatest challenges in high-altitude medicine. No gender difference in the ability to acclimatise has been recognised. It is widely accepted by mountain guides and elite mountaineers that rest days on prolonged expeditions should be spent in trekking to higher altitudes and back in an effort to promote acclimatisation to the higher altitude. This has led to the afore-mentioned axiom of 'climb high, sleep low'. The possible beneficial effect of exercise on acclimatisation may explain the observation that subjects living in a hypobaric chamber for a number of days at a simulated altitude do not appear to acclimatise to the extent that they would on a mountain.[330] It should be noted, however, that exercise is recognised as a risk factor for the development of acute mountain sickness.[331] Perhaps individual climbers have a safe level of exercise beyond which they are at risk of succumbing to acute mountain sickness.

The rate of ascent is an important consideration in designing a safe acclimatisation schedule. A rule of thumb is that, above an altitude of 3000m, each night's camp should be no higher than 300m above the previous night's one, and that a rest day should be added every 2-3 days.[332] This is quite a conservative acclimatisation schedule and not often adhered to in modern expeditions. The author is aware of commercial mountain guides who rapidly convey trekkers toward the summit of Mount Kilimanjaro in Tanzania in 4 days with a predictably high incidence of high-altitude illness, when a safer acclimatisation schedule would mandate a minimum period of 6 days on the mountain. Even a brief recent exposure to high altitude confers some protection against the development of AMS.[333]

Contrary to popular medical opinion, polycythaemia does not contribute significantly to the process of acclimatisation for most travellers to high altitude. It takes several days before an increased rate of red blood cell production can be detected, and the process is not complete for several weeks. As was mentioned previously, the early transient increase in erythrocyte concentration is not caused by an increased rate of red blood cell production, but by a reduced plasma volume from dehydration, secondary to the hyperventilation, inappropriate reduction in thirst sensation, reduced fluid intake, and hormonally-induced diuresis which all occur at high altitude.

Anecdotal experience suggests that there is a phenomenon of carry-over acclimatisation whereby the beneficial effects of acclimatisation persist for some time after returning to a lower altitude. One study[334] demonstrated that a group of subjects who had been at 4300m for 3 weeks retained their acclimatisation level after 8 days at low altitude compared with a group who had no altitude exposure. It is widely believed that the effect of acclimatisation probably falls off exponentially with time over a period of 2-3 weeks. Whether previous altitude exposure hastens an individual traveller's acclimatisation in the future is still uncertain but this is certainly the impression in the mountaineering community.

Acute mountain sickness

Epidemiology and Clinical Presentation

Acute mountain sickness is a common occurrence in travellers who ascend from near sea level to altitudes higher than about 2500m[335], but it has been reported at altitudes as low as 2000m. According to the Lake Louise consensus criteria, AMS may be defined as the presence of headache plus at least one of the following symptoms: gastrointestinal upset, fatigue or weakness, dizziness or lightheadedness, and difficulty sleeping, occurring several hours after reaching a higher altitude.[336] This definition is imperfect, however, as some of the symptoms it specifies may result from a recent long journey, a demanding climb, an uncomfortable sleeping environment or gastroenteritis.[337]

In the Everest region of Nepal, about 50% of trekkers who walk to altitudes higher than 4000m over 5 or more days develop AMS[338], while as many as 84% of

trekkers who fly directly to 3860m are affected.[339] Whether AMS occurs or not is determined by the rate of ascent, the absolute altitude reached, the sleeping altitude, and certain poorly understood physiologic factors which increase an individual's susceptibility. Recognised risk factors include a previous history of AMS, permanent residence at an altitude below 900m[340], exertion[331], neck irradiation or surgery[341], but not lack of physical fitness.[342] In a previous study it was found that a large proportion of trekkers wrongly assumed that physical fitness is protective against the development of AMS.[303]

It is of interest that a small proportion of mountaineers studied consider themselves to be sick when fulfilling the criterion score for AMS as defined by the Lake Louise consensus group.[343] The situation is further complicated by the fact that there are no diagnostic tests for the presence of AMS. Typically, symptoms of AMS begin 6 to 12 hours after ascent[344] and, unless further ascent is undertaken while the symptoms are present, the condition usually resolves within 2 or 3 days. The golden rules must be observed to avoid developing higher grades of AMS or progressing to high-altitude cerebral oedema: no further ascent until symptoms have disappeared and descent when symptoms do not improve after a day of rest. A flexible travel itinerary has been advocated so that the trekker can incorporate additional rest days if required.[335]

Pathogenesis

The pathophysiology of AMS is still incompletely understood but presents some fascinating insights. Several reviews have suggested that AMS is caused by cerebral oedema and raised intracranial pressure.[335,344] Although the brain itself is insensitive to pain, swelling would stimulate the pain-sensitive sensory fibres in the meninges and its vessels and account for the headache of AMS.[345] The raised intracranial pressure could reasonably explain the nausea and vomiting which are distressing features of the condition and which compromise the trekker's ability to maintain adequate caloric intake and hydration. Recent cerebral MRI studies have examined changes in brain and CSF volume occurring during simulated conditions of hypobaric hypoxia. It is not possible to directly assess raised intracranial pressure by MRI, but its presence may be inferred from observing brain

compression, displacement of midline structures, and effacement of the CSF-containing ventricles.[337]

One study showed no signs of intra- or extracellular brain swelling after 6 to 10 hours at a simulated altitude of 4500m in subjects with and without AMS.[346] An older study found a mean brain volume increase of 2.7% (36ml), located mainly in the grey matter, after 32 hours at a simulated altitude of 4572m; the volume increase did not differ between subjects with and without AMS, however.[347] It has previously been hypothesised that individual variation in susceptibility to AMS may depend on the ability to buffer an increase in intracranial pressure by displacing CSF from the intracranial to the spinal CSF compartments.[348] Two MRI studies reported a 10% reduction in intracranial CSF volume, but this did not correlate with the occurrence of AMS after 10 to 12 hours of exposure at simulated altitudes of 4500m[346] and 4800m.[349]

Opening CSF pressure, as measured at lumbar puncture, was normal after a hypoxic exposure of 16 hours and was not different in subjects with and without AMS.[350] Singh and co-workers[351] reported a CSF lumbar pressure 6 to 21 cm H_2O higher compared with measurements made after recovery in a group of 34 Indian soldiers who were rapidly transported from sea level to an altitude of 5867m in the Himalayas. It is likely that these soldiers had high-altitude cerebral oedema, but whether this potentially rapidly fatal condition is preceded by lesser degrees of cerebral oedema corresponding to the symptoms of AMS, is still a matter for debate.

It is well known that cerebral blood flow increases significantly at high altitude[352] and, by dilating cerebral resistance vessels, always leads to an increased brain volume. No correlation has been established, however, between changes in cerebral blood flow and AMS, which accords well with the findings in the MRI studies mentioned earlier. The magnitude of brain volume increases appears to be negligible unless one postulates that either hypoxia sensitises pain receptors by an unknown mechanism or that brain volume changes preferentially affect particular parts of the brain.

An alternative, or perhaps additive, mechanism by which hypobaric hypoxia gives rise to AMS has been proposed that implicates neuro-oxidative stress mediated by oxygen free-radicals which target the blood-brain barrier. The human brain is particularly prone to damaging redox reactions by virtue of its modest

antioxidant defences, high density of mitochondria, abundance of transition metal ions, reactive microglia, autooxidisable neurotransmitters and membrane lipids rich in polyunsaturated fatty-acid side chains.[353] Few studies exist to support this oxidative stress theory, due in part to methodological difficulties in detecting free radicals. Prophylaxis of AMS by administering an antioxidant cocktail during an ascent to 5180m attenuated AMS symptoms in one study.[354] This, and other similar studies, has been limited by small sample sizes and slow ascent rates. Furthermore, blood sampling has been confined to the peripheral venous blood distal to the proposed site of production of the free radicals concerned.

One study[350] used electron paramagnetic resonance spectroscopy and MRI in an attempt to address these limitations. Compared to normoxic control subjects, a progressive increase in blood and CSF concentrations of free radicals was detected during a 16 to 18 hour simulated exposure to 4600m. These radical species may have been derived from the oxidative catalysis of iron and not copper, which is consistent with previous reports of cerebral oedema being localised to the genu and splenium of the corpus callosum in severe AMS[355] and high-altitude cerebral oedema.[356] In the future, interventional studies which target delivery of free radical scavenging agents to the blood-brain barrier and cerebral parenchyma may help to unravel the underlying pathophysiology of AMS.

Management

Patients with mild to moderate AMS should rest and avoid exertion at their current altitude. They should not be left alone and they should be encouraged to report any worsening of the symptoms which may herald the onset of HACE. If the symptoms do not remit with 24 hours of rest, the patient should descend under supervision. In the meantime, analgesics, in particular aspirin and ibuprofen, and anti-emetic agents, should be provided, and the subject kept well hydrated.

Acetazolamide, a carbonic anhydrase inhibitor which promotes the renal excretion of bicarbonate ions, may be used both to prevent and to treat AMS. A meta-analysis[357] concluded that 500mg of acetazolamide daily produced clinically relevant decreases in AMS symptom scores. A systematic review[358] generated much controversy by concluding that a dose of 500mg was not sufficient for the prevention of AMS. Recently it was demonstrated that 125mg of acetazolamide

twice daily, the dose favoured by the Himalayan Rescue Association and by this author, was effective in reducing the incidence of AMS and the severity of symptoms in 222 trekkers who ascended from 3440m in one or two days to 4928m.[359] Acetazolamide is also widely used to lessen periodic breathing and improve sleep quality at high altitude in a dose of 125mg taken one hour before going to bed.[360]

In the largest trial examining the therapeutic benefit of the antioxidant *gingko biloba*, it was found to be no more effective in combination with acetazolamide than acetazolamide alone.[361] It remains to be seen if a sufficiently powered study in a high-risk setting will be performed to confirm suggestions that a period of preloading is necessary to maximise the antioxidative capacity of *gingko*.[337]

High-altitude cerebral oedema

Epidemiology and Clinical Presentation

High-altitude cerebral oedema is a 'mysterious and infrequent malady' which afflicts persons who have recently arrived at high altitude.[362] It is generally preceded by acute mountain sickness or high-altitude pulmonary oedema and so it should, in theory, be eminently preventable. It is typified by mental status changes ranging from drowsiness and confusion to coma, neuropsychiatric manifestations including hallucinations, and an ataxic gait.[363] Recognising the onset of gait ataxia at high altitude is of paramount importance if HACE is to be detected early in patients concealing the symptoms of AMS.[364] Physical findings include disturbed consciousness, ataxia and papilloedema. One author suggested, "If the patient seems mildly drunk at altitude they have cerebral oedema".[365] It is widely accepted that HACE is an extension, both clinically and pathophysiologically, of AMS[335] and it is therefore reasonable to suggest that the pathogenetic theories proposed for AMS might also be operable in the case of HACE.

HACE occurs in unacclimatised persons at altitudes above 2000m and usually occurs in the setting of an abrupt ascent to over 3000m.[362] The lowest altitude of occurrence reported in the literature is 2100m.[366] Elite climbers who are

apparently well acclimatised at extreme altitudes over 7000m occasionally succumb to rapidly progressive HACE[365] and it is a modern trend for such climbers to carry dexamethasone on summit day to treat the condition. The precise incidence of HACE is unclear but it has been reported in 1% of all trekkers between 4243 and 5500m in Nepal, with an increased incidence of 3.4% in those who suffered AMS.[338] A remarkable incidence of 31% was recorded in a group of Vedic pilgrims in Nepal who ascended in two days from 2000 to 4300m to sleep at the higher altitude.[367] It was reported that 14% of 150 patients with HAPE in the Colorado Rocky mountains had concurrent HACE in one study.[368] It is believed that HACE is less common than HAPE, and much less common than AMS.

HACE usually arises as a progression of AMS over a period of 24 to 36 hours, but AMS has been known to progress to HACE within a few hours. The mean altitude at which HACE was diagnosed in one review was 4730m, but was 810m lower when associated with HAPE.[306] The risk factors for HACE are identical to those for AMS.[362] Later in this review, I will consider the putative genetic predisposing factors which underlie the development of HAPE. Unlike HAPE, these genetic polymorphisms have not yet been investigated in the case of HACE.

Pathogenesis

The link between AMS and HACE has already been mentioned but the sequence of pathologic events which lead from AMS to HACE is the subject of much speculation. The most popular theory in the literature is that HACE arises as a result of vasogenic cerebral oedema, brought about by a disruption in the blood-brain barrier. The CSF opening pressure is markedly elevated in patients with HACE and autopsies have confirmed the presence of gross cerebral oedema.[369] MRI studies have revealed the presence of oedema in the white matter of the corpus callosum, with sparing of the grey matter.[356] The time course of both onset and resolution upon descent, the observation that patients recover completely if they survive, and the prompt response to steroids all support the vasogenic theory. Whether or not there is also an element of cytotoxic oedema whereby the brain cells themselves swell is a matter for further investigation.

Vasogenic cerebral oedema may result from increased blood pressure in the cerebral capillaries which could be due to impaired cerebral autoregulation at high altitude.[370] There may be impaired cerebral venous return which could arise from

restrictions in venous outflow imposed by anatomical abnormalities. This theory has been validated in patients with benign intracranial hypertension[371] and is made more plausible by the finding of seemingly random individual susceptibility to HACE. Studies of cerebral venous anatomy in volunteers with AMS may reveal predisposing structural abnormalities. It is of interest that HAPE, by increasing intrathoracic pressure, may impede venous return from the brain and so precipitate the onset of HACE.[372] While good animal models exist for HAPE, there are no such models available to HACE investigators, and it is understandably difficult to accurately assess cerebral capillary pressure and brain biochemistry in the intact human at high altitude.

Numerous chemical mediators of blood-brain barrier leakage have been postulated to account for the cerebral oedema of HACE. These include bradykinin, histamine, arachidonic acid, hydroxyl free radicals and iNOS-generated nitric oxide.[362] Vascular endothelial growth factor (VEGF) was first suggested as a contributory factor to the elevated vascular permeability of HACE by Severinghaus.[373] This has since been supported by a mice study[374] which demonstrated hypoxia-induced VEGF expression and prevention of vascular leakage in the brain through VEGF-blockade by a specific antibody. Dexamethasone appeared to prevent and reverse hypoxia-induced brain swelling by inhibiting VEGF expression. Studying the genetics of VEGF expression in response to hypoxia might shed some light on the marked individual susceptibility to HACE.

In a comprehensive review on the subject of HACE, Hackett and Roach[362] conclude that in order to characterise the link between brain swelling in AMS and vasogenic oedema in HACE serial measurements of changes in brain volume and compliance as patients progress from being well to being diagnosed with AMS are required. It may not be ethical to prospectively follow patients with AMS and to image their brains if they develop HACE because the latter is a preventable condition which is rapidly fatal if untreated.

Management

Once coma supervenes in a patient with HACE, death is likely despite aggressive therapy.[351] Recovery is usually rapid if treatment is instituted at the first sign of HACE and slower when treatment is delayed. The average time to recovery in a

recent series was 2.4 weeks.[356] Treatment involves immediate descent or simulated descent in a portable hyperbaric chamber, when descent is delayed due to weather or terrain considerations. HACE generally requires a greater degree of descent than either AMS or HAPE and recovery time is more prolonged.

In addition to descent and oxygen if available, treatment also includes high doses of the steroid dexamethasone, usually 8mg intravenously or intramuscularly, followed by 4mg orally every 6 hours. Because carbon dioxide is a cerebral vasodilator it would appear intuitive that intubating and hyperventilating the patient might be a reasonable approach to managing the HACE patient by blowing off carbon dioxide. It should be recalled, however, that these patients already have a respiratory alkalosis, and hyperventilation could cause cerebral ischaemia by losing too much carbon dioxide. Oxygen alone is preferable as it is known to reduce cerebral blood flow and intracranial pressure at high altitude.[375]

High-altitude pulmonary oedema

Epidemiology and Clinical Presentation

While the detailed pathogenesis of both AMS and HACE remain to be elucidated, much is already known about the pathophysiology of high-altitude pulmonary oedema (HAPE). HAPE is a potentially fatal condition that typically occurs 2 to 4 days after ascent to altitudes in excess of 3000m.[376] With usual ascent rates, the incidence of HAPE is 1-2%, making it more common than HACE but far less common than AMS. Incidence rates of as high as 10% have been reported in people ascending rapidly to 4500m without acclimatisation.[377] A variant of HAPE termed *reascent high-altitude pulmonary oedema* occurs in residents of high altitude who travel to a lowland area and then return to high altitude. HAPE is often preceded by AMS but it may occur *de novo* without significant warning.

The main symptom of HAPE is shortness of breath with reduced exercise tolerance. It was confused with heart failure or pneumonia in earlier descriptions in the late 19th and early 20th centuries.[378,379] Classically, the person lingers at the back of the trekking party and may not be able to breathe comfortably at rest. A dry cough is often followed by the production of frothy, blood-stained sputum. Examination may reveal tachycardia and tachypnoea, as well as crackles which

are most commonly heard in the right axilla, reflecting the unusual predilection of HAPE for the middle lobe of the right lung.[306] Symptoms tend to worsen at night, perhaps because of the arterial oxygen desaturation which occurs on recumbency, and coma may occur during sleeping hours in severe cases.

Pathogenesis

HAPE is characterised by the extravasation of protein-rich fluid from the intra- to the extravascular space in the lung. The pathogenesis of HAPE is still a subject of intense study, but strong evidence exists to implicate pulmonary hypertension in its causation.[380] Cardiac catheterisation studies[381] have recorded pulmonary artery systolic pressures as high as 144 mmHg (normal range, 60 to 80 mmHg). It is thought that the pulmonary hypertension is secondary to a patchy pulmonary vasoconstriction, such that some pulmonary capillaries are exposed to the high pressure because they are unable to adequately vasoconstrict due to a paucity of smooth muscle in their walls. This leads to so-called stress failure of the pulmonary capillary walls with consequent leakage of oedema fluid and red blood cells into the alveoli.

Cardiac catheterisation studies have confirmed that the pulmonary artery wedge pressures are normal in HAPE, so that this is not a form of left-sided heart failure.[382] Furthermore, studies of alveolar fluid obtained by bronchoalveolar lavage have shown that this is a high-permeability type of pulmonary oedema by virtue of the finding of high molecular weight proteins in the fluid.[383] Later in the course of the disease, the alveolar oedema fluid contains inflammatory markers[384], raising questions about the role of inflammation in the pathogenesis of HAPE. People who are susceptible to HAPE tend to exhibit an unusually strong hypoxic pulmonary vasoconstrictor response which may be genetically determined.[385]

Some insights have been gained from study of potential vasoactive mediators. Thromboxane B2 was found in the bronchoalveolar lavage fluid of patients with HAPE[384] while the potent pulmonary vasoconstrictor endothelin-1 was increased in individuals with HAPE in another study.[386] Red wine is known to reduce endothlin-1 levels[387] but is not otherwise recommended at high altitude. It has been suggested that a defect in synthesis of the vasodilator nitric oxide in the alveolar epithelium may contribute to the exaggerated hypoxic pulmonary vasoconstrictor response in some subjects suffering from HAPE.[388] A study by

Busch et al.[389] revealed that, when exposed to hypoxia, HAPE-susceptible mountaineers had a decreased level of nitric oxide exhalation compared to controls, resulting in diminished pulmonary vasodilatation and elevated pulmonary artery pressures.

A restricted pulmonary vascular bed, such as occurs with congenital unilateral absence of a single pulmonary artery, is a recognised risk factor for the development of HAPE.[390] Strenuous exercise[391] and cold weather[392] are known to augment pulmonary artery pressure and are additional risk factors for its occurrence. Patients with concurrent respiratory tract infections may be particularly susceptible to developing HAPE.[393] Studies have elegantly shown that the ultrastructural changes in the pulmonary capillary endothelium and alveolar epithelium, including distortion of type IV collagen in the basement membranes, are readily reversible.[394] This rapid reversal of pathologic changes is consistent with the very rapid improvement in patients' symptoms when they descend to a lower altitude. It is intriguing that if HAPE does not arise within 4 or 5 days of arrival to high altitude, it does not develop at all unless the altitude is increased further. This has been attributed to vascular remodelling of the pulmonary arteries due to the alveolar hypoxia. This remodelling may serve to protect the downstream pulmonary capillaries from direct transmission of high intravascular pressures. It may also explain the phenomenon of reascent HAPE mentioned earlier where presumably, some vascular smooth muscle involutes during the time spent at high altitude.[304]

It was suggested earlier that VEGF may be important in the pathogenesis of HACE. In the case of HAPE, however, high altitude exposure in both normal and HAPE-susceptible subjects did not elevate VEGF levels[395], thus undermining its role in the development of HAPE. Kaner and Crystal[396] hypothesise, however, that exposure of the pulmonary capillary endothelium to the high levels of VEGF present on the alveolar epithelial surface could lead to an increase in alveolar-capillary endothelial permeability.

The role of alveolar fluid clearance in HAPE has received increasing attention in recent years. Dada et al.[397] discovered a time-dependent decrease in Na^+-K^+ ATPase activity in epithelial cells exposed to hypoxia, a phenomenon exploited by the use of salmeterol to increase the rate of alveolar fluid clearance in patients with HAPE.[398] There has been much interest in the possibility of

predicting the development of HAPE by detecting the presence of certain genetic markers in the blood. Droma et al.[399] found a positive association between endothelial nitric oxide synthase gene polymorphisms and HAPE. Hanaoka et al.[400] showed that individuals who are susceptible to HAPE have increased pulmonary artery pressures under hypoxic conditions compared to control subjects, with a greater cephalad redistribution of blood flow in a subgroup with HLA-DR6 alleles that was absent in HAPE-resistant subjects. Dehnert et al.[401] were unable to find an association between insertion or deletion polymorphisms in the angiotensin-converting enzyme gene in HAPE-susceptible subjects. It is hoped that the identification of gene alterations may lead ultimately to gene therapy to prevent HAPE, or at least to the identification of travellers susceptible to HAPE.

Management

The prevention and treatment of HAPE proceed logically from an understanding of its pathogenesis. In people who have previously developed HAPE, the vasodilator calcium channel blocker nifedipine (20mg of the slow-release preparation every 8 hours) reduces the incidence.[402] The cardinal principle for the treatment of patients with HAPE is to remove the patient to a lower altitude without delay. Oxygen should be administered as it reduces pulmonary artery pressure rapidly. Descent may be simulated in a hyperbaric chamber held with the head tilted upwards at an angle of 30 degrees. Nifedipine should also be administered at a dose of 20mg orally every 6 to 12 hours. As alluded to earlier, there is emerging evidence that the long-acting beta-adrenoceptor agonist salmeterol may be beneficial in patients with HAPE by accelerating the clearance of alveolar fluid. The phospodiesterase inhibitor sildenafil, better known for the treatment of erectile dysfunction at sea level, may also be useful in HAPE by lowering pulmonary artery pressure.[403] Preliminary evidence suggests that the antioxidant *gingko biloba* prevents the development of early HAPE in rats by attenuating hypoxic pulmonary vasoconstriction.[404]

Chronic mountain sickness

Epidemiology and Clinical Presentation

Chronic mountain sickness (CMS) was first described in 1925 by Carlos Monge M. who subsequently went on to describe a series of such patients with red cell concentrations that were higher than expected at altitude.[405] Outside South America, CMS was described in Leadville (3100m), a mining town in Colorado, in the late 1940s.[406] Reports of CMS from the Himalayas revealed that the condition is prevalent in the immigrant Han Chinese population in Lhasa, Tibet (3658m) but rare in the native Tibetan population.[407]

Patients with CMS present with symptoms of reduced cerebral blood flow such as headache, dizziness, somnolence, difficulty concentrating and loss of mental acuity. Reduced exercise tolerance is common and patients may gain weight as a result. Curiously the symptoms abate on descending to sea level, only to reappear on return to altitude.[310] Patients with CMS can be easily recognised by their distinctly cyanotic appearance, resulting from a far higher concentration of deoxygenated haemoglobin in their blood. The signs may be striking in the Andean Indians:

> "The combination of virtually black lips and wine red mucosal surfaces against the olive green pigmentation of the Indian skin gives the patient with Monge's disease a striking appearance".[408]

The packed cell volume is markedly raised with values as high as 83 per cent being recorded.[409] The increased viscosity of the blood leads to an elevated systemic blood pressure and a significantly higher pulmonary artery pressure than healthy high altitude residents.[410] As expected there is right ventricular hypertrophy and associated changes on the electrocardiogram.[411] Men are affected more commonly than women and the average age at diagnosis is 40 years. The male preponderance may be due in part to the protective effect conferred by female sex hormones in premenopausal women which act to stimulate ventilation.[412] It is remarkable that the haemoglobin concentration in Himalayan patients with CMS tends to be lower than the values from the Peruvian Andes, raising the possibility that there is greater genetic adaptation to altitude in Tibetans who have lived at high altitude for longer.

Pathogenesis

In patients with apparently normal lungs, the pathogenesis of CMS is unclear. Severinghaus et al.[352] determined that patients with CMS have a blunted hypoxic ventilatory response compared with healthy controls residing at the same altitude. The possibility of CMS arising in high-altitude residents with frequent apnoeic episodes during sleep was supported by a study which found that CMS patients had more disturbed breathing and lower mean arterial oxygen saturation values when asleep than a matched control group.[413] As expected, erythropoietin levels are higher at altitude than at sea level, but one study did not demonstrate any difference between subjects with and without CMS in terms of mean erythropoietin levels.[414]

Management

For patients who do not wish to descend to sea level for family or economic reasons, venesection, or the deliberate drawing of blood, not only lowers the raised haematocrit but also improves many of the neurological symptoms. It also improves gas exchange[415] and exercise performance[406] in some subjects. In Leadville, Colorado, where about 60 patients with CMS are regularly bled, the local blood bank has no shortage of blood donors.[416] An alternative to venesection for residents at high altitude is the use of respiratory stimulants such as medroxyprogesterone acetate.[417] Acetazolamide, so useful in patients with AMS and HACE, has not been investigated as a respiratory stimulant in patients with this condition.

Subacute mountain sickness

Two distinct syndromes have been described in the English literature in recent years which are collectively named subacute mountain sickness. Subacute infantile mountain sickness (SIMS) affects infants of Han Chinese origin who are brought from the low-lying plains of China to live in Tibet at altitudes over 3000m.[418] The condition is usually fatal within a few months at altitude. The second entity of adult subacute mountain sickness was first reported in Indian soldiers posted for over 10 weeks at altitudes of 6000m in the Western

Himalayas.[419] These disorders share a similar protracted time course and both conditions are associated with exaggerated pulmonary hypertension.

The prevalence of SIMS in one study was 3.66% in Han infants and 1.52% in Han children in general.[420] The prevalence increased with altitude and decreased with age. Greater awareness of this condition has persuaded Han mothers to give birth at lower altitudes and not to bring their children to Tibet until they are over a year old. Affected infants present with features of congestive cardiac failure, including dyspnoea, cough, sleeplessness, cyanosis and puffy features.

At autopsy, an enlarged heart, a dilated right ventricle, and a dilated pulmonary trunk are evident. The right atrium is dilated, but the left atrium is spared. Histology of the pulmonary artery shows medial hypertrophy with muscularisation of the pulmonary arterioles.[421] The pulmonary artery pressure measured in one study of patients diagnosed with SIMS was significantly higher than in the control subjects.[422] Thus, it appears that an exaggerated pulmonary vasoconstrictor response in Han Chinese infants forms the basis of this syndrome. It is reasonable to conclude that the pulmonary circulation of the Tibetan population may be adapted to hypoxia, whereas that of the lowland natives is not.

While pulmonary hypertension plays a central role in the development of SIMS, its role in adult subacute mountain sickness is less clear. When the Indian soldiers affected were studied at sea level within 72 hours of being airlifted from their posts, they showed only a mildly elevated pulmonary artery pressure, which was unresponsive to oxygen inhalation and did not fully resolve until 12 to 16 weeks at low altitude. The pulmonary artery pressures may have been much higher at extreme altitudes where the degree of hypobaric hypoxia was much greater and the soldiers were engaged in strenuous physical activity most of the day.[421]

The finding of a 23% increase in total body sodium and a 20% increase in total body water in the Indian soldiers implicates salt and water retention in the pathogenesis of adult subacute mountain sickness. Plasma renin activity was unchanged while serum aldosterone rose by 107%. Plasma cortisol rose by a factor of 2.5 times and growth hormone by 16 times the normal values. Renal blood flow was also reduced. These endocrine and renal abnormalities are similar to those observed in patients with severe congestive cardiac failure due to dilated

cardiomyopathy.[423] The precise sequence of events leading to the fluid retention in this condition remains to be fully elucidated. Although adult subacute mountain sickness still affects soldiers stationed at high altitude for prolonged periods[424], the occurrence of this syndrome has decreased considerably following measures taken to reduce the period of stay of soldiers at extreme altitude.

Suggestions for further study

The future of high-altitude medical research will focus on uncovering the precise link between hypobaric hypoxia and the development of high-altitude illness. High-resolution imaging techniques such as diffusion-weighted MRI, positron emission tomography, and single-photon CT techniques will enable investigators to study changes in the lungs in HAPE and in the brain in AMS and HACE. In particular, the mechanisms underlying the heterogeneous vasoconstriction in the lungs in response to hypoxia in HAPE, as well as the precise nature of the blood-brain barrier leakage and the ratio of brain volume to intracranial volume in HACE, will all shed light on the pathophysiology of high-altitude diseases. The development of an animal model for HACE will allow us to better characterise the substances leading to increased permeability of the blood-brain barrier, and may lead to the identification of potential therapeutic agents.

As health professionals, we need to improve our ability to predict travellers' personal risk of AMS and the ideal ascent rates necessary to prevent this disorder. Research may lead to the discovery of susceptibility marker genes which, when incorporated into mathematical models, will help to predict the likelihood of developing AMS.[425] Comprehensive databases of individual ascent profiles which are correlated with demographic information and measurements of AMS, such as are available to SCUBA divers in hyperbaric medicine, should be compiled. Therapeutic agents such as sildenafil, salmeterol, *gingko biloba* and garlic[426] require more careful assessment and the precise indications of these and existing prophylactic drugs need to be clarified. Finally, public awareness campaigns, targeted at health professionals, travel medicine clinics, mountaineering clubs and travel agents, should aim to reduce the incidence of high-altitude illness and promote safer travel above the clouds.

Preparing the traveller for safe travel to high altitude

On the basis of the research outlined above and in light of my own practical field experience, the following recommendations for the prevention of high-altitude illness can be reasonably asserted:

1. Acclimatisation at an intermediate altitude according to recommended rates of ascent is the principal method of preventing AMS. Treks or climbs should be organised to allow a gradual ascent and a stay at an intermediate altitude. Travellers should have a flexible travel itinerary when in high-altitude regions of the world.
2. Visitors to high altitude should have access to experienced, appropriately trained medical personnel when undertaking a trip to very high or extreme altitude.
3. Pre-existing medical conditions should be carefully considered and stabilised before high-altitude travel is planned.
4. Undue exertion at altitude should be avoided but daytime sleep, even when suffering from AMS, should be discouraged as it will lead to hypoventilation and exacerbate the hypoxia.
5. Acetazolamide is not currently recommended for routine prophylaxis of AMS but should be used where there is a history of severe AMS, a forced rapid ascent is necessary, and also for the treatment of severe AMS and HACE.
6. Climbers who are affected by periodic breathing and disturbed sleep at high altitude should consider taking acetazolamide prior to sleep.
7. Considerable potassium may be lost due to the diuresis that occurs in response to altitude acclimatisation and in travellers taking acetazolamide, and the diet should be supplemented with additional potassium, such as from fruit, soup and nuts.
8. Adequate fluid intake and a high carbohydrate diet are desirable at high altitude.
9. Alcohol, codeine (much beloved by earlier Everest explorers), sedating antihistamines and sedative-hypnotics should be avoided due to their respiratory depressant effects.
10. Smoking should be avoided at high altitude.

11. Light physical activity should be encouraged rather than allowing trekkers to sleep for long periods in their tents or lodges during the day.
12. Patients who become sick at high altitude have high-altitude illness until proved otherwise.
13. Patients with AMS should never be left alone and should be encouraged to report any worsening of their symptoms.
14. If the symptoms of AMS do not improve after 24 hours of rest, if they progress to HACE or if the patient develops HAPE, immediate descent should be arranged.

Conclusions

High-altitude illness occurs commonly in its least severe form (AMS) and far less commonly in its most complicated forms (HACE and HAPE). Travellers to high altitude should be counselled regarding the risk of high-altitude illness and the necessary steps to take if it develops in them or in a travelling companion. Although much is understood about the links between the hypobaric hypoxia of high altitude and the development of high-altitude illness, gaps in our knowledge prevent the accurate prediction of high-altitude illness in intending travellers and the identification of drugs which may prevent or ameliorate the symptoms. The coming years will witness considerable advances in the understanding of the causes and management of this fascinating condition and enable people to travel more safely to the high-altitude regions of the world.

3.4. Pathogenesis of High Altitude Cerebral Oedema – A Novel Hypothesis

High altitude cerebral oedema (HACE) is an encephalopathy that is thought to represent the most severe end of the spectrum of acute mountain sickness (AMS).[427,428] It is characterised by ataxic gait, severe lassitude, confusion, impaired cognition, drowsiness, stupor, and coma.[427] Hepatic encephalopathy (HE) is seen in patients with liver failure, and it shares signs and symptoms with HACE, such as altered sleep patterns, ataxia, disorientation, confusion, stupor, and coma.[429] In this condition, hyperammonaemia causes glutamate to be converted to glutamine in astrocytes in the brain in order to detoxify excess ammonia.[431] However, glutamine is an osmolyte, and this leads to cerebral oedema. This process is known to contribute to the signs and symptoms of HE.[430,431]

MRI T2-weighted brain imaging of HE patients shows high signal intensity in white matter, which corresponds to oedema. MRI T2 high signal intensities are also seen in the white matter of patients with HACE.[427,430] An MRI imaging study looking at diffusion co-efficient values indicated that a cytotoxic mechanism may be at play in AMS.[428] The precise pathophysiology of HACE is unknown. Currently, the vasogenic model postulated by Hackett and Roach is the most widely supported; it has, however, been described as "speculative".[428]

At high altitude there is a respiratory alkalosis, with significant hypoxaemia. It has been found that the concentration of ammonia in blood is increased during exercise in a hypoxic environment.[433] Bicarbonate is an essential substrate for the urea cycle to detoxify ammonia into urea in the liver, and the low levels of HCO_3^- found at high altitude would be expected to retard the urea cycle, contributing to hyperammonaemia. As is seen in HE, this excess ammonia would be expected to combine with glutamate in astrocytes, generating glutamine. Furthermore, *in vitro* studies indicate that a hypoxic environment favours the production of glutamine by increasing glutamine synthetase activity, and decreasing glutaminase activity.[437,438] SNAT3 and SNAT5 are major glutamine transporters in astrocyte cell membranes.[437,438] In order to remove glutamine from the cell they exchange it for a H^+.[439] Furthermore, SNAT3 is co-expressed with NBCe1 in these cells. This

transporter takes up HCO_3^- when SNAT3 swaps glutamine for H^+ in order to buffer the intracellular pH.[437] However at altitude, where there is a paucity of extracellular H^+ and HCO_3^- it is likely that this system fails and glutamine becomes trapped in the astrocytes. It has been shown *in vitro* that an alkaline medium will decrease glutamine efflux, and favour glutamine influx in cells expressing SNAT3.[4368,437]

Thus under the unique physiological conditions of high altitude, glutamine may accumulate in astrocytes and, because glutamine acts as an osmolyte, it may cause cytotoxic cerebral oedema. A novel hypothesis is therefore proposed for the pathophysiology of HACE. It suggests a cytotoxic mechanism for the disease, explained by defects in metabolism unique to high altitude, and does not implicate defective ATP production. MRI images from HACE patients show oedema in the white matter.[427] Glutamine synthetase production and activity are much higher in white matter than in grey matter[439.440], which could help explain this observation. This model also implies a distortion of the glutamate/glutamine cycle, which is important for neurotransmitter regulation. This could be a contributory factor to the neuropsychological impairments of high altitude Illness.

Acetazolamide and dexamethasone are the mainstay of chemoprophylaxis and treatment of AMS and HACE.[427] According to this model, acetazolamide could bring benefit by reducing systemic pH and allowing more efflux of glutamine from astrocytes. Dexamethasone is known to induce activity of urea cycle enzymes[441], and this could help explain its prophylactic benefit. However it is unclear, under this model, how dexamethasone is effective in treating established disease.

There is a need for experimental research using an animal model to investigate this hypothesis further. Measuring CSF/blood glutamine ratios at altitude would be revealing. Investigating the effect of glutamine synthetase inhibitors on cerebral oedema at altitude would also be of interest. The significance of glutamine and ammonia metabolism in the evolution of HACE remains to be determined. If it proves to be an important factor, a high-caloric/protein-free diet, benzoic acid, and phenylacetate may prove useful in the prophylaxis and treatment of HACE.

Acknowledgements

I am very grateful to Dr. James Gleeson for his contribution to the elaboration of this novel hypothesis which we both agree deserves further experimental testing.

3.5. Analysis of Pre-Travel Health Advice for Travellers to High Altitude

Introduction

Travel to altitude carries well recognised health risks, including the development of potentially fatal high altitude illness.[442] In most cases, the speed of development of symptoms does not preclude early detection of illness and rapid descent in the case of high altitude pulmonary oedema or high altitude cerebral oedema. Trekking parties are sometimes quite large and there may not be adequate supervision of clients' health status by preoccupied mountaineering guides and porters who may be very focused on the high demands of conveying lowland trekkers to a given summit.

Although buddy systems are encouraged at altitude, this is not always effectively employed, and expedition medical personnel are the exception rather than the rule on commercial treks to high altitude. A high degree of self reliance is critical in a wilderness environment and this is particularly so at high elevations, where facilities are often rudimentary and the remoteness of the location may hamper any attempts at rescue of an incapacitated traveller. It is therefore important that individuals who engage in adventure travel to high altitude be fully aware of the dangers inherent in this activity, be familiar with the presentation of the various forms of high altitude illness, and be prepared to take appropriate action if they or a travelling companion develop high altitude illness.

There is also an onus on expedition providers to educate trekkers on the health risks they may face at altitude. Little has been published about the quality of advice provided to amateur trekking enthusiasts by their expedition leaders and the companies in which they are employed. It is common practice for members of the travelling public to consult the internet for information regarding available treks to high altitude and to arrange all of their travel plans without the intervention of an intermediate travel agent. Visiting a website which advertises a trek to an altitude environment represents an opportunity to receive balanced information about the health benefits and risks involved. This study aimed to evaluate the health advice given to travellers on websites advertising high altitude treks.

Methods

Active websites advertising high altitude treks to the travelling public were identified. Each website was interrogated using pre-defined criteria to extract information relating to the specific advice provided about altitude illness and its prevention. Websites were also examined to determine if prospective trekkers would have access to a portable hyperbaric chamber, which is a potentially lifesaving piece of equipment used to simulate rapid descent by raising the ambient atmospheric pressure of the victim of severe acute mountain sickness, high altitude cerebral oedema or high altitude pulmonary oedema.[443]

Twenty health information quality variables were analysed and an aggregate quality score index with a maximum score of 20 was derived for each website examined. Four sub-sections were analysed to include the following elements of the health information provided on the commercial website: fitness to travel assessment; health advice provision; details of intra-trek support provided; and website user friendly interface. Data were entered in a database and analysed using Microsoft Excel software.

Results

Of 74 eligible websites analysed, 81% referred to altitude travel health risks. Table 3.10 displays the summary findings in relation to the 4 sub-sections examined. Seventy percent mentioned acute mountain sickness, while 30% discussed high altitude cerebral oedema and/or high altitude pulmonary oedema. Sixty-two percent advocated gradual acclimatisation to altitude. Over a third of websites discussed the use of a portable hyperbaric chamber, while a quarter of sites provided information about drugs used to manage high altitude illness. Forty-two percent of companies invited clients to share their medical history in preparation for their trek, while 39% stated that an expedition doctor would accompany the trekkers on their travels. The overall mean score of the websites (maximum 20) was 9.01, based on an aggregate of the 20 variables examined.

Table 3.10 Sub-section analysis of altitude trekking websites

Variable	% of websites (n)	Sub-section score (maximum)
Fitness to travel assessment		1.47 (3)
Mentions travel insurance	93	
Invites client medical history	42	
Requests medical form completion	11	
Health advice provision*		4.05 (9)
Outlines risks of altitude travel	81	
Mentions acute mountain sickness (AMS)	70	
Stresses importance of acclimatisation	62	
Gives extra information on altitude illness	41	
Access to portable hyperbaric chamber	38	
Advises on prevention of altitude illness	31	
Mentions HACE and/or HAPE	30	
Outlines management of AMS	26	
Discusses drugs used for prevention	24	
Intra-trek support		2 (4)
Mentions trekking crew support	96	
Advises to visit own doctor beforehand	39	
Recommends visit to travel clinic	35	
Access to expedition doctor on trek	30	
User friendly nature of website		1.96 (4)
Information easily accessible	80	
Testimonials provided	80	
Links to other websites	30	
Health information simplified	5	

*AMS = acute mountain sickness; HACE = high altitude cerebral oedema; HAPE = high altitude pulmonary oedema.

Discussion

This is the first study to investigate the quality of health-related information provided by online commercial expedition companies to the travelling public. While it is limited by the subjective nature of the quality assessments made by the researcher, in the absence of a validated instrument, it does give a constructive insight into the important, but poorly studied, issue of health literacy and commercial responsibility in relation to travel. The assumption is made that, if information is not available on the company's website, then it will not be accessible to the traveller after they register for a given trek, but this may not be a valid inference. Nevertheless, since the commercial website may be the first point of contact with the travel industry for the individual traveller, the degree to which relevant and detailed health information is offered is generally reflective of the commitment shown to the traveller's health and safety needs.

Positive trends were revealed in this study in relation to the following elements of pre-travel health advice: travel health insurance, overall risks of high altitude travel, acute mountain sickness, the necessity for adequate acclimatisation to altitude, access to a trained expedition crew, and testimonials from previous trekkers. Testimonials are subject to bias, however, and no attempt was made in this study to evaluate the balance of positive and negative comments posted on the websites.

The main areas of weakness exposed by this analysis stem from a failure to adequately assess the traveller's fitness to trek, either by use of a screening questionnaire or by communicating the trekker's medical history. Few absolute contraindications to altitude travel exist, but the effects of pre-existing medical conditions on the capacity to perform moderately intense aerobic exercise in a hypoxic environment must be given careful consideration.[444] Very few websites elaborated on the importance of preventing high altitude illness, either by early recognition of acute mountain sickness or use of chemoprophylaxis, including acetazolamide or nifedipine. Just over a third of websites mention the use of a portable hyperbaric chamber, and less than a third of sites provide access to an expedition physician either before or during the trek. This potentially exposes the traveller to undue risk in a harsh environment. It is of concern that so few of the websites provided links to authoritative sources of online

information about the health risks of high altitude travel. The language used to explain high altitude illness was considered to be unduly complicated by the researcher, raising important questions about health literacy in the online travel health community.

Conclusion

This study yields valuable information about the extent of pre-travel health advice provided by trekking companies to prospective clients. Deficiencies are revealed regarding severe high altitude illness, and access to an expedition doctor and hyperbaric chamber. Companies should make every effort to inform and protect these vulnerable travellers.

Acknowledgements

I am grateful to Mr. Max Javaherian, a medical student at NUI Galway, for his assistance in retrieving information from relevant websites for the purposes of this study.

3.6. The Emergency Use of Portable Hyperbaric Chambers at Altitude[4]

Acute mountain sickness, if not properly managed, may progress to the potentially fatal high altitude cerebral oedema (HACE), and may co-exist with high altitude pulmonary oedema (HAPE), the latter of which is responsible for most deaths from high altitude illness. In an earlier review of the subject, Zafren asserted that death from high altitude illness is almost always avoidable.[442] Symptoms of acute mountain sickness in a study by Santantonio et al.[445] were experienced by almost half of the cohort who had reached an altitude above 2,500m. The authors comment that the majority of travellers had been informed about altitude-related health risks through non-medical sources, including the internet and friends. It is suggested that the apparent failure to provide pre-travel health advice specific for high altitude illness prevention may be related to deficient knowledge and training on the part of travel medicine practitioners. Equally, non-expert travel health providers may not routinely advise travellers on the correct management of high altitude illness, should it occur subsequently to a traveller who had sought pre-travel health advice.

Part of the accepted management of severe AMS, HACE and HAPE is the use of a portable hyperbaric chamber, a lightweight piece of equipment inflatable to a pressure of 2 psi (100 mmHg) with a foot pump, thereby pressurising the victim, and simulating a rapid descent of 1500m to 2500m.[443] The recommendations for the practice of travel medicine, published by the Faculty of Travel Medicine, include in their standards of practice the necessity for healthcare professionals engaged in the provision of pre-travel health advice to be able to demonstrate "familiarity with the correct use of a portable hyperbaric chamber".[446] There is no substitute for planning a controlled ascent profile which does not exceed the recommended rate, thus allowing adequate time for the traveller, often a recreational trekker, to acclimatise to the hypobaric hypoxia. When severe AMS, HACE or HAPE do occur, urgent descent or evacuation to a lower altitude, at least to an elevation where the victim last felt well, is mandatory. This is not always

[4] Adapted, with the permission of the publishers, from the following invited editorial: Flaherty GT. Under pressure: facilitating the emergency use of portable hyperbaric chambers at altitude. Travel Med Infect Dis. 2014 Sep-Oct;12(5):420-1.

feasible, however, owing to terrain or weather considerations, or to the difficulty of mobilising guides and porters who can accompany or, in more severe cases, stretcher the victim to the lower altitude. Helicopter evacuation, even if it is available in a remote wilderness environment with its attendant telecommunication challenges, is not always possible. Pharmacologic management of high altitude illness should be undertaken under experienced medical supervision and, where self-treatment or unqualified assistance is provided, the risks to the patient with high altitude illness may be considerable. Most expeditions to high altitude do not have ready access to medical personnel with appropriate knowledge of, and training in, high altitude medicine. In such situations, and even where pharmacotherapy (primarily nifedipine and/or oxygen for HAPE, and dexamethasone for severe AMS or HACE) can be safely administered, it is of significant advantage to be able to offer prompt pressurisation in a portable hyperbaric chamber, at the very least to facilitate the supervised descent of an incapacitated victim. Oxygen is not easily available to most trekkers and its lack of portability renders it impractical for all but the most well equipped expeditions to extreme altitude.

Portable hyperbaric chambers, when they are available on a given route, are normally positioned at the highest camp in a multi-stage ascent, where altitude illness is more likely to occur, and where transporting the device to a lower elevation is easier than carrying it to a higher altitude. It is particularly suited to camp-sites located in a saddle or valley, where an ill patient would have to ascend before being able to descend to a safer altitude. There are very few contraindications to the use of portable hyperbaric chambers but it is important to be aware of the risk of otic barotrauma which could result from its incorrect use. Relief of symptoms is rapid, lasting for several hours, thus allowing the patient to be conveyed to a lower altitude. There is a lack of controlled studies of the use of portable hyperbaric chambers in the management of severe HACE or HAPE, but experience from their use in the management of severe AMS consistently demonstrates their effectiveness.[447] The author of this thesis has used a portable hyperbaric chamber on expeditions to very high altitude in the Himalaya, and has found it to be easily transported and highly effective in the management of severe altitude illness. There are multiple commercially available portable hyperbaric chambers, each with its own advantages and disadvantages, and further advice

on specific products is available from the International Mountaineering and Climbing Federation (UIAA).[443]

There is no legislation or published regulations mandating that hyperbaric chambers should be made available to every commercially organised altitude trekking party, but the potential for successful litigation undoubtedly exists if a victim of severe high altitude illness were to succumb to the condition in the absence of a functional portable hyperbaric chamber, or if the expedition leaders were not aware of the location of the nearest chamber or trained in its use. Some high altitude routes are better served than others in this regard. There are two portable hyperbaric chambers, for example, at the Himalayan Rescue Association Aid-Post in Pheriche (4,371m), along the Everest Base Camp trail. Some commercial trekking companies hire a portable hyperbaric chamber, while a minority purchase the device. There is a professional and ethical responsibility on expedition physicians or nurses to develop competence in the use of portable hyperbaric chambers and to conduct planned chamber demonstration exercises before ascent, allowing each group member to inflate and deflate the chamber under supervision (Appendix 5). There are several useful instructional videos available online which team members can view before they travel.[448]

There is a need to engage with commercial expedition companies, mountaineering clubs and national mountaineering societies, and to offer education on high altitude illness, its prevention and its management. Each of us has a responsibility as travel medicine professionals to provide accurate and specific advice to our travellers to high altitude and not to consider high altitude medicine as the exclusive domain of the few recognised experts in the field. Introducing knowledge of the management of high altitude illness, including the practical use of a portable hyperbaric chamber, into relevant undergraduate and postgraduate curricula would be very beneficial. These steps alone would help to safeguard the health of individuals who wish to travel to high places.

3.7. Pulse Oximetry and Ascent Profile in the Himalayas

Introduction

An increasing number of travellers engage in high-altitude trekking. Since most high-altitude treks do not have access to expedition doctors, responsibility for establishing a safe ascent profile rests with the trek leader. Arbitrary decisions on when to ascend are often based on logistical factors irrespective of the performance of the trekking group. Eighty per cent of all altitude-related deaths occur in organised trekking groups rather than in elite mountaineers. Since the clinical diagnosis of acute mountain sickness (AMS) is unreliable and because trekkers may conceal symptoms, a need exists for a tool which will help to identify those who are not acclimatising at the expected rate. Pulse oximetry is a non-invasive means of measuring arterial oxygenation (SpO_2) and pulse rate. Pulse rate[449] and oxygen saturation[450] are associated with presence of AMS, and SpO_2 values during short-term exposure to hypoxia predict susceptibility to AMS.[451] This study was performed to investigate whether pulse oximetry may be used to identify slow acclimatisers as early as possible and to guide a trekking team in establishing a favourable acclimatisation schedule.

Methods

The study research protocol met the requirements of the local clinical research ethics committee. Twenty trekkers (11 male, 9 female), ordinarily lowland residents, participated in the study during a charity trek to very high altitude at Everest Base Camp (5364m) and Kala Pathar (5550m) in Nepal (Figure 3.20, Table 3.11). The mean age of the cohort was 42 years (range 20-60 years). Sixteen of the trekking party had previous experience of travel to altitude, and 5 trekkers reported AMS on a previous trek. None of the subjects took acetazolamide to aid their acclimatisation to altitude. After flying from Kathmandu to Lukla (2784m), the trekking party took 10 days to reach Everest Base Camp. SpO_2 and resting heart rate (RHR) values were measured daily before the evening meal using a BCI® 3301 Hand-held Pulse Oximeter (Cardiac Services Ltd.) after the subjects had rested for 15 minutes with warm fingers. Caffeine intake and

smoking were prohibited in the hour before measurements were recorded. Trekkers who had a Lake Louise questionnaire score of 2 or more had AMS.

Table 3.11 Proposed ascent schedule

Day	Destination	Altitude (m)	# Nights
1	Phakding	2610	1
2	Namche Bazaar	3440	1-2
3	Deboche	3771	1
4	Dingboche	4360	1
5	Lobuche	4940	1
6	Gorak Shep	5147	2
7	Everest Base Camp	5364	0
8	Kala Pathar	5550	0

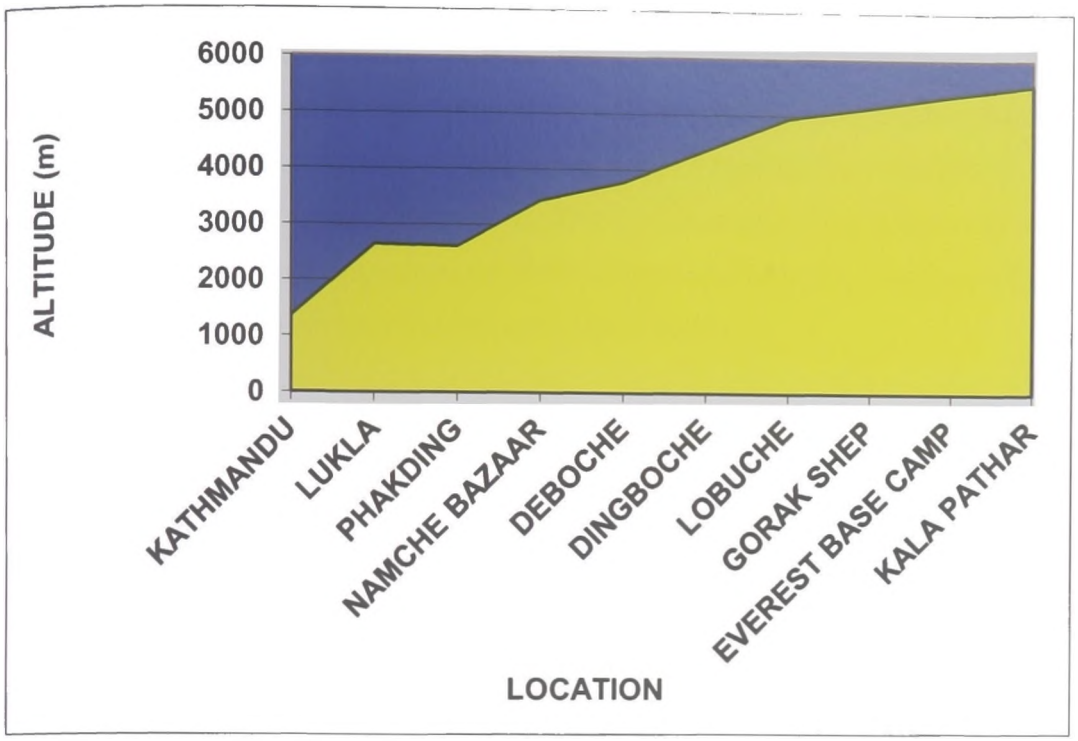

Figure 3.20 Elevation profile of trekking route

Results

The mean RHR of the group increased from 81 beats per minute in Kathmandu at 1355m (Figures 3.21 and 3.22) to a maximum of 94 beats per minute at Dingboche (4360m). Following an extra day of acclimatisation in Dingboche the mean RHR decreased to 86. The SpO_2 values declined from a group mean of 94.5% (range 92-97%) in Kathmandu (Figure 3.23) to a nadir of 76% at Lobuche (4940m), with the greatest drop occurring between Deboche (3751m) and Dingboche (4360m). A decision was made to spend an additional night in Lobuche to aid acclimatisation on the basis of these measurements (Figure 3.24).

The RHR declined and the SpO_2 increased toward normal values at the end of the second day spent at the same altitude, reflecting the increased acclimatisation of the group following a rest day. Individual trekkers whose SpO_2 or RHR did not improve by the end of the rest day were more likely to have AMS. These trekkers were monitored more closely for signs of worsening high-altitude illness. Thirty five percent of trekkers satisfied the Lake Louise criteria for the diagnosis of mild AMS

and 10% of trekkers developed moderate AMS (Figure 3.25). One female trekker with moderate AMS at Lobuche (4940m) recovered after an extra night at Duglha (4620m). The peak observed incidence of AMS occurred at 4000-5000m. There was no case of HACE or HAPE. Trekkers who suffered from AMS reached a lower mean maximum altitude than unaffected travelling companions (Figure 3.26).

The most common non-altitude related source of morbidity in this group of trekkers was respiratory tract infections. The small sample size precludes a correlational analysis of any possible association between the presence of a respiratory tract infection and the occurrence of AMS.

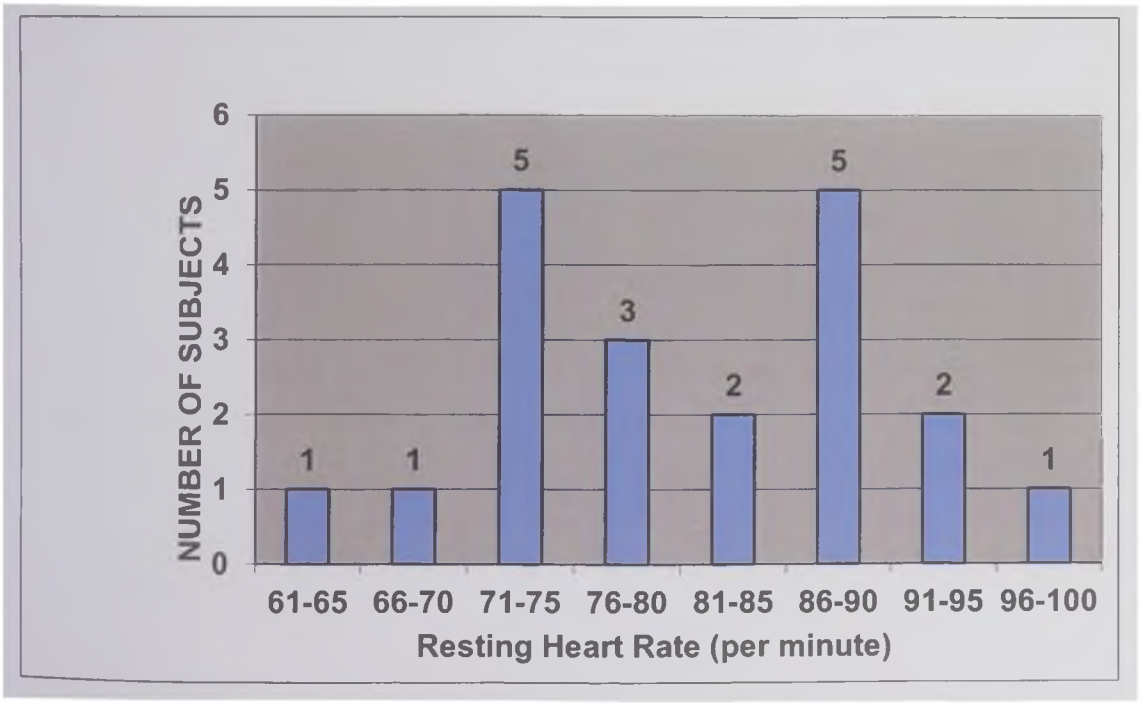

Figure 3.21 Baseline distribution of resting heart rate

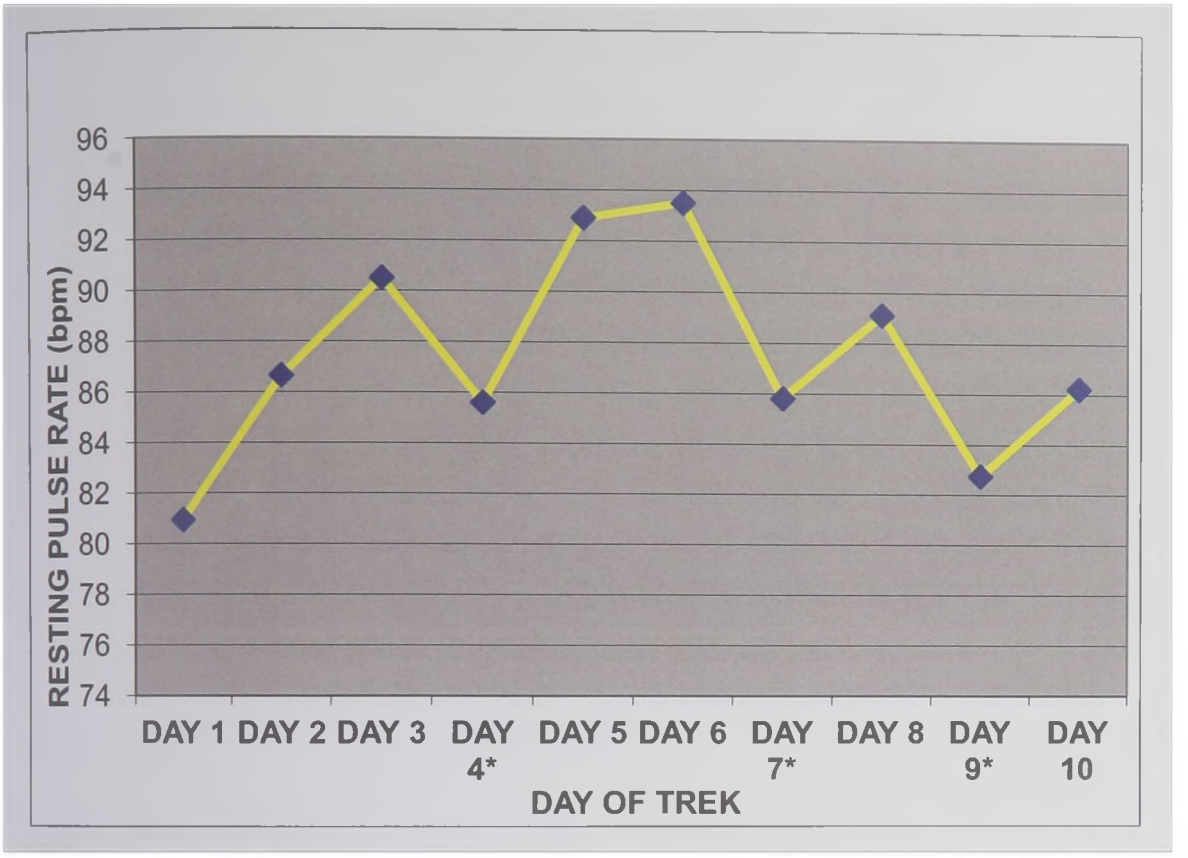

Figure 3.22 Variation in resting heart rate during ascent (asterisks indicate an extra night spent at the altitude concerned)

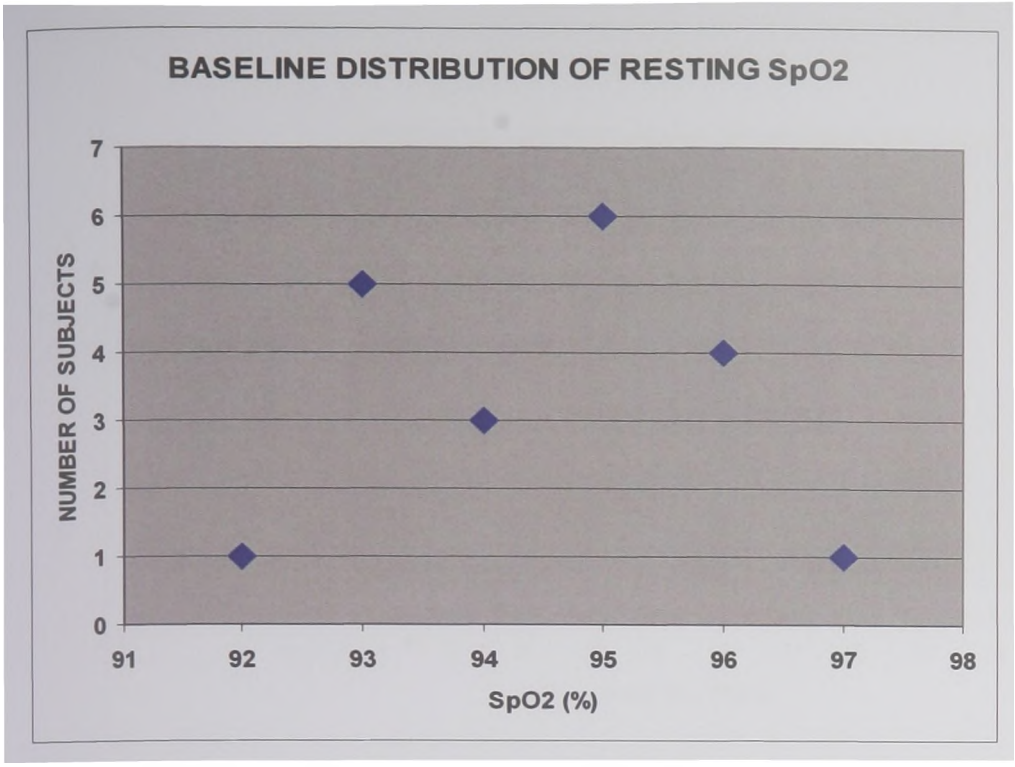

Figure 3.23 Baseline distribution of resting SpO_2 values

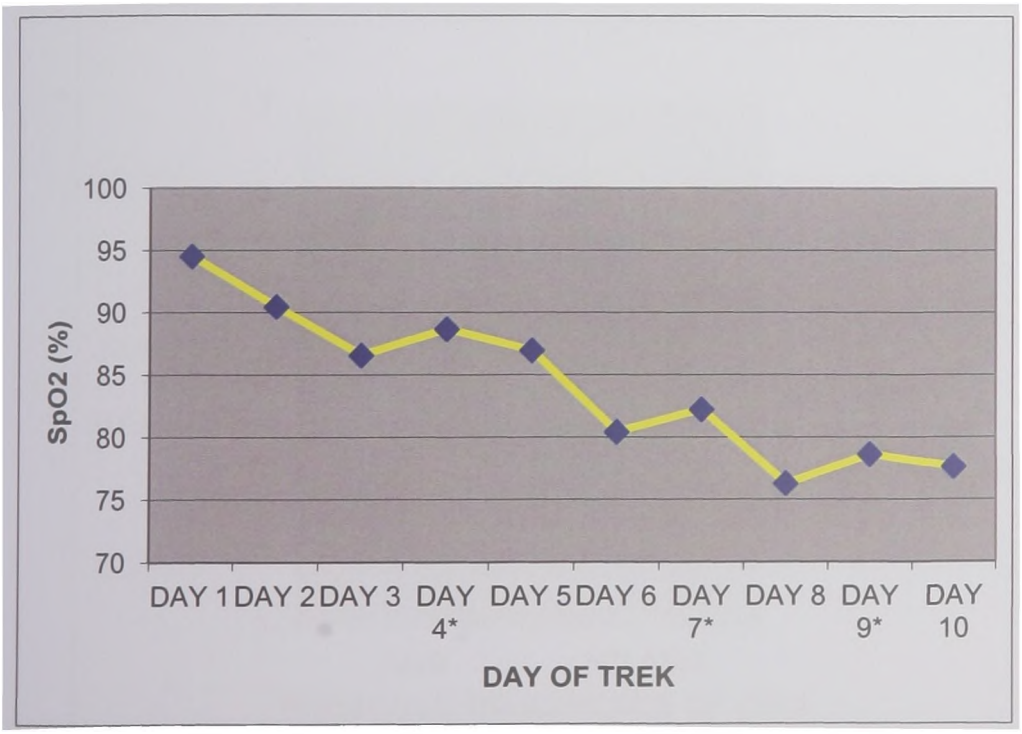

Figure 3.24 Oxygen saturation levels at successive campsites (asterisks indicate an extra night at that altitude).

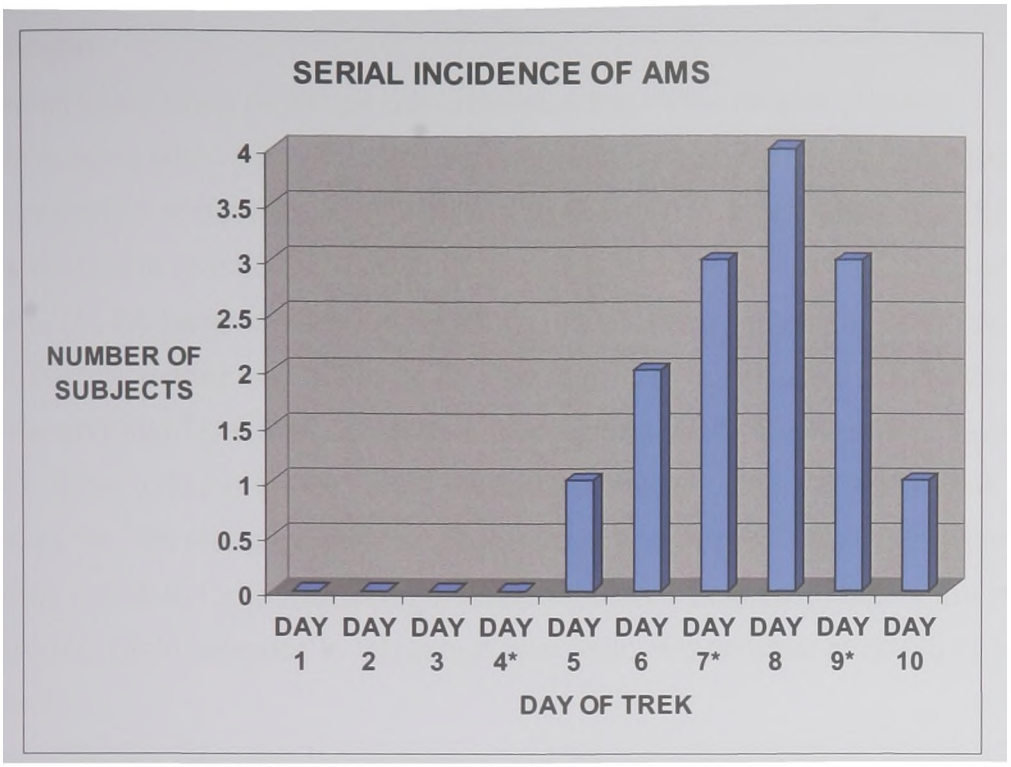

Figure 3.25 Serial incidence of acute mountain sickness

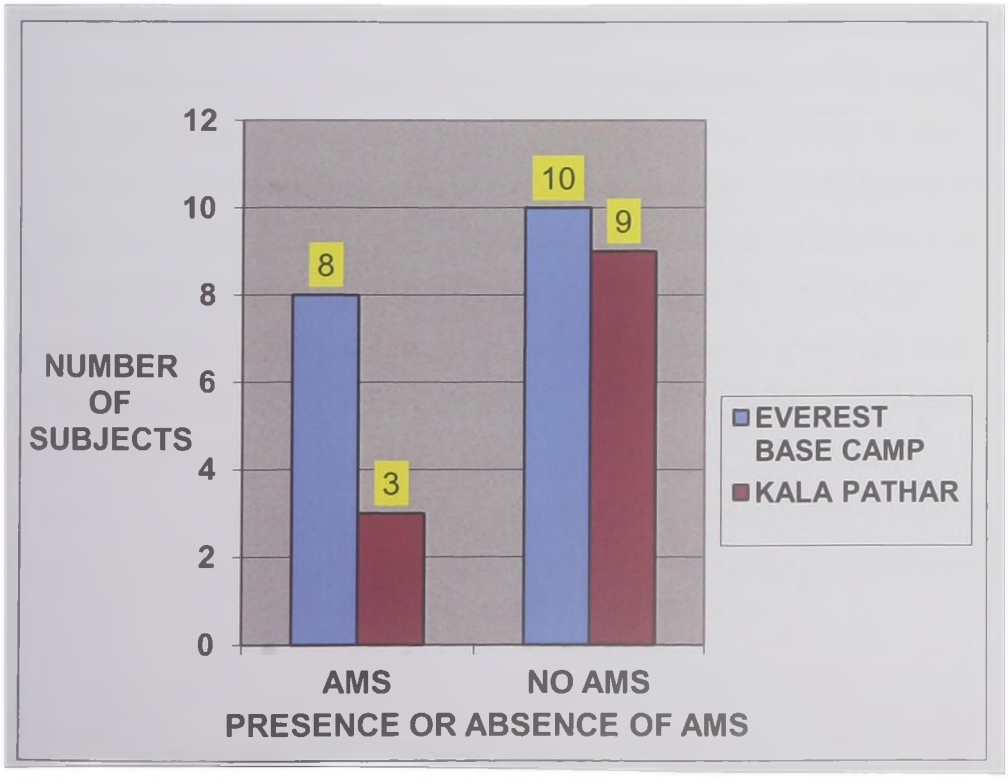

Figure 3.26 Influence of acute mountain sickness on altitude attained

Discussion

This small scale study develops our understanding of the benefit of using objective, non-invasive physiologic measurements, including resting heart rate and capillary oxygen saturation, to inform flexible changes to a high altitude ascent profile in order to reduce the burden of acute mountain sickness in a group of trekkers. On the basis of early identification of slow acclimatisers in a trekking group, the trek leader was better positioned to predict the onset of acute mountain sickness and plan campsite accommodation appropriately. Even greater flexibility exists in other trekking routes where the trekkers camp in tents rather than in lodges as they do along the Everest Base Camp trail. Maximum altitude attained positively correlated with incidence of acute mountain sickness. Most of the cases of acute mountain sickness in this group were mild and no case of HACE or HAPE occurred.

Future studies involving larger numbers of trekkers along various trekking routes may provide guidance in establishing safe acclimatisation schedules. The relative merit of basing acclimatisation decisions on group RHR and/or SpO_2 means should be further studied. The high altitude medicine community is beginning to focus more on designing trekking route-specific ascent profiles which will be of practical use to trekking parties.[452] Flexible group trekking itineraries should be encouraged and there must be improved cooperation between trekking companies, their porters and guides, and local accommodation providers. More favourable ascent profiles may reduce the incidence of AMS and HACE. The study was limited by the following factors: small sample size; observer bias and dual role of researcher as volunteer expedition physician; baseline variability in resting pulse rate secondary to other unmeasured factors; difficulties in standardising measurement conditions in a wilderness environment; imprecision of AMS clinical diagnosis; and possible lack of reliability of symptom disclosures.

Conclusions

Pulse oximetry is a simple, non-invasive means of identifying suboptimal individual and group acclimatisation rates in a remote high altitude trekking environment. Pulse oximetry data enable more objective decisions to be made about a safe rate and profile of ascent and allow earlier detection of worsening high altitude illness.

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Pulse oximetry enabled the trek leader to make more confident decisions about the rate of ascent and about individual trekkers' acclimatisation. Further studies involving larger numbers of trekkers along various trekking routes may provide guidance in recommending specific acclimatisation schedules which minimise the incidence of AMS.

Acknowledgements

I am very grateful to the charity fundraising trekkers who agreed to participate in this study; to Croí, the West of Ireland Cardiac Foundation, for their support in facilitating data collection during a trek in the Nepalese Himalayas; and to Mr. Gavin Bate, lead mountaineering guide for his support throughout this successful trek.

CHAPTER 4

Tropical Infectious Diseases in Travel Medicine

4.1. Malaria Awareness in the Visiting Friends and Relatives Population

Introduction

It is estimated that 30,000 of the 40 million people who visit malaria-endemic regions from non-tropical countries each year will contract malaria.[453] Travellers' knowledge of the mode of malaria transmission, mosquito bite avoidance measures and chemoprophylaxis is essential to prevent malaria in high-risk travellers. People born in malaria-endemic areas who are permanently resident abroad are 8 times more likely to contract malaria when they travel to their native countries than are other travellers.[454] This visiting friends and relatives (VFR) population tend to account for most cases of imported malaria.[455]

Official statistics from the Republic of Ireland demonstrate a sharp rise in the number of cases of imported malaria from 21 in 2003 to 96 in 2006 (Figure 4.1). The vast majority of these cases occurred in the African VFR population living in Ireland. VFRs may not perceive themselves to be at risk of malaria having grown up in a malaria-endemic country and perhaps having contracted malaria in the past and survived. Persistence of partial immunity to *Plasmodium falciparum* depends on re-exposure once outside endemic regions.[456] The children of VFRs born outside a malaria region are at greatest risk of disease since they do not possess even partial immunity to the malaria parasites.

Many VFRs stay with family members for prolonged periods in rural areas in which they may encounter increased malaria risks because of the absence of air conditioning, window screens and impregnated mosquito bed nets. Even when VFRs do seek pre-travel health advice, which is far less likely than other travellers[457], compliance with recommendations is suboptimal.[458] Language barriers and traditional health beliefs may also increase the vulnerability of this patient population.

This observational study was carried out to describe the travel trends and to ascertain the level of awareness of malaria among a sample of the African VFR population living in the west of Ireland. A particular focus of the study was the self-

perceived risk of malaria reported by this group and the extent of their knowledge of malaria preventive measures.

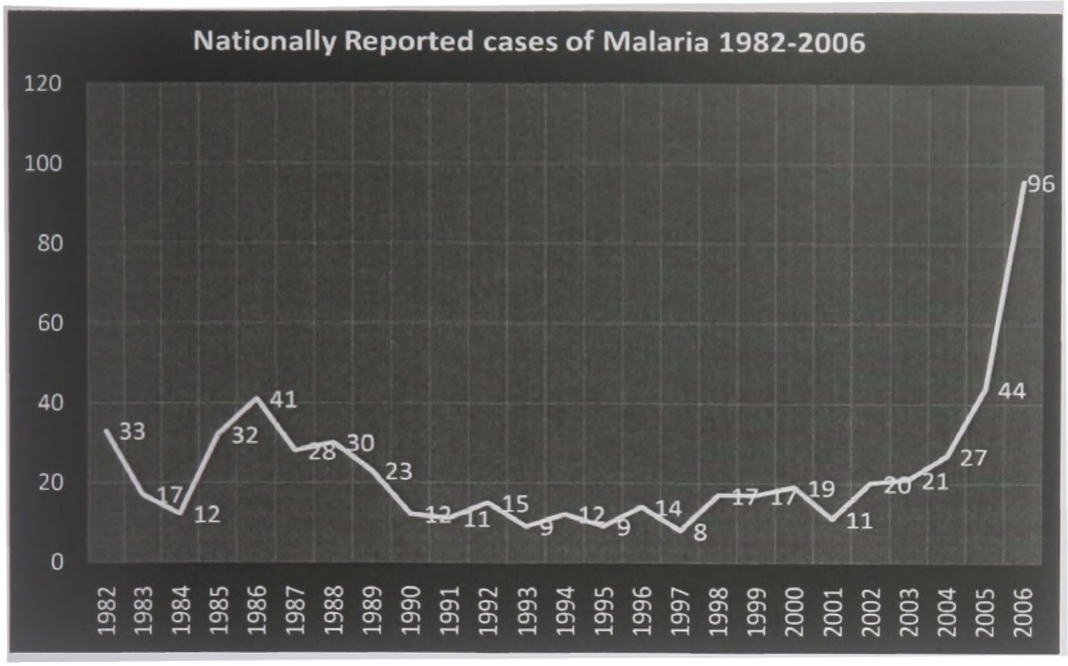

Figure 4.1 Reported cases of malaria in the Republic of Ireland, 1982-2006[459]

Methods

The study protocol was approved by the local clinical research ethics committee. Efforts were made to access members of the VFR population living in the city of Galway, a major urban centre in the west of Ireland, by approaching African community representatives and church leaders. A 43-item questionnaire, which had been piloted previously, was administered to 68 adult members of the African VFR community who agreed to participate in the study. Study respondents were assured that their responses would be treated confidentially and that anonymity would be preserved. No language barriers requiring translation of the survey were encountered. A mixture of open-string type and multiple choice questions was used to acquire demographic information, data on travel practices, and to probe understanding of the transmission and clinical significance of malaria, as well as the knowledge of and willingness to employ malaria preventive strategies. Data were analysed using SPSS 12.0 software.

Results

Demographics

Sixty-eight subjects were recruited consecutively into this study, 65% (n=44) of whom were female. The average age of participants was 34 years (range 22-49 years). Seventy-seven percent (n=52) of those surveyed had children. Approximately half (n=35) of the sample surveyed was defined as economic migrants and half (n=33) were currently seeking asylum or refugee status in the Republic of Ireland. Nine malaria-endemic African countries were represented in this sample, with the majority of potential VFRs (61%, n=41) having been born in Nigeria. Of the 40% (n=27) of VFRs who stated that they return to Africa on a regular basis, 65% (n=44) reported that they stay exclusively with their family while in Africa.

Knowledge of malaria

Ninety-five percent (n=65) of VFR travellers were aware that malaria is spread via the bite of an infected mosquito. Sixty-one percent (n=41) of subjects, however, did not know that malaria is transmitted between dusk and dawn. When asked to rate malaria in terms of disease severity on a scale from "not serious" to "severe", 28% (n=19) believed that malaria was not a serious disease. The majority (79%, n=54) of those who underestimated the seriousness of malaria were female. Seventy-seven percent (n=52) of those questioned admitted to having contracted malaria before in their country of origin, most of them on more than one occasion. The vast majority of VFR subjects (97%, n=66) reported that family and friends had contracted malaria in the past. Seventeen percent (n=12) of the potential VFRs in this study did not perceive themselves to be at risk of contracting malaria when they return to Africa in the future, even though they have all lived in Ireland for longer than partial immunity to Falciparum malaria could persist. Of those who believed that they were at risk of malaria, 60% (n=34) of them did not know which part of the day represented the greatest threat for malaria transmission.

Malaria prevention

Both mosquito bed nets and chemoprophylactic drugs were widely recognised as preventive measures although insect repellents were not commonly cited as an

effective method of preventing malaria transmission. Chloroquine was over-represented among the list of effective prophylactic drugs mentioned by the VFR travellers. Fifty-nine percent (n=40) of respondents believed that the best available malaria chemoprophylaxis was less than 75% protective against malaria. Only 12% (n=8) of the sample was aware that malaria chemoprophylactic drugs must be taken prior to arrival in a malaria area, while present in the area and for a period of time after leaving the last malaria area. No differences in knowledge of malaria preventive measures were noted when the data were analysed according to gender, country of origin, or whether the subjects had children. Over 50% (n=35) of the sample studied did not believe that malaria is imported into Ireland. Eighty percent (n=54) of those surveyed would seek pre-travel health advice prior to travelling to Africa, the majority from their family doctor. The majority of those who would not seek such advice believed that Irish-trained doctors are not educated about malaria.

Discussion

Transmission of malaria is a significant problem among the VFR population living in developed countries. Cullen reported that, of the 909 patients with a diagnosis of imported malaria notified to the Centers for Disease Control and Prevention who had indicated their purpose for travel, 604 (66%) belonged to the VFR population.[460] The current study, although limited by its small sample size and possible selection bias, reveals a worrying lack of awareness of critical aspects of malaria transmission and prevention among a sample of actual and potential African VFRs residing in the west of Ireland. There is a general lack of awareness of the time of day when malaria is transmitted. This has implications for the practice of mosquito bite avoidance measures.

The serious nature of malaria was underestimated by many of the subjects in this study. While the majority of VFRs recognised their personal risk of malaria, those that believe they are immune to malaria are unlikely to protect themselves against the disease and represent a particularly vulnerable sub-group of VFRs. Knowledge of malaria chemoprophylaxis was also deficient in the sample surveyed. In the United States of America, barriers to prevention of malaria in the

VFR population have been identified at a systems level, such as low insurance coverage; a patient level, including misperception of disease risk; and at the level of the healthcare provider, who may have an inadequate knowledge of travel medicine.[461] It has been argued that primary care healthcare professionals should be more proactive in screening for high-risk travel among their VFR patients who attend for other reasons, and should take steps to develop their competency in the practice of travel medicine.[462] Hagmann supports the concept of active screening of VFRs for planned travel activities in order to identify future VFR travellers and anticipate high-risk travel itineraries, which would require specific pre-departure health counselling.[463]

Behrens and colleagues[464] attributed an observed decline in the incidence of imported VFR malaria from West Africa to the United Kingdom to changing chemoprophylaxis patterns and/or increased travel to urban areas of West Africa with a declining malaria risk, or to a possible reduction in malaria transmission throughout West Africa. Previous researchers have asserted that knowledge of malaria, self-perceived risk, travel experience, and standard of pre-travel health advice do not correlate with use of chemoprophylaxis in VFR travellers, and therefore alternative strategies are required to reduce the burden of malaria in this population.[465]

Conclusion

This study provides useful information to public health officials attempting to address the emerging problem of imported malaria in the Republic of Ireland. The study should be extended to the entire VFR population living in Ireland, and focused, culturally sensitive educational campaigns should be designed to increase the level of malaria awareness among this vulnerable group of travellers as well as addressing the travel medicine educational needs of their healthcare providers.

Acknowledgements

I wish to thank Dr. John Donnellan for his assistance with data collection for this research project.

4.2. Increasing Traveller Awareness of the Risk of Rabies Infection

Introduction

Transmission of Rabies Virus

Rabies is a viral zoonosis, or animal disease transmissible to humans, caused by rhabdoviruses of the genus *Lyssavirus*. Infection of humans occurs when the rabies virus, carried in the saliva of a rabid animal, enters the body through penetrating bite wounds, open cuts in the skin, or contact with mucous membranes. Thus, a bite, lick or scratch is sufficient to transmit the infection. Dogs are the most important reservoir of rabies infection worldwide, with more than 99.9% of human deaths from rabies resulting from dog bites.[466]

Clinical Presentation of Human Rabies Infection

Rabies causes an acute, progressive encephalomyelitis, which is almost always fatal.[467] In most cases of rabies, the initial signs include a sense of foreboding, fever, malaise, headache, and paraesthesiae around the site of the animal bite. Hallucinations and aerophobia are followed by fear of water due to spasm of pharyngeal and oesophageal muscles, with eventual delirium, convulsions and death within days of onset. The less common form of the disease, present in about 30% of cases, is referred to as paralytic rabies, and is characterised by sensory loss, pain, and paralysis.[468] There is no effective treatment to prevent death in humans exposed to the rabies virus once symptoms have appeared.[469]

Epidemiology of Rabies Infection

It is estimated that more than 50,000 deaths occur worldwide each year due to rabies infection.[470] Most rabies infections occur in tropical and subtropical areas where the virus circulates in both domestic and stray animals.[471] Africa and Asia account for most of the cases due to rabies in humans worldwide, with the majority of cases being reported in India.[469] Official figures may underestimate the actual burden of disease, such that the incidence of human rabies infection may be 100 times greater than that reported. Many countries endemic for the rabies virus are

popular tourist destinations for travellers from developed countries. The annual number of reported human deaths due to rabies in Europe is as many as 27.[472]

Risk Assessment of Travellers

Travellers to rabies-endemic countries are susceptible to the risk of exposure to rabies virus through animal scratches or bites. It is alarming to consider that of 1,882 tourists who visited Thailand for an average of 17 days in one study, 24 received dog bites and 9% of the travellers recalled that they were licked by dogs.[473] During a 3-year period in a travel medicine clinic in Kathmandu, Nepal, 56 travellers were treated for possible rabies exposure.[474] Travellers to rabies-endemic areas face the risk of rabies exposure, which is related to the incidence of rabies in the area, the animal population density, and the probability of contact with an infected animal. This risk is compounded by the risk of adverse reactions from brain-tissue derived rabies vaccines still available in developing countries and infectious diseases possibly transmitted by unpurified rabies immunoglobulin. Most travellers staying in tourist resorts are at very low risk of acquiring rabies infection, but walking or jogging in the streets of big-city slums where stray dogs roam freely, or trekking for several days away from urban centres, are associated with a greater risk.

Pre-exposure Prophylaxis

Modern, highly purified rabies vaccines prepared on primary and continuous cell lines and in developing eggs are far better tolerated than the older, brain-tissue vaccines. In India each year up to half a million people still receive brain-tissue vaccines after exposure to suspected rabid animals.[475] Pre-exposure prophylaxis consists of 3 intramuscular or intradermal doses of cell culture-derived rabies vaccine administered on days 0, 7, and 21-28. Antibody levels are not routinely checked after pre- or postexposure vaccination as the rabies vaccine is assumed to be effective if administered according to WHO guidelines.[476]

Post-exposure Treatment

After receiving a bite from a rabid animal, pre-vaccinated patients are advised to thoroughly cleanse the wound with soap and water and to receive two booster

doses of the vaccine on days 0 and 3, in order to induce an anamnestic B cell response against the virus. Nonvaccinated patients must not only receive a full 28-day course of rabies vaccine on days 0, 3, 7, 14, and 28, but also a series of passive immunisations with human or equine rabies immunoglobulin.[476] As much as possible of the rabies immunoglobulin should be injected into and around the wound; the remaining product should be injected intramuscularly at a site distant from the vaccine injection site. Treatment should be instituted as early as possible after exposure. The sometimes prolonged incubation period of the virus mandates that treatment should not be withheld from exposed persons, irrespective of the elapsed time interval following exposure.[470] There are no reports of pre-immunised travellers dying of rabies after receiving booster vaccine. For travellers to remote regions, where the risk of becoming exposed to rabies may be greater, it may be difficult or impossible to access safe post-exposure treatment without delay. The treatment may be prohibitively expensive for the uninsured backpacker on a tight budget and may be declined as a result.[477] A course of post-exposure prophylaxis may cost as much as $1,500 for the medication alone in a well-known travel medicine clinic in Nepal, where rabies immunoglobulin is reliably stocked.[478] Because of a shortage of rabies immunoglobulin in developing countries, fewer than 1% of those requiring the lifesaving treatment receive it.[469]

Rationale for Present Investigation

From my experience of working as a travel medicine physician in a busy Irish tropical medicine clinic, it has been my impression that travellers are often poorly aware of the nature of rabies infection and are surprised to learn of its deadly outcome. Many travellers appear to underestimate their personal risk of exposure to rabies-infected animals and as a result may not agree to receive the vaccine. Such travellers are dependent on receiving prompt, safe postexposure treatment from well-trained local doctors in the developing world. Storage conditions for these vaccines may not be properly maintained so a considerable risk of rabies infection exists for non-vaccinated travellers seeking postexposure treatment. Pre-immunised travellers may develop a false sense of confidence if they do not realise that their treatment is not complete in the event of being exposed to rabies. It may be important to reinforce the information given to these travellers if they are to take the necessary steps having been exposed to rabies virus. This study was

designed to assess the level of awareness of rabies in a sample of travellers attending an Irish travel medicine clinic and to assess whether or not the information provided verbally during the initial consultation should be reinforced in written form before the travellers complete their rabies pre-exposure prophylaxis.

Aims and Objectives

Aims:

The aims of this study were twofold:

1. To investigate a perceived lack of awareness of rabies infection in travellers attending the Tropical Medical Bureau travel medicine clinics.
2. To implement practical measures which would serve to improve travellers' knowledge of rabies and reduce their risk of contracting this disease when travelling to rabies-endemic countries.

Objectives:

The study had the following specific objectives:

1. To survey a sample of travellers attending the Tropical Medical Bureau travel medicine clinic in order to ascertain their baseline level of awareness of rabies infection, including its mode of transmission, clinical presentation and prevention.
2. To assess the travellers' self-perceived level of risk of acquiring rabies during their intended travels to rabies-endemic countries.
3. To determine if travellers are familiar with the necessary steps to take in the event of possibly becoming exposed to the rabies virus.
4. To examine the durability of the information provided to the travellers during their pre-travel medical consultation by resurveying them at the time of administration of their final pre-exposure rabies vaccine.
5. To respond to any educational needs revealed in the study by designing a suitable information leaflet which will provide information on the course of action to be followed in the event of being exposed to rabies.

Methods

Baseline Questionnaire

Ethics committee approval was not required for this study. A baseline questionnaire (Appendix 6) comprising 30 items was designed and circulated within the Tropical Medical Bureau for consideration. Following suggestions from clinic staff, minor changes were made to the questionnaire to eliminate ambiguity. The first three respondents served as pilot subjects for the study.

After being greeted by the clinic manager, travellers attending the clinic are asked to fill out a card which records demographic information, details of the travel itinerary where known, medical history and previous travel vaccines. The client is then introduced to the doctor who transfers the information provided on the card to a purpose-designed computer program. A detailed discussion of the travel itinerary follows and specific, tailored information is given to the client to educate them about their risk of travel-related disease and its prevention. A slideshow is used to supplement the information provided verbally. A copy of the Tropical Medical Bureau information pamphlet is given to each client. A standard WHO-approved yellow vaccination card acts as a written record of all vaccines received by the client traveller.

During a 3-month observation period, clients who expressed an intention to travel to rabies-endemic countries were invited to participate in this study. Where a group of travellers attended the same consultation, one client only was invited to take part in the study. No information was provided on rabies until the questionnaire was completed. Clients were informed that the clinic was conducting a survey to "see how much people know about rabies…in order to design an information leaflet to help them avoid getting the disease". Clients were assured that the questionnaires were anonymous and confidential within the clinic and that they would be identified solely by a number written on a sticker affixed to their consultation card. This number matched the number written on the top of the baseline questionnaire and enabled the practice nurses to identify the client subsequently as a study participant so that the follow-up questionnaire could be administered. The questionnaire took no more than five minutes to complete. Where open questions were used, the subject's own words were recorded

verbatim. Subjects were advised to reply "don't know" where they did not have any knowledge of the answer to a particular item.

Pre-travel Health Advice

Following completion of the questionnaire, the following information was provided to the clients in a standardised manner:

1. Rabies is a viral illness which is spread by the bite, scratch or lick of a warm-blooded animal in certain countries. Ireland is currently rabies-free.
2. Dogs are the most common carriers of the disease, but other animals including cats, monkeys, foxes and bats may transmit the disease.
3. It may not be possible to recognise a rabid animal from its external appearance or behaviour so all animal bites in endemic countries must be regarded as potential rabies exposures.
4. Once the rabies virus enters the body it travels along the nerves until it reaches the brain.
5. Once the virus has reached the brain, rabies infection results, which is almost uniformly fatal.
6. No effective treatment exists to save the life of a person who has developed rabies.
7. Activities such as trekking, cycling or petting animals will increase the risk of being exposed to the rabies virus.
8. Your risk of coming into contact with a rabid animal is (low, moderate or high).
9. Rabies infection can be effectively prevented by avoiding contact with animals and by receiving rabies vaccine before you travel and after you are exposed.
10. The vaccine consists of three injections, given on days 0, 7 and 21/28, which provide immunity for 3 years.
11. The vaccine must be supplemented by a further 2 doses of vaccine administered on days 0 and 3 following exposure.
12. As soon as a potential rabies exposure has occurred, you should wash out the wound with soap and water, apply an antiseptic, avoid having the wound sutured, and seek immediate medical advice, informing the doctor

that you require two post-exposure doses of vaccine and not rabies immunoglobulin.

13. Where possible, try to contact the owner of the animal to learn of its fate.

Follow-up Questionnaire

Where pre-exposure rabies prophylaxis was accepted by the study participant, the client was informed that a brief survey would be completed by the practice nurse following receipt of the third dose of rabies vaccine. The purpose of this follow-up questionnaire was to "check if you recalled correctly the information on rabies given on this visit". The follow-up questionnaire contained three items (Appendix 6). Subjects were asked if they considered themselves to be at risk of rabies on their upcoming travels and if so, to what extent they were at risk. Respondents were asked to list in sequence the practical steps they would take in the event of being exposed to rabies during their travels. The practice nurses recorded the client's own words without prompting. After the questionnaire was completed, the practice nurse gave specific preventive advice where knowledge of measures to be taken was lacking in individual travellers.

Data Analysis

Results were entered in a Microsoft Excel database and subsequently analysed by SPSS software.

Results

Demographic Profile of Travellers

Thirty travellers were recruited into the study, 14 of whom were male and 16 were female. The average age of this cohort of travellers was 26.8 years (range: 19-54 years). The majority of the participants were students (30%, n=9). Only 2 travellers had previous medical training; one was a nurse and the other a third year medical student who had not yet started her Microbiology course.

Travel Itinerary

The majority of the travellers (97%) had at least 3 weeks remaining before their planned departure date. Although the duration of travel was not recorded in the questionnaire, each subject planned to spend at least 4 weeks in a rabies-endemic region. The majority of travellers (77%, n=23) were travelling to Asia, with the majority of these visiting South East Asia, including Thailand, Cambodia and Vietnam. Data are unavailable for the number of travellers specifically visiting the Indian subcontinent. Twenty-three percent (n=7) of the participants intended to visit South America, while only 7% (n=2) were travelling to Africa. This is broadly representative of the typical profile of our clients, although in recent years an increasing proportion of our travellers are taking extended trips to South America, in many cases as part of a 'round-the-world' trip. The travellers in this study intended to use a mixture of accommodation types, with 40% (n=12) staying exclusively in hotels. A large proportion of the sample (57%, n=17) intended to trek during their holiday, with 2 travellers relying solely on tented accommodation throughout their trip. Reflecting the considerable degree of uncertainty about their itinerary in general, 40% (n=12) were unsure whether they would be trekking during their trip, but most were visiting areas where trekking is generally popular among tourists.

Baseline Knowledge of Rabies

All 30 of the study subjects had heard of rabies before. Fifteen (50%) erroneously believed that rabies was currently endemic in Ireland, while a further 5 individuals were unsure if rabies was present in Ireland. Ninety percent (n=27) of those questioned reported that rabies is transmitted to humans via the saliva of an animal but only 1 respondent mentioned that a scratch could be sufficient to transmit the disease. The majority of subjects (83%, n=25) identified dogs as the principal animal responsible for spreading the disease to humans. Six subjects (20%) implicated monkeys in the transmission of the disease, while 3 participants (10%) believed that bats could infect humans with rabies. Two travellers were unable to name an animal carrier of the rabies virus. When asked how they would recognise rabies infection in an animal, 16 travellers (53%) referred to "frothing at the mouth" or "foaming at the mouth", while 4 individuals (13%) suggested that the animals may be more aggressive than usual. Nine travellers (30%) either gave

inappropriate responses to the question (e.g. "yellow eyes") or did not know how to recognise an animal with rabies. A single traveller correctly suggested that the rabid animal may appear perfectly normal.

Travellers' Perception of Rabies Risk

Travellers were asked to identify activities or situations where they would anticipate an increased risk of being exposed to rabies. Ten (33%) of those questioned identified trekking as a risk factor for rabies exposure. Many of the alternative responses were either incorrect or vague and 27% (n=8) could not recall any situation which would confer an increased risk of rabies exposure. A third of the cohort (n=10) admitted that they would pet dogs or cats in foreign countries. Eight respondents had previously received a bite from a dog, with 6 of these exposures occurring in Ireland and 1 each in the UK and Greece. Four travellers (13%) did not consider themselves at risk of acquiring rabies during their next trip to a rabies-endemic country or were unsure of their level of risk (Figure 4.2). For those travellers who acknowledged that they could become exposed to rabies, 8 (31%) individuals declared themselves to be at low risk. Although the questionnaire did not specifically include the study coordinator's assessment of the risk in individual cases, it is the author's impression that every traveller was at moderate-to-high risk of rabies exposure due to the duration of travel and the proposed activities involved. Thirteen travellers (43%) did not know how rabies would manifest itself clinically in an infected individual. Five travellers (17%) believed that rabies was never fatal; of the 25 travellers who were aware that rabies may be fatal, the average fatality risk offered was 42%. Twenty-one (70%) participants incorrectly stated that an effective treatment exists for humans infected with the rabies virus. The majority of these travellers (71%, n=15) suggested that such treatment would be moderately to highly effective. The majority of subjects (97%, n=29) were aware that a rabies vaccine existed which could prevent the disease.

Travellers' Knowledge of Post-exposure Measures

When asked what measures they would take in the event of being exposed to rabies, 29 out of the 30 study participants reported that they would seek urgent medical advice from a local doctor, clinic or hospital. Three subjects (10%)

declared that they would wash or disinfect the wound before seeking medical attention. All travellers stated that they would still seek medical advice even if the owner of the potentially rabid animal involved assured them that it was vaccinated against rabies. Five individuals (17%) believed that further vaccination was unnecessary if they had received the appropriate course of pre-exposure vaccinations before their trip. A course of rabies vaccination was recommended in each traveller but was not possible in one case where only a week remained before departure and the subject was unwilling to receive the third booster dose at her destination. In the case of two subjects, the vaccine was declined due to needle phobia.

A follow-up questionnaire was completed for 24 of the 27 travellers who had received the rabies vaccination regimen. All of these travellers deemed themselves to be at risk of being exposed to rabies at follow-up. Eight of these travellers (33%) considered their risk of rabies exposure to be low (Figure 4.2). When subjects were asked what action they would take in the event of rabies exposure, all of them stated that they would seek a medical opinion without delay. Five travellers (21%) specifically mentioned the necessity of receiving post-exposure vaccinations. Twelve subjects (50%) stated that they would wash and/or disinfect the wound as a first-aid measure. Among the inappropriate responses received were the following: bleed the wound, consult GP in Ireland upon return, leave the country, capture the animal, and "suck out the poison".

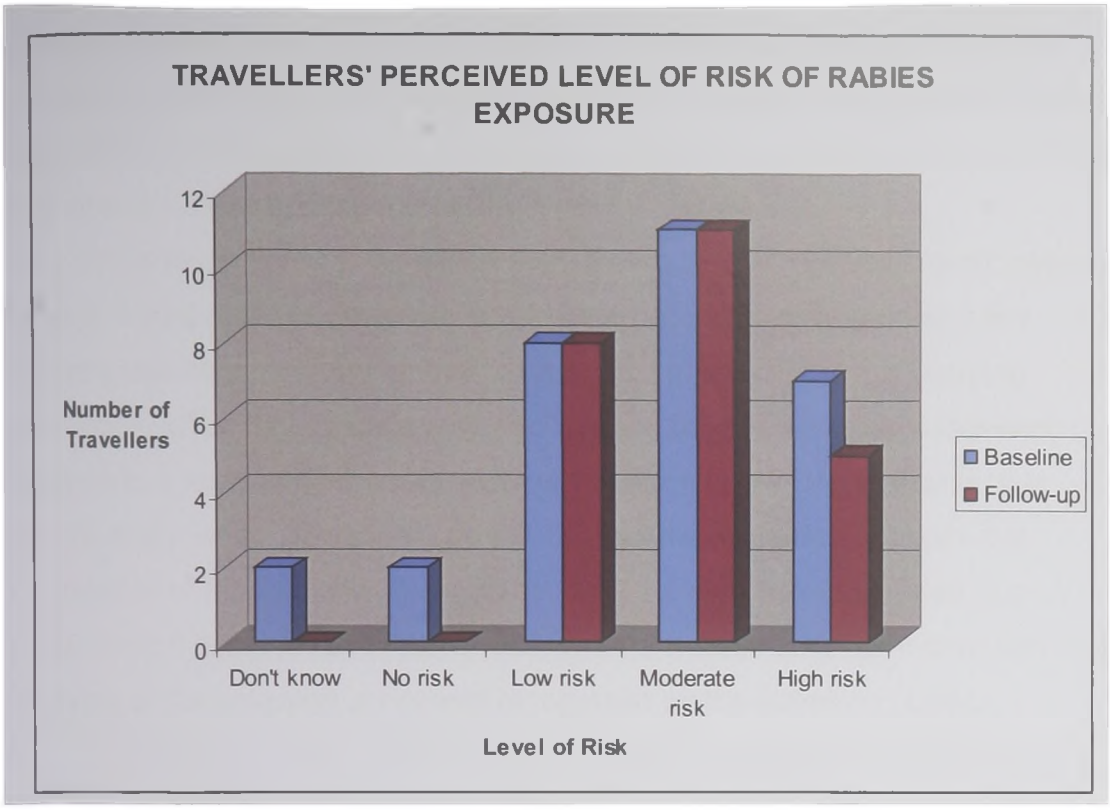

Figure 4.2 Travellers' perceived level of risk of rabies exposure

Discussion

This is the first study to examine the issue of rabies awareness among travellers attending an Irish travel medicine clinic for pre-travel health advice. It is significant that such a large proportion (30%) of the sample surveyed were students. Student travellers and backpackers on tight budgets are more likely to seek "only the essential shots" and may decline recommended vaccines such as rabies and hepatitis B for financial reasons.

It is noteworthy that, even though 77% of the travellers in this study planned on visiting Asia, which has the greatest reported incidence of human rabies infection, 13% of them still did not recognise that they were at risk and, of those that did, 31% believed that risk to be low. With such a high percentage of the subjects trekking or potentially trekking (97%) during their trip, it is reasonable to assume that their risk of being exposed to rabies was at least moderately high. Only a third of travellers in this study associated trekking with possible rabies

exposure, highlighting the need for vigilance in this group. In a travel clinic in Kathmandu, Nepal, a common starting point for Himalayan treks, during a 3-year period, 56 travellers were treated for possible exposure to rabies, giving an annual incidence of 1.9 per 1,000 persons.[474]

While the majority of travellers were aware that dogs can transmit rabies to humans, a third of those surveyed admitted to petting dogs abroad and few travellers identified monkeys or bats as potential threats. This is a worrying observation, given that so-called "cryptic" human cases without a recognised exposure to a rabid animal, have become the norm in the United States. It is possible that a similar situation exists in South America, where vampire bat transmission of rabies is well recognised. Only a single traveller stated that an animal scratch could result in rabies transmission, confirming our impression that this mode of transmission is not well recognised by the travelling public.

It is of concern that 17% of those questioned believed that rabies is not a fatal disease, with the case fatality ratio being grossly underestimated at 42%. Historically, 5 patients have survived rabies and in these cases some form of prophylaxis had been received.[468] Travellers who believe that a disease can be effectively treated may not appreciate the rationale behind vaccinating against that disease. In the present study, 70% of the travellers incorrectly assumed that rabies infection can be effectively treated and 17% believed that no further treatment was necessary if pre-exposure prophylaxis had been administered. Vaccinators should address this sense of complacency by ensuring that travellers clearly understand the role of pre-exposure prophylaxis and the need for post-exposure treatment following potential exposure.[479]

While it is reassuring that most travellers in this study would seek urgent medical advice in the event of being exposed to rabies, only 10% of the study participants stated that they would take first-aid measures by washing the wound immediately. When questioned at follow-up 3-4 weeks after receiving their initial rabies vaccine, 33% of the travellers believed that they were at low risk of rabies exposure. It is likely that by underestimating their risk, these travellers may not exercise the caution required to avoid rabies exposure. It is interesting that the travellers did not revise their perceived level of risk in light of the pre-travel health advice they received.

It is encouraging that 21% of those surveyed at follow-up mentioned that they would require additional rabies vaccines following exposure. It is conceivable that some health professionals working in rural parts of developing countries may not have the necessary training to provide competent post-exposure advice. In a cohort of experienced travel health advisors in Germany, there were significant deficiencies highlighted in their assessment of specific rabies exposure scenarios.[470] In this situation, it is even more important for the vaccinated traveller to understand the necessity for post-exposure treatment.

When asked about the immediate steps they would take if exposed to rabies, 50% of those surveyed at follow-up mentioned that they would wash and/or disinfect the wound. This represents a significant improvement on the first-aid knowledge at baseline in these travellers but it does call into question the durability of the detailed advice given during the initial consultation. While our travel medicine clinic does provide an informative booklet reinforcing the pre-travel health advice given during the consultation, the section devoted to rabies is very brief and advises the travellers to seek immediate medical advice. This study underscores the need for a more detailed source of information, preferably one which the traveller can easily refer to in an emergency.

This observational study is limited by its small sample size which precluded a more detailed statistical analysis from being performed. Because of the small numbers involved, no attempt was made to correlate the level of awareness of travellers at baseline and at follow-up with other variables, such as their demographic characteristics or travel itinerary.

Recommendations

The findings of this study prompted the design of a brief information leaflet (Appendix 7) which can be folded in two and stapled into the traveller's yellow-coloured vaccination record. The information leaflet provides concise but specific advice which should help the traveller cope with a rabies emergency. The insert incorporates the standard WHO and CDC guidelines.[469,480] It is now routinely employed in the Tropical Medical Bureau clinic.

Conclusions

Although limited by its small sample size, this study yielded some interesting observations:

1. Though their travel itinerary places them at considerable risk of rabies exposure, a significant proportion of travellers attending an Irish travel medicine clinic underestimate their personal risk. This underestimation persists at follow-up despite educational efforts to the contrary.
2. Many travellers do not recognise trekking as a risk factor for rabies exposure.
3. While most travellers are aware that dogs can transmit rabies, very few understand the risk posed by other warm-blooded animals such as monkeys and bats.
4. The extreme case fatality ratio of rabies infection is not appreciated by most travellers, the majority of whom expect to be safely treated in the event of developing rabies.
5. Most travellers understand the importance of consulting a doctor following potential rabies exposure but a minority of travellers are aware of the need for immediate first-aid treatment. Awareness of first-aid measures is improved by providing pre-travel health advice.
6. Travellers' knowledge of the information provided during their medical consultation decays rapidly. This study points to the importance of reinforcing this advice by providing a quick reference guide to rabies which can be inserted into the traveller's vaccination booklet.

Acknowledgements

I am grateful to Joyce Keaveney, Travel Health Nurse at the Tropical Medical Bureau clinic in Galway, for her assistance with administering the follow-up questionnaire to the travellers who participated in this study.

4.3. Prevention of Dengue Infection in Travellers

Introduction

Dengue is a potentially fatal arboviral disease which has emerged as an increasing threat to European travellers visiting tropical regions.[481] Baaten and colleagues reported an incidence of dengue infection of 14.6 per 1000 person-months in Dutch travellers to dengue-endemic countries.[482] Dengue infection poses a diagnostic challenge to Irish healthcare workers who are increasingly likely to encounter illness in returned travellers who have visited dengue-endemic regions.[483] Lack of awareness of dengue infection among travel medicine practitioners may limit the quality of the information provided to intending travellers to dengue-endemic countries. Since tropical infectious diseases do not feature prominently in Irish undergraduate or postgraduate medical curricula, the potential exists for missed or delayed diagnosis of dengue infection in returned travellers. This cross-sectional survey explores the level of awareness of dengue infection among the Irish travel medicine community.

Methods

The study protocol satisfied the requirements of the local research ethics committee. A 24-item survey assessing awareness of various aspects of dengue infection, including global distribution, mode of transmission, incubation period, recent outbreaks, case-fatality rate, biting pattern of the *Aedes* mosquito, familiarity with the dengue skin rash, complications, investigations, and management of the disease, was distributed via an electronic Survey Monkey® link to members of the Travel Medicine Society of Ireland (TMSI). Responses were collected between June and November 2009. A reminder email was sent 2 months after the original notice. Results were imported into a Microsoft Excel database and analysed using descriptive and inferential statistics.

Results

Seventy TMSI members responded to the survey (20% response rate), 72% (n=50) of whom had received prior training in travel medicine, mostly by means of regional education seminars (76%, n=38) hosted by the TMSI (Table 4.1). The majority of respondents correctly identified the causative organism and 92.9% (n=65) identified mosquito bites as its mode of transmission. 38.6% (n=27) recalled the typical incubation period. 87.1% (n=61) of respondents suggested Asia as the region of greatest risk. Over half of respondents (57.7%, n=38) correctly recalled the geographical location of at least one recent outbreak of dengue infection, but few (24.3%, n=17) correctly estimated the case-fatality rate. Half of the respondents (n=35) were aware that risk is highest in urban areas, while a greater proportion (69.1%, n=47) correctly identified daytime as the period of greatest risk.

A quarter (n=17) of respondents were familiar with the appearance of the typical dengue skin rash, 1 in 5 could describe the distribution of the rash (n=14), and the greatest proportion of respondents underestimated its frequency by stating that this rash occurs in 21-40% of symptomatic patients (Figure 4.3). Almost 45% (n=31) of respondents were aware of dengue haemorrhagic fever, but very few (10%, n=7) were aware of dengue shock syndrome as potential complications.

A poor knowledge of the investigations and the clinical indications for hospitalisation was demonstrated, with only 29% (n=20) of travel health providers demonstrating knowledge of the laboratory diagnosis of suspected dengue virus infection and less than half (n=33) of those surveyed demonstrating a working knowledge of the clinical indications for hospitalisation of a dengue infected traveller. While the majority of healthcare professionals were able to recall valid mosquito bite avoidance measures, 23.1% (n=16) of respondents admitted that they do not routinely educate travellers visiting dengue-endemic areas about the disease and its prevention.

Table 4.1 Professional profile of dengue survey respondents

Professional Role	n	%
Consultant	3	4.3
GP	46	65.7
Nurse	19	27.1
Other	2	2.9
Prior training in travel medicine		
Yes	42	60
- TMSI regional seminars	30	42
- International conferences	16	32
- Diploma	7	14
No	28	40
Weekly clinical commitment to travel medicine		
<10%	50	72.5
11 – 20%	15	21.7
>20%	5	5.8

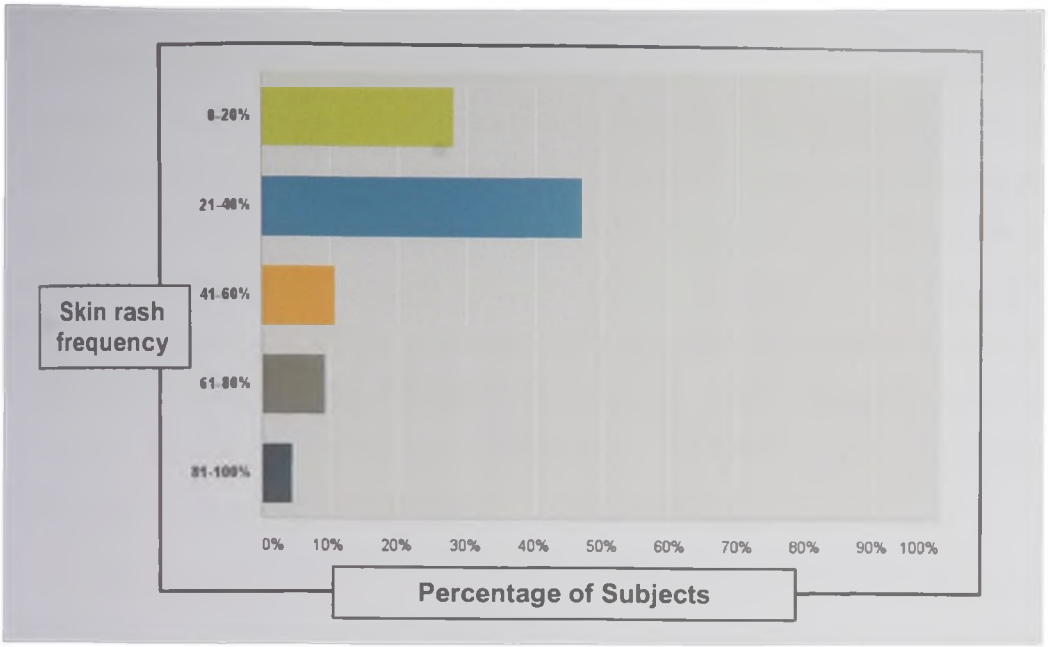

Figure 4.3 Knowledge of frequency of characteristic dengue skin rash

Discussion

Dengue is a potentially life-threatening infection which requires early recognition, prompt triage, and appropriate management, particularly regarding fluid management given the plasma leakage which occurs in this condition. Previous studies have investigated the levels of awareness of dengue infection among inhabitants of dengue-endemic countries, including Saudi Arabia[484], Nepal[485], and Pakistan.[486] The potential for diagnostic delay is a particular risk in non-endemic countries where awareness of dengue may be suboptimal among frontline clinicians.

This study is one of the few to examine the clinical practice of healthcare professionals who provide pre-travel health advice to travellers to dengue-endemic regions of the world. Clinicians practising travel medicine as members of the Travel Medicine Society of Ireland demonstrated inconsistent knowledge of fundamental aspects of dengue infection, a disease which is not endemic in Europe but which has the potential to present to the Irish health service as an imported, travel-related infection. Deficiencies were exposed in the members' knowledge of the distribution and epidemiology of dengue infection, its clinical manifestations, potential complications, and management guidelines. In a

prospective study of clinicians' awareness of dengue classification systems in Malaysia[487], the authors determined that dengue haemorrhagic fever and dengue shock syndrome were under-recognised by clinicians managing patients with dengue infection, which they argue may lead to delayed recognition of these complications of severe dengue infection. Lee and colleagues surveyed primary care physicians in Singapore to assess their knowledge, attitudes and practices in relation to dengue infection.[488] While the authors could not identify significant gaps in dengue knowledge, there was considerable variation in clinical approaches according to physician age profile and practice setting.

Efforts to raise public awareness of dengue infection among Irish travellers must be accompanied by an increased emphasis on tropical infectious diseases in undergraduate health professional curricula. The Travel Medicine Society of Ireland has responded to the findings of this study by providing workshops on dengue infection and other tropical infectious diseases at its regional educational seminars and by publishing relevant articles aimed at busy clinicians in its quarterly newsletter, *Taisteal*.

Conclusion

Notwithstanding the low response rate, the results of this survey suggest a lack of knowledge of dengue infection, its epidemiology, prevention, clinical features and management among travel medicine practitioners in Ireland. Educational initiatives are currently being developed at undergraduate (special study modules in tropical and travel medicine), and postgraduate (basic travel health course) levels in Ireland to address this and other learning needs.

4.4. Yellow fever vaccination practices in Ireland

Standards of Yellow Fever Vaccination and Travel Medicine Practice in the Republic of Ireland

Introduction

Yellow fever (YF) is a viral haemorrhagic fever caused by a flavivirus related to Japanese encephalitis virus and transmitted by the bite of an infected *Aedes* or *Haemagogus* mosquito which acquires the virus by feeding on infected non-human or human primates. Clinical infection varies from a mild, non-specific febrile illness to severe disease with jaundice and haemorrhage. The disease occurs throughout sub-Saharan Africa and tropical South America, where it is endemic, with intermittent epidemics. The majority of outbreaks in Africa have occurred in West Africa but an increased number of cases have been reported in recent years from Central African countries. Most cases in South America are reported from the Orinoco, Amazon and Araguaia river basins with the highest cumulative incidence occurring in Bolivia and Peru.[489]

No cases of YF have been reported from North America and Europe since the early 1900s and, while transmission has never been identified in Asia or Australia, these regions are at risk for importation of the virus, as many of their urban areas have both the vector *Aedes aegypti*, as well as large non-immune human populations. This explains why certain non-endemic countries such as India and Australia require proof of YF vaccination from travellers arriving from YF-endemic countries. The World Health Organisation estimates that 200,000 cases of YF occur annually, with case-fatality ratios of approximately 20% in Africa and 50% in South America, the latter due to enhanced diagnostic testing rather than increased disease virulence.[490] Management is supportive with patients requiring critical care support with mechanical ventilation or haemodialysis if there is multisystem organ involvement.

Between 1970 and 2009, there were 9 reported cases of YF in unvaccinated travellers from Europe and the United States who had travelled to West Africa (5 cases) or South America (4 cases); 8 of these 9 travellers died.[489] The risk for a traveller of contracting the virus depends on immunisation status, mosquito bite

avoidance, location of travel, duration of exposure, recreational activities, and the local rate of virus transmission which shows an increased risk in the mid-to-late rainy season in West Africa and South America. Crude estimates of the risks of illness and death due to YF for the unvaccinated traveller are 10 deaths out of 50 cases per 100,000 population for West Africa, and 1 death out of 5 cases per 100,000 population for South America.[491] For international travel, YF vaccine must be administered at a designated and registered YF vaccination centre which is regulated in the Republic of Ireland by the Health Service Executive under authority from the Minister of Health. Studies show that 80-100% of vaccinated persons develop protective neutralising antibodies by day 10 following vaccination.[492] This explains why International Health Regulations mandate that proof of YF vaccination as a condition of entry for travellers arriving from certain countries becomes valid only after 10 days have elapsed between administration of the vaccine and arrival at the border of the host country. The YF vaccination certificate is valid for 10 years although this recommendation has recently been revised by the World Health Organisation, based on recent evidence demonstrating long-term persistence of YF antibodies.[493] A single dose of the vaccine is now considered sufficient to confer sustained life-long protective immunity against the disease, rendering a booster dose unnecessary.

YF vaccine is generally well tolerated with the most common systemic side effects in one large study being mild headache (33% of subjects), myalgia (25%), malaise (19%) and fever (15%).[494] Yellow fever-vaccine associated neurologic disease and yellow fever vaccine-associated viscerotropic disease are serious but rare adverse effects of YF vaccine, occurring in 0.8 and 0.4 cases per 100,000 doses administered, respectively.[495] The rate of both syndromes is higher in vaccinees aged over 60 years making advanced age a precaution to the use of the vaccine.[496] Where a medical contraindication exists to the administration of YF vaccine, a licensed physician may issue a medical waiver by completing and signing the Medical Contraindications to Vaccination section of the International Certificate of Vaccination or Prophylaxis, which was last updated in December 2007. The vaccination certificate itself must be complete and accurate in every detail as a legal document in order to be valid. Failure to secure validation can lead to the quarantine for up to 6 days, revaccination or denial of entry of the traveller.

Conformity to professional standards for the administration of yellow fever vaccination is required under legally binding International Health Regulations (IHRs).[497] Previous studies have examined standards of yellow fever vaccination practice in England[498], Wales and Northern Ireland[499], and Canada .[500] This is the first study to examine the approaches to yellow fever vaccination adopted by travel medicine practitioners in the Republic of Ireland. The objectives of the study were: (i) to describe levels of professional training of practitioners working in Yellow Fever Vaccination Centres (YFVCs); (ii) to investigate the extent to which standards of practice reflect those specified under IHRs; and (iii) to identify professional training needs in relation to YFVCs.

Methods

The protocol for this cross-sectional study met with the requirements of the local research ethics committee. A 27-item piloted postal questionnaire was distributed to all licensed YFVCs in the Republic of Ireland. Respondents provided information on their practice type, professional training, storage and administration of vaccines, maintenance of patient records, travel medicine activity levels, yellow fever vaccination policies, international certificates of vaccination, protocols for managing adverse events, travel medicine information sources consulted, and resource and training needs. The questionnaire contained supplementary information describing the IHR (2005) standards for designated YFVCs.

Results

Responses were received from 246 healthcare professionals, 91% of whom were engaged in General Practice, working in designated YFVCs (38% response rate). A minority of respondents (16.2%, n=38) had received a formal qualification in travel medicine (Figure 4.4). Just over half of those clinics surveyed (53.4%, n=128) completed an average of 5 or fewer travel health consultations per week (Figure 4.5). Ninety percent of respondents (n=218) administered fewer than 50 doses of yellow fever vaccine annually (Figure 4.6). Deficiencies were identified in respect of vaccine refrigeration protocols, record keeping (Figure 4.7), attendance at YFVC training sessions, and protocols for the management of adverse events

(Table 4.2). A hierarchy of resource and training needs in relation to yellow fever vaccination was constructed from the preferences declared by clinicians participating in the study (Table 4.3).

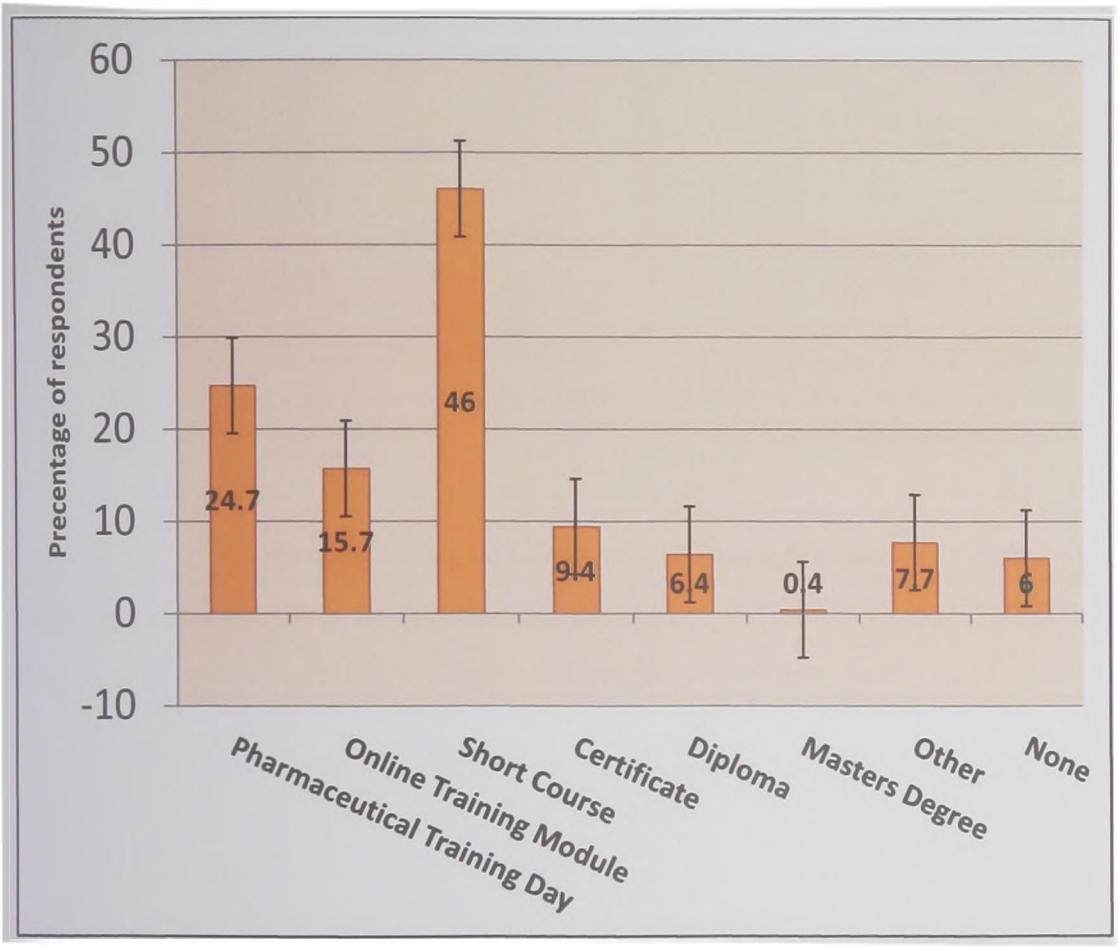

Figure 4.4 Relevant professional training of travel medicine practitioners

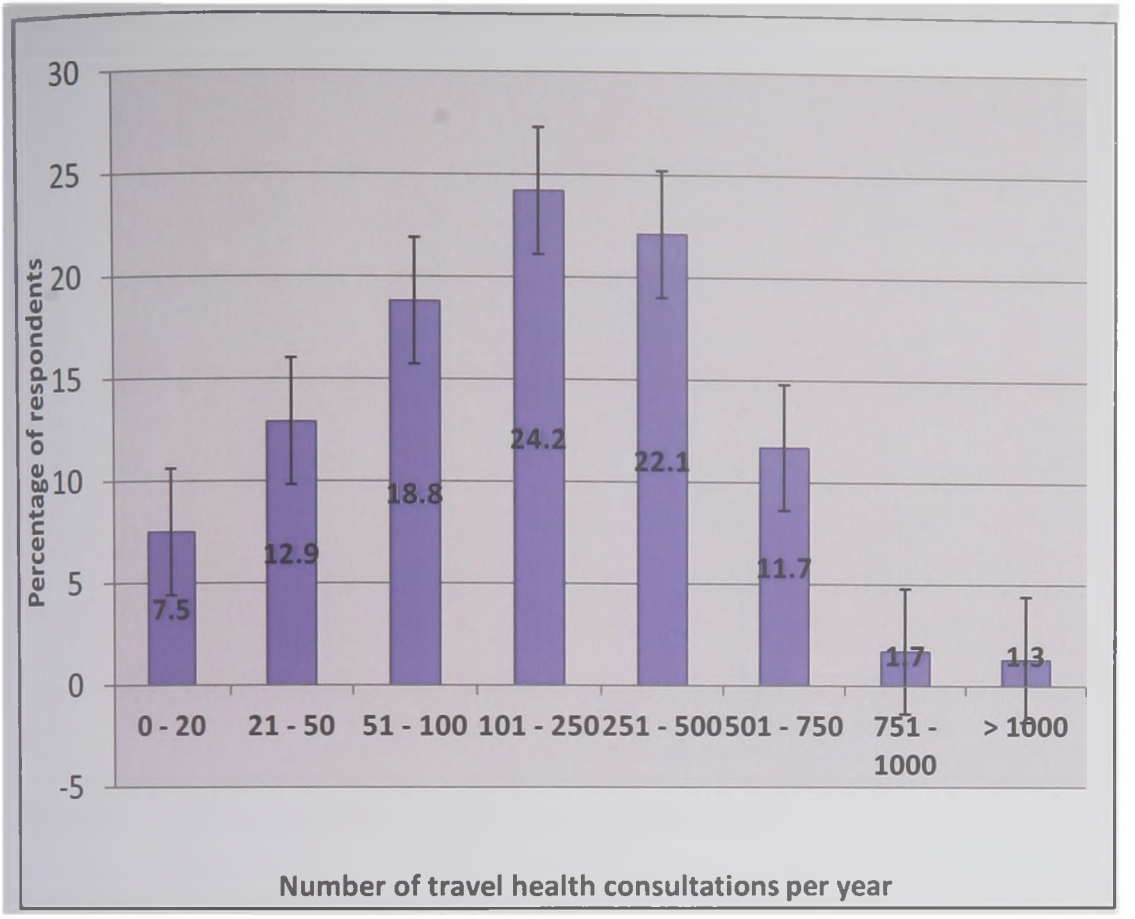

Figure 4.5 Annual travel health consultations

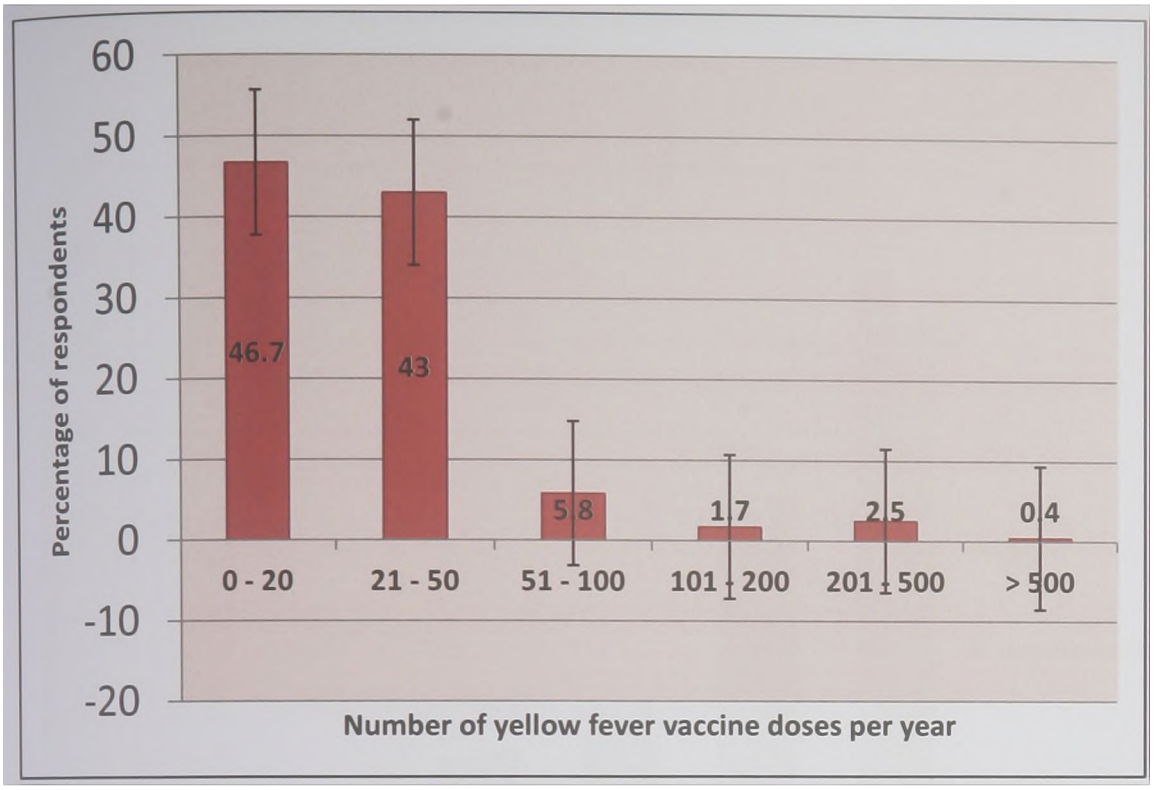

Figure 4.6 Number of yellow fever vaccine doses administered per year

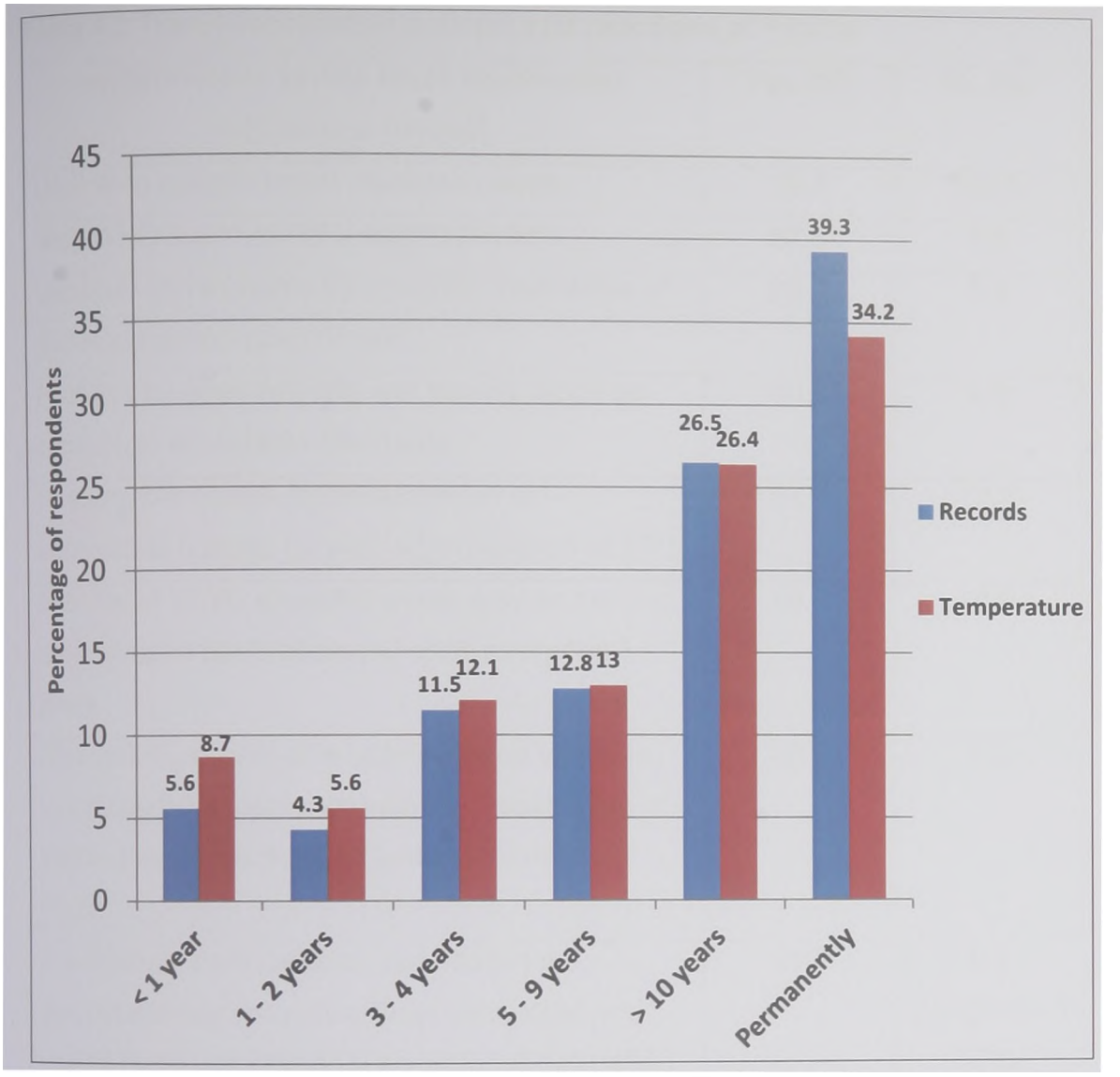

Figure 4.7 Period for which refrigerator temperature and patient records are retained

Table 4.2 Travel vaccination policies and practices of YFVCs

Adherence to yellow fever vaccination regulations (n=246)	Yes (%)	No (%)
Dedicated specific travel medicine clinics	10.7	89.3
Only WHO approved YFV administered*	97.5	2.5
Vaccines administered by or under supervision of qualified medical practitioner	99.2	0.8
Facilities for administering and storing vaccines conform to acceptable standards	99.2	0.8
Responsible person for development of appropriate policies for safe administration of YFV	87.7	12.3
Member of YFVC attended a yellow fever training session upon application and once every two years	49.4	50.6
Appropriate records of all administered vaccines maintained in accordance with the Designation of Yellow Fever Vaccination Centres, Information Pack	95.5	4.5
International certificates of vaccination or prophylaxis against yellow fever completed and signed by the vaccinator in accordance with WHO International Health Regulations (2005)	95.5	0.8 [Uncertain = 3.7%]
Vaccine associated adverse events reported to the Irish Medicines Board	97.9	2.1
Written protocol for vasovagal collapse available	75.9	24.1
Written protocol for anaphylactic shock available	95.0	5.0
Annual returns of vaccine utilisation returned to Health Service Executive	33.3	66.7
Agree that centre's status as a designated YFVC should be renewed at annual or biennial intervals, and appropriate fees should be paid for license renewals	40.5	40.9 [Uncertain = 18.6]

*WHO = World Health Organisation; YFV = Yellow fever vaccine

Table 4.3 Preferred sources of travel health information

Internet sources (n = 244)	%	Print sources (n = 243)	%	Telephone sources (n = 242)	%
Travax	65.6	Immunisation Guidelines for Ireland	60.5	Travax	43.8
WHO International Travel and Health	40.6	WHO International Travel and Health	46.1	Travel Centre, Royal College of Surgeons, Dublin (Mercer's Hospital)	23.6
CDC Health Information for International Travel*	32.0	Health Information for Overseas travel (UK Department of Health)	27.6	Tropical Medical Bureau	21.5
Fit For Travel	20.1	Vaccine wall charts for immunisation against infectious disease	27.6	Pharmaceutical companies	19.0
Tropical Medical Bureau	19.7	CDC Health Information for International Travel	9.9	NaTHNaC	5.8
MASTA†	8.6			MASTA	5.0
NaTHNaC‡	7.0				

*CDC=Centers for Disease Control and Prevention

†MASTA=Medical Advisory Service for Travellers Abroad

‡NaTHNaC=National Travel Health Network and Centre

Discussion

Administration of yellow fever vaccine is complicated by the changing epidemiology of the disease and the risk of rare but potentially fatal adverse events associated with the live attenuated vaccine. Yellow fever vaccine is also required for entry into certain countries and the practice of administering yellow fever vaccine is governed by International Health Regulations. In 2005, the National Travel Health Network and Centre (NaTHNaC), a public health body based in the United Kingdom, established a programme of registration, training, standards of clinical practice, and audit for Yellow Fever Vaccination Centres (YFVCs) operating in its jurisdiction, in accordance with the specifications of the International Health Regulations.[498] Their training programme has generated improvements in the standards observed at designated YFVCs and it has increased the confidence of healthcare professionals administering the vaccine. The authors conclude that elements of the NaTHNaC programme could serve as a model for improvement of clinical standards in travel medicine internationally. Currently, no such system exists in the Republic of Ireland.

This study is the first of its kind to describe the adherence to yellow fever vaccination guidelines of travel medicine professionals who are licensed to administer the yellow fever vaccine in the Republic of Ireland. While the minority of study participants had gained a formal qualification in travel medicine, many were engaged in a relatively high volume of travel medicine clinical consultations. The study demonstrated high concordance levels with best international practice in terms of supervision of vaccine administration, use of WHO-approved vaccines, accurate completion of international certificates for vaccination or prophylaxis, and development of written protocols for management of anaphylactic shock. Weaknesses were revealed in relation to duration of retention of patient data and refrigerator temperature records, training in yellow fever vaccination, clinical protocols for management of vasovagal syncope, and returns of vaccine utilisation to the Health Service Executive.

In response to the findings of this study, the Travel Medicine Society of Ireland invited Professor David Hill, former Director of NathNaC in the UK, to address its members at a regional educational seminar, and to share his experiences with the introduction of a formal programme of registration, training, and clinical audit in England, Wales and Northern Ireland. This study will serve as a useful catalyst to

the introduction of a similar system in the Republic of Ireland, and this will hopefully lead to safer administration of yellow fever vaccine and an overall improvement in training standards in travel medicine.

Conclusion

This study is the first of its kind to describe patterns of yellow fever vaccination and travel medicine practice in the Republic of Ireland and it highlights specific deficiencies in relation to training, vaccine storage, administration and documentation. The expressed training needs of those surveyed should be addressed and the information obtained shared with the appropriate health service authority in an effort to standardise YFVC practices in this jurisdiction and thus align them with best international practice.

Acknowledgments

I am very grateful to Dr. Peter Noone, Consultant in Occupational Health with the Health Service Executive, and Mr. Mohammed Hamza, a final year medical student at NUI Galway, for their assistance with questionnaire design and data entry, respectively.

CHAPTER 5
Assessing the Ill Returned Traveller

5.1. Recognition of Tropical Illness in Returned Travellers

Introduction

With the marked increase in international travel[502], and the growth of the migrant population living in Western European countries, multidisciplinary healthcare workers practising in Ireland are increasingly likely to encounter tropical illness in the returned traveller. Although most post-travel-related health problems in travellers to developing countries are mild, up to 8% of travellers seek care from a physician when they return to their home country.[503-506] Common diagnoses revealed by the GeoSentinel Surveillance Network Database in Europe include enteric fever, acute viral hepatitis, and influenza.[507] Life-threatening infectious diseases, such as *Plasmodium falciparum* malaria, melioidosis, and African trypanosomiasis, were reported in a study of GeoSentinel records of 53 tropical or travel disease units in 24 countries.[508] Lack of awareness of the possibility of tropical infectious disease in the differential diagnosis of an ill returned traveller could precipitate potentially complicated or fatal diagnostic delay.

Little is known about the preparedness of frontline emergency department clinical personnel in European healthcare institutions to promptly diagnose imported tropical infectious diseases in returning travellers. The current study aimed to establish the level of awareness of tropical diseases in a sample of healthcare professionals working in a major Irish teaching hospital; to evaluate their level of awareness of the geographical distribution of tropical diseases; and to characterise the ability of the healthcare team to record a detailed travel history, recognise tropical illness in returned travellers, identify the tropical disease risks associated with specific travel itineraries, and express their training needs in relation to clinical tropical medicine.

Methods

The research protocol for this descriptive, cross-sectional survey was approved by the local clinical research ethics committee. A self-administered questionnaire was distributed to a convenience sample of Emergency Department (ED) doctors (16-item questionnaire) and triage nurses (13-item questionnaire) working at University Hospital Galway in Ireland. The questionnaire enquired about the previous training, if any, received by the healthcare team in tropical medicine, their awareness of the components of a comprehensive travel history, their ability to recognise tropical illness in returned travellers, their knowledge of the geographical distribution of tropical diseases, and of the infectious disease risks posed by specific travel itineraries. Survey respondents were also asked about their degree of confidence in managing a patient with imported malaria. The study also invited the ED clinicians to nominate their preferred educational activities in relation to clinical tropical medicine. Data were entered into a Microsoft Excel database and analysed using descriptive statistics.

Results

Fifty healthcare workers completed the survey (29 doctors and 21 nurses). The majority of medical respondents (76%, n=22) were non-consultant hospital doctors. Forty-five percent (n=9) of the nurses surveyed worked on a weekly basis as triage nurses in the Emergency Department. Most of the doctors (72%, n=21) and nurses (57%, n=12) in the survey had not previously worked in a tropical or sub-tropical region (Figure 5.1). The majority of doctors (66%, n=16) and nurses (67%, n=14) had not received formal training in tropical or travel medicine. The training received by doctors was considered to be less than satisfactory in 38% (n=5) of cases, and by nurses in 60% (n=3, Figure 5.2).

The following items were not routinely included in the travel histories of the clinicians surveyed: illness in a travelling companion, water and food consumption practices, insect bites, and animal bites (Figure 5.3). Tropical illness was unlikely to be considered in patients presenting to the ED with shortness of breath, skin rash, joint pain, headache, fatigue and confusion (Figure 5.4).

There was a poor level of diagnostic confidence in relation to a range of tropical infectious diseases with a significant proportion of both medical (Figure 5.5) and nursing (Figure 5.6) staff declaring unfamiliarity with important tropical diseases. Deficiencies were revealed in the knowledge of the global distribution of certain tropical diseases (Figure 5.7). There was a tendency for doctors to overestimate the global distribution of malaria and yellow fever, while underestimating the prevalence of dengue infection (Table 5.1), upon considering specific travel itineraries. There was a reasonable level of awareness of the incidence of imported malaria in Ireland. Twenty-five percent (n=7) of medical respondents underestimated the annual incidence of imported malaria. A sizeable proportion of doctors (79%, n=23) were less than confident in their ability to manage a patient with malaria in an Irish hospital setting (Figure 5.8). The educational activities preferred by the majority of respondents were tropical disease manuals, designated workshops and wall charts (Figure 5.9).

Table 5.1 Physician knowledge of global distribution of tropical disease

Travel itinerary	Den. *n* (%)	Mal. *n* (%)	Sch. *n* (%)	Hep. *n* (%)	Typ. *n* (%)	YF *n* (%)	JE *n* (%)
Business man spent 4 nights in a hotel in Southern India (n=25)	13 (52)	17 (68)	3 (12)	19 (76)	12 (48)	6 (24)	1 (4)
Medical student spent 2 months in rural Philippines (n=24)	16 (67)	16 (67)	8 (33)	16 (67)	12 (50)	11 (46)	11 (46)
Aid worker spent 4 months in Ethiopia (n=26)	9 (23)	21 (81)	13 (50)	13 (50)	13 (50)	10 (38)	1 (4)
Flew from Lima to Cuzco and trekked the Inca trail (n=25)	7 (28)	10 (40)	7 (28)	11 (44)	11 (44)	13 (52)	1 (4)
Spent 1 week in Istanbul, Turkey (n=23)	1 (4)	2 (9)	3 (13)	17 (74)	10 (43)	2 (9)	0 (0)
Flew to Buenos Aires and visited the Iguassu falls (n=23)	7 (30)	14 (61)	6 (26)	15 (65)	11 (48)	6 (26)	1 (4)
Trans-Siberian railway from Moscow to Beijing (n=22)	7 (32)	4 (18)	2 (9)	14 (64)	12 (55)	3 (14)	10 (45)
Flew from Rio de Janeiro to Manaus in the Amazon (n=24)	13 (54)	20 (83)	10 (42)	13 (54)	10 (42)	12 (50)	3 (13)
Honeymoon couple travelled on a 1-week Nile cruise (n=24)	7 (29)	12 (50)	10 (42)	17 (71)	16 (67)	4 (17)	2 (8)
Family spent 2 weeks in Cape Town, South Africa (n=20)	5 (25)	11 (55)	3 (15)	15 (75)	9 (45)	3 (15)	1 (5)
Flew from Bangkok to Hanoi visiting coastal Vietnam (n=23)	13 (57)	13 (57)	7 (30)	13 (57)	11 (48)	10 (43)	14 (61)
Flew to Bangkok and spent 2 weeks on Phuket (n=21)	6 (29)	10 (48)	6 (29)	16 (76)	9 (43)	6 (29)	6 (29)
Stopped over in Singapore for 2 nights en route to Perth (n=16)	3 (19)	6 (38)	3 (19)	9 (56)	5 (31)	3 (19)	6 (38)
Two-week trip to Cuba (n=18)	6 (33)	10 (56)	3 (17)	15 (83)	2 (11)	2 (11)	1 (6)

Abbreviations: Den. = Dengue infection; Mal. = Malaria; Sch. = Schistosomiasis; Hep. = Hepatitis A; Typ. = Typhoid fever; YF = Yellow fever; JE = Japanese encephalitis

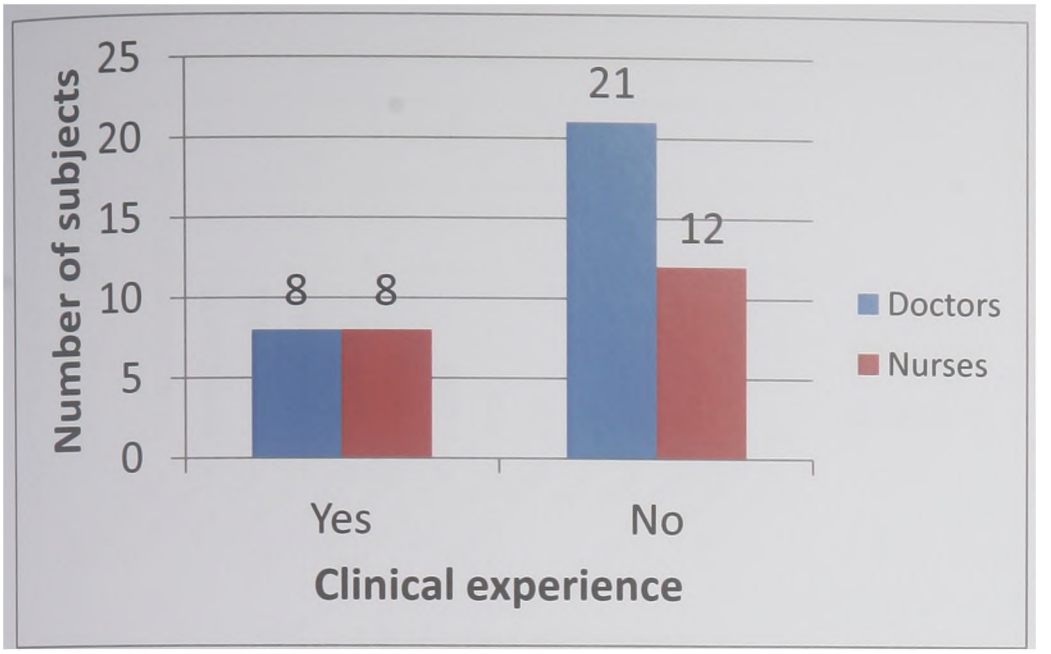

Figure 5.1 Previous clinical experience in tropical regions

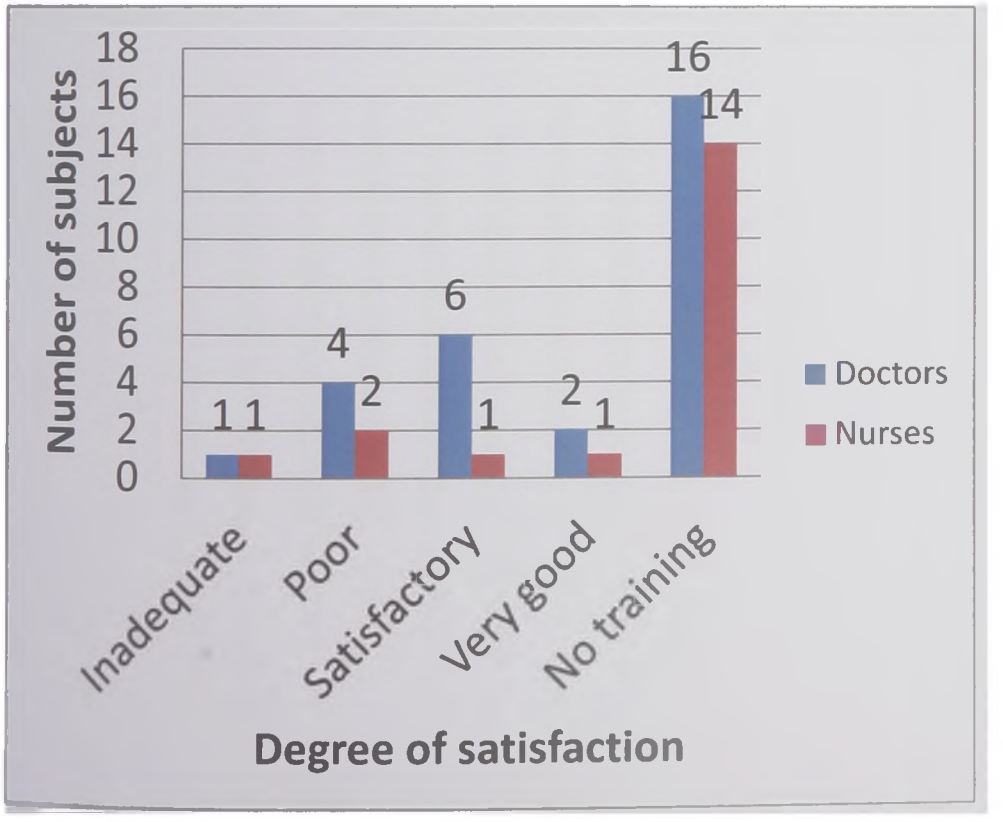

Figure 5.2 Satisfaction with previous tropical medicine training

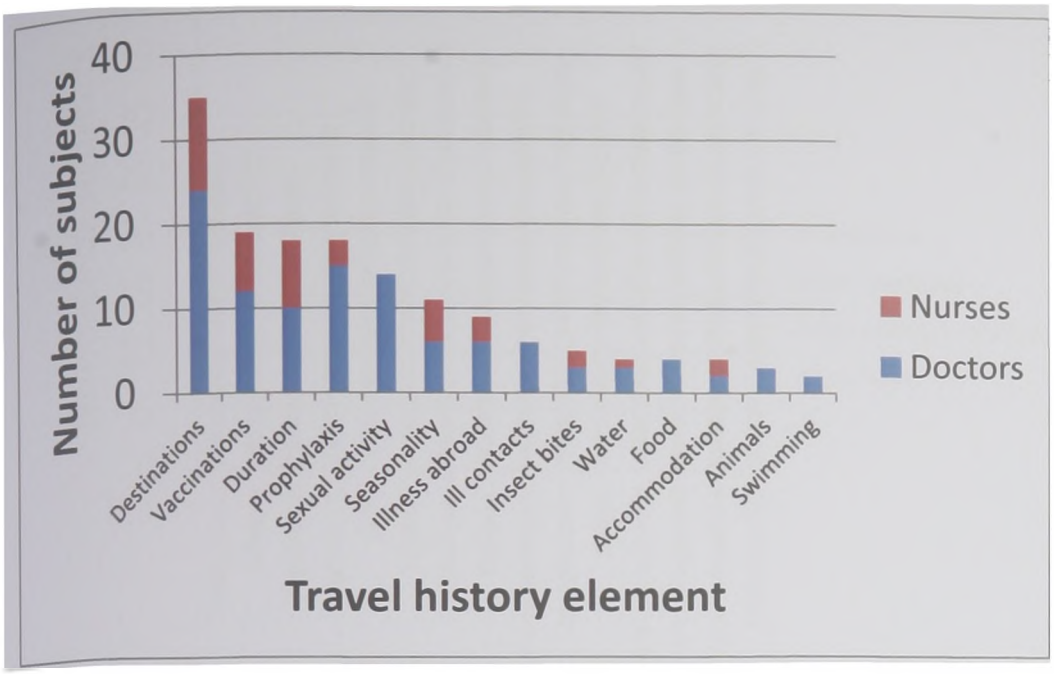

Figure 5.3 Elements of travel history routinely recorded

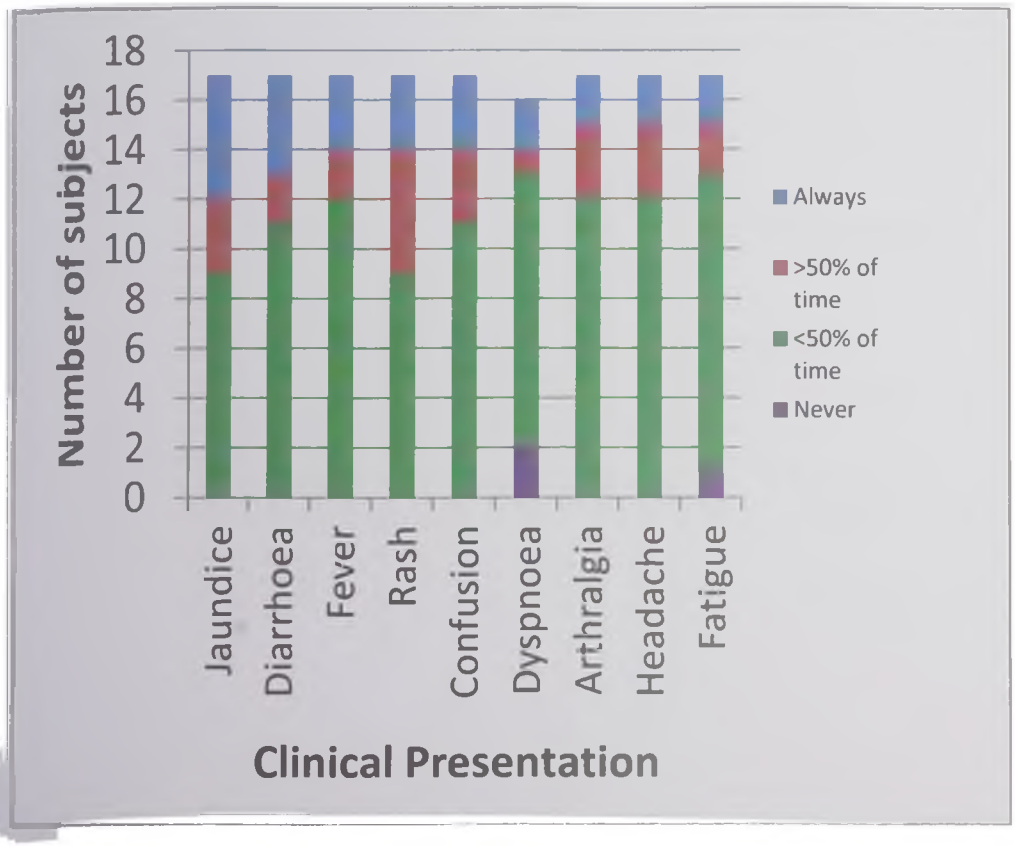

Figure 5.4 Likelihood of NCHDs considering tropical disease in returned travellers (NCHD = non-consultant hospital doctor)

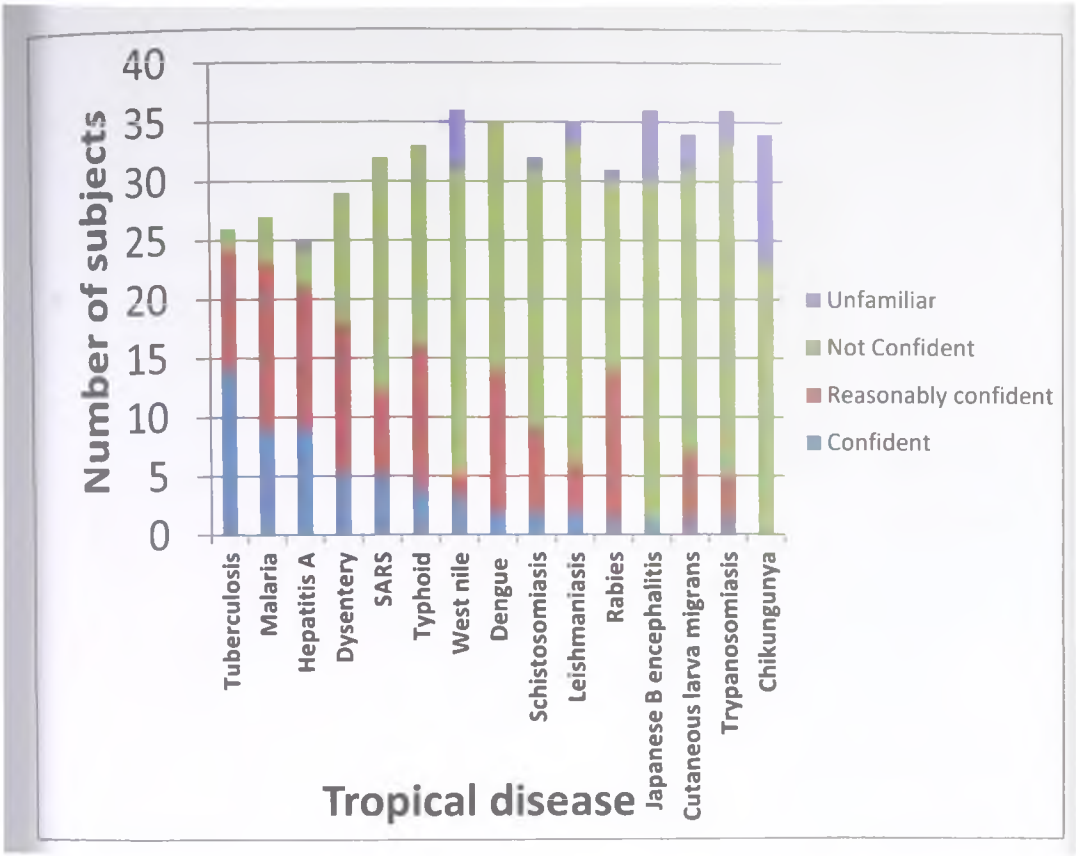

Figure 5.5 Recognition of specific tropical diseases by all doctors

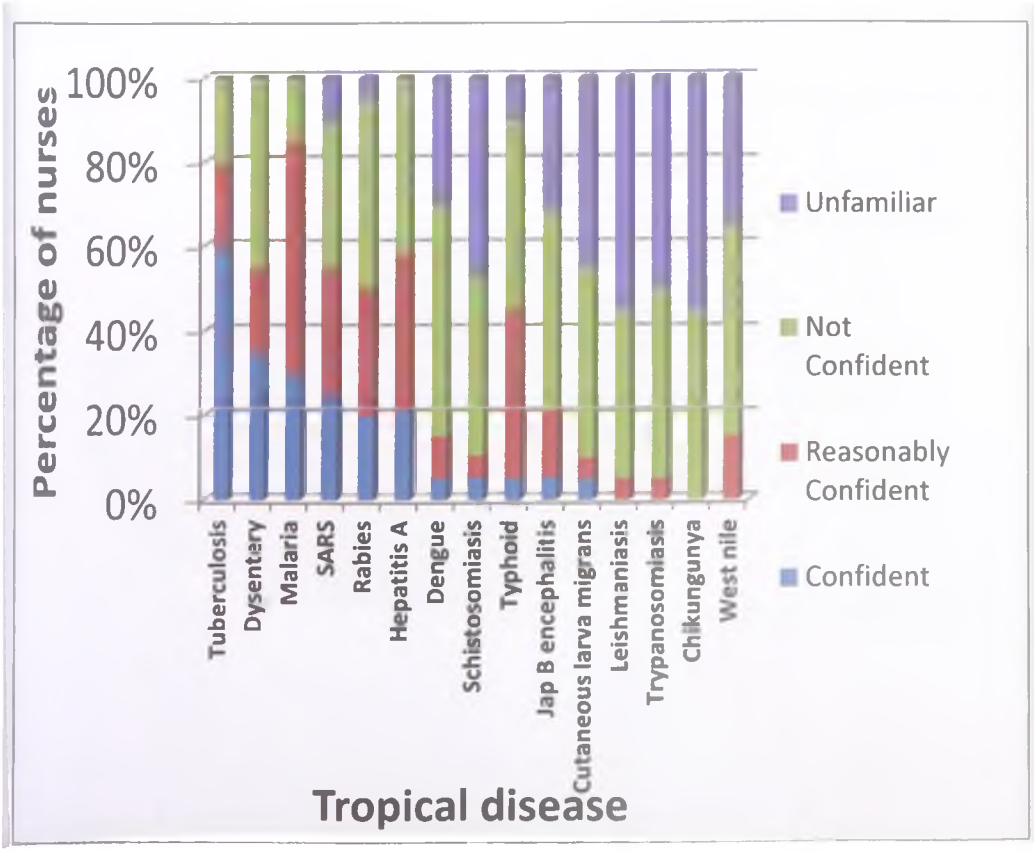

Figure 5.6 Recognition of specific tropical diseases by nurses

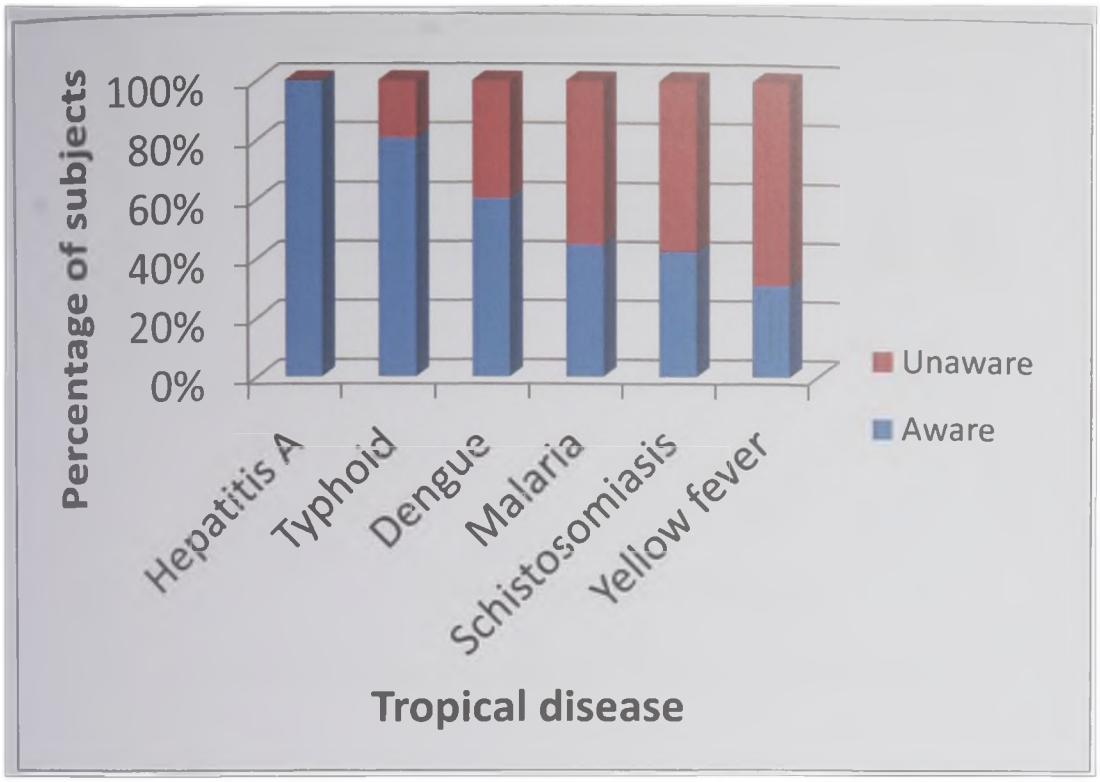

Figure 5.7 Knowledge of global distribution of tropical disease

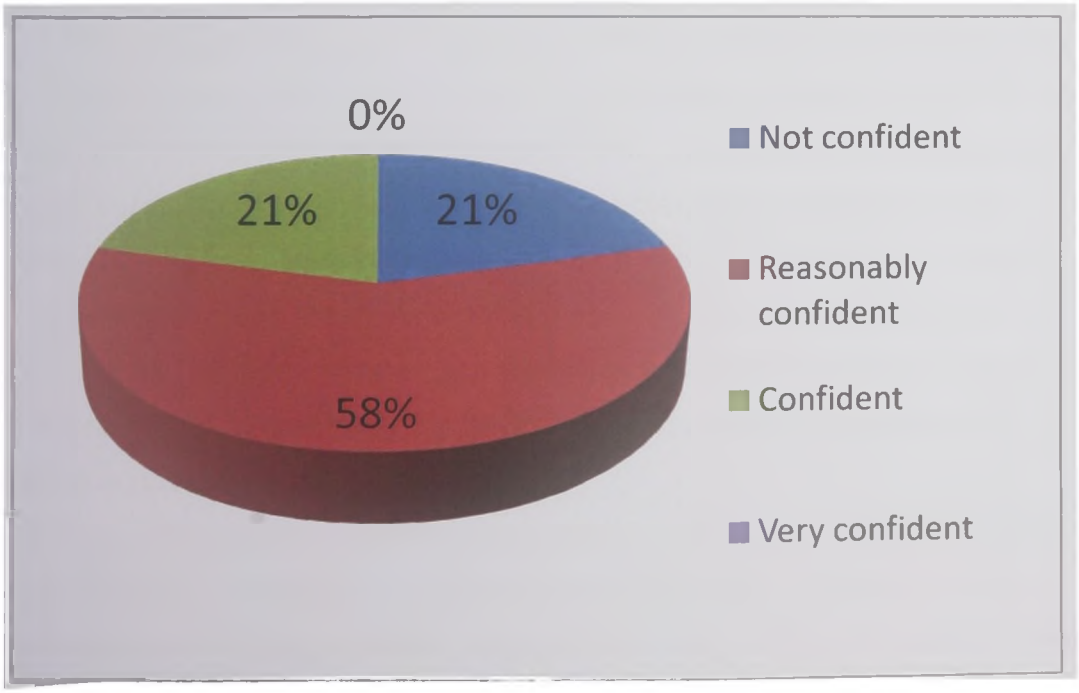

Figure 5.8 Confidence in management of malaria

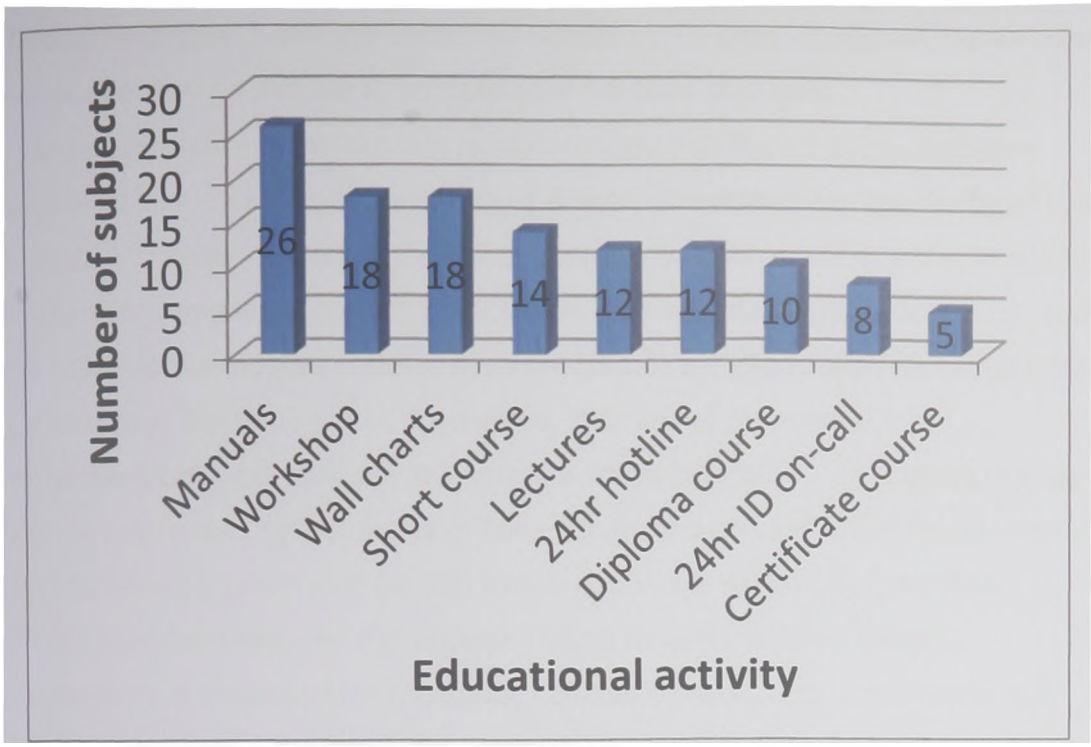

Figure 5.9 Preferred tropical medicine educational activities

Discussion

This study, though limited by its sample size and non-random sampling method, provides useful insights into the familiarity of Emergency Department doctors and nurses with respect to the recognition and management of tropical infectious diseases in returned travellers presenting for emergency hospital care with a variety of symptoms. The lack of previous experience of working in a tropical healthcare setting was prominent in this group, and it is possible that many of those who had worked in a tropical country originated from such countries as the questionnaire did not record ethnicity or the country where basic nursing or medical education were undertaken.

Over two thirds of those surveyed had not completed any formal training in tropical medicine, reflecting the general lack of emphasis on this subject in undergraduate and postgraduate medical and nursing curricula. Currently there is no active taught postgraduate programme in tropical medicine in Ireland and the respected full-time courses available locally in the London School of Hygiene and

Tropical Medicine[509] and the Liverpool School of Tropical Medicine[510] offer limited places and may be difficult to complete for full-time clinicians.

In a post-travel evaluation, it is recommended that the clinician considers several factors, including the severity of illness, travel itinerary, the timing of illness in relation to travel, underlying medical conditions which could affect susceptibility to infection, vaccines received, compliance with malaria chemoprophylaxis, and the individual's exposure history, which must include information on insect bites, contaminated food and water, freshwater swimming, purpose of trip, accommodation type, and any treatment accessed locally.[511] In a study of long-term travellers visiting GeoSentinel sites, Chen and co-workers[512] found that long-term travellers experienced greater levels of chronic diarrhoea, giardiasis, *Plasmodium falciparum* or *Plasmodium vivax* malaria, chronic fatigue, eosinophilia, cutaneous leishmaniasis, schistosomiasis, and amoebiasis. In a study of a large, multicentre database of febrile returned travellers, Wilson and colleagues[513] found that over 17% of travellers with fever had a vaccine-preventable infection or falciparum malaria, and that malaria was responsible for 33% of the 21 deaths recorded in febrile returned travellers. Important clues may arise in the initial investigation of the ill returned traveller, including the possibility of helminthic infection in the returning traveller with eosinophilia.[514]

An interesting finding in the current study was the reluctance of healthcare staff to routinely record a detailed travel history and to consider tropical disease when faced with a patient who presents with a variety of common symptoms, such as fever, headache and arthralgia. The ill patient may not volunteer a history of travel, or may be too unwell to provide a reliable history, and the Emergency Department clinicians may not prioritise tropical illness in their differential diagnosis owing to lack of familiarity or case exposure. This failure to consider tropical infections was compounded by a stated lack of familiarity with a range of common tropical infectious diseases, all of which may be imported by an asymptomatic traveller returning from endemic parts of the world during the incubation period of the disease. While there was a tendency to overestimate the global distribution of malaria, there were poor levels of confidence in managing malaria in an Irish hospital setting. This is especially significant given the increased burden of imported malaria in Ireland in recent years, predominantly among the Visiting Friends and Relatives population.[515]

Most of the Emergency Department healthcare team members selected convenient educational activities from the list provided, with only 20% opting for a diploma course in tropical medicine. This may reflect their busy working lives with multiple competing responsibilities, the general nature of their typical diagnostic load, or the low priority given to tropical medicine in their careers to date.

Future studies should include larger random samples from hospitals throughout Ireland and other European countries, and should directly compare knowledge, attitudes and practices of indigenous and international graduates. A standardised curriculum in tropical medicine, delivered in common to nursing and medical students, should be designed as a first attempt to address the learning needs identified by this pilot study.

Conclusions

This study is the first of its kind in Ireland to examine the preparedness of frontline Emergency Department clinical workers to diagnose and manage imported tropical infectious diseases in a hospital setting. Deficiencies were highlighted in the recording of a travel history and there was a generally poor ability to recognise tropical illness in patients with a variety of presenting symptoms. Enhanced opportunities for training in tropical medicine should be provided to front-line healthcare professionals in Ireland.

Acknowledgements

I wish to express my gratitude to Dr. Andrew Scott for assisting with data collection, and the nursing and medical personnel of the Emergency department of University Hospital, Galway for their cooperation with this study.

5.2. Obtaining a Reliable Travel History from Returned Travellers

Introduction

The potential for importation of communicable infectious diseases from tropical and sub-tropical regions poses a public health threat and a burden on the health services of the traveller's native country. Failure to obtain a comprehensive travel history in the returned traveller may lead to diagnostic delay which may have fatal consequences. A previous Irish study by this author has examined the awareness of tropical diseases in returned travellers among emergency room healthcare professionals working in an Irish hospital.[516] No studies to date have examined the issue of quality control in respect to the travel history recorded by doctors practising in non-tropical countries. This study investigated the quality of the travel history recorded by doctors from travellers returning from the tropics to a university teaching hospital in the west of Ireland.

Methods

The study received approval from the Clinical Research Ethics Committee of Galway University Hospitals. A retrospective study of the case notes of patients presenting to University Hospital Galway between 2005 and 2009 was performed. Patient records were cross-referenced with the Microbiology laboratory diagnostic database. In each case a diagnosis of a tropical infectious disease had been confirmed by microbiologic analysis. A case review proforma recorded demographic details and historical items relating to information regarding patients' potential exposure to infectious diseases during travel. All data were anonymised for data protection purposes.

Results

Fifty-six returned travellers (32 male, 24 female) with a mean age of 23 years were identified. The majority were Irish-born (n=23) with 26 of the remaining patients belonging to the Visiting Friends and Relatives category. The most common travel destinations were West Africa (n=26) and Asia (n=16). Fever (n=43) was the most

common symptom in these travellers, and malaria was the most frequently diagnosed tropical disease (Figure 5.10). Approximately 45% (n=25) of patient records examined did not include any reference to the grade of healthcare professional who had obtained the history from the returned traveller (Figure 5.11). Figures 5.12 (i-iv) illustrate the limited extent to which particular elements of the travel history were documented in the returned travellers' hospital case notes. Two-thirds of returned travellers were not given preventive advice to reduce their risk of developing travel-related illness in the future (Figure 5.12.iii).

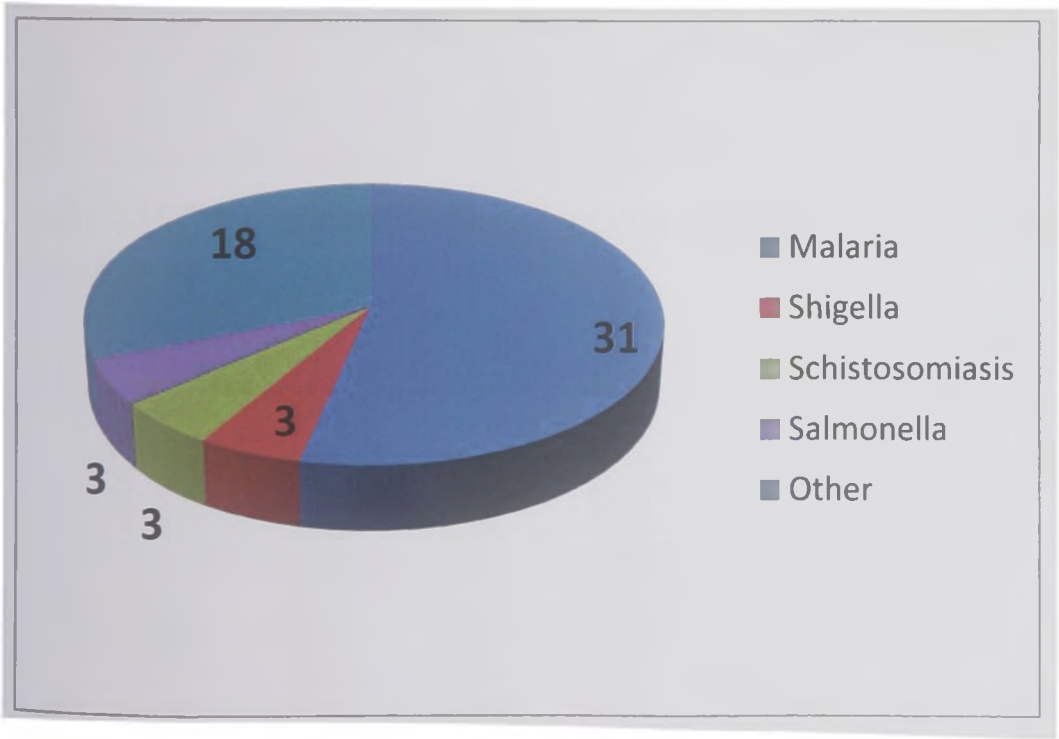

Figure 5.10 Tropical infectious disease diagnoses in returned travellers (n=58)

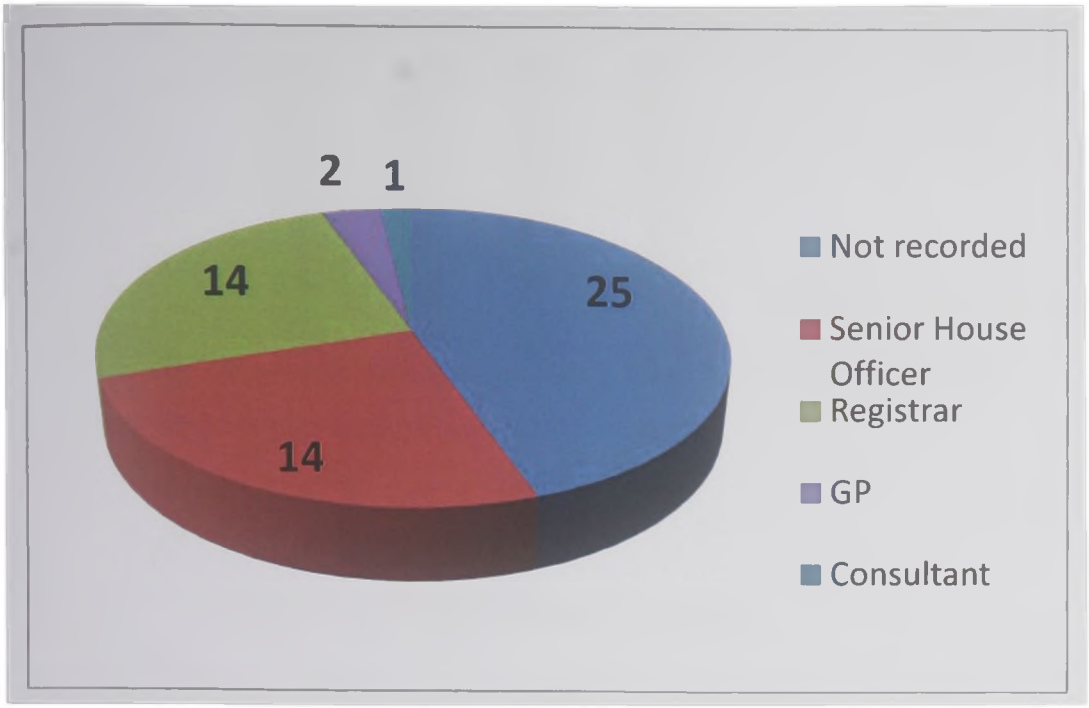

Figure 5.11 Grade of healthcare professional assessing returned traveller (n=56)

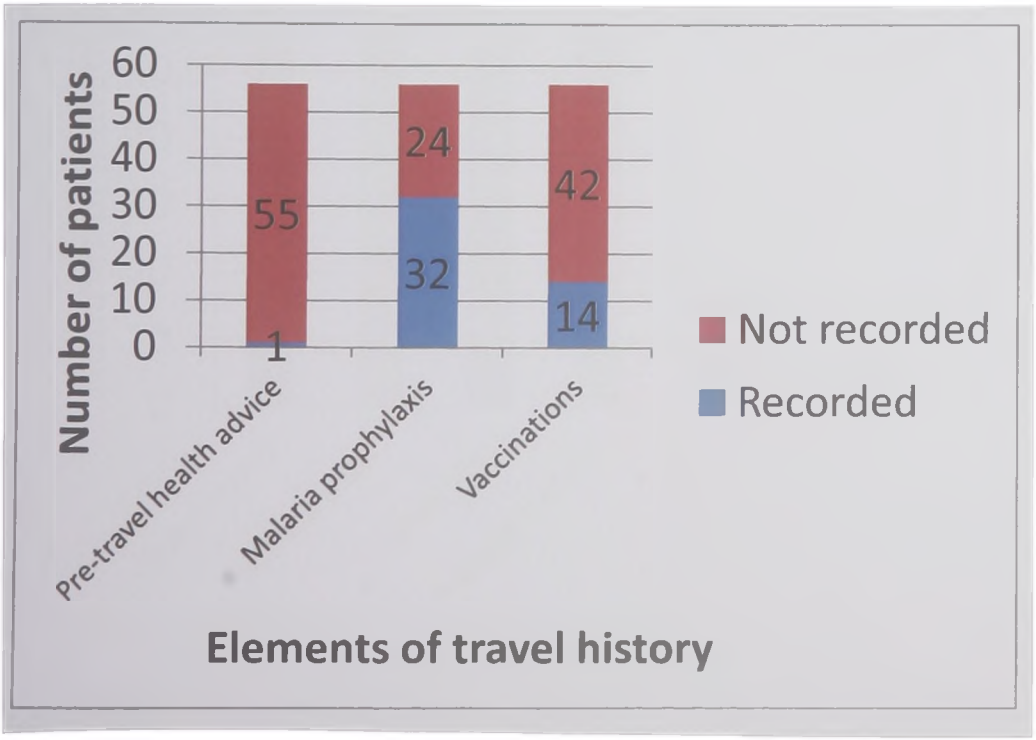

Figure 5.12.i Documentation of elements of travel history relating to prophylaxis

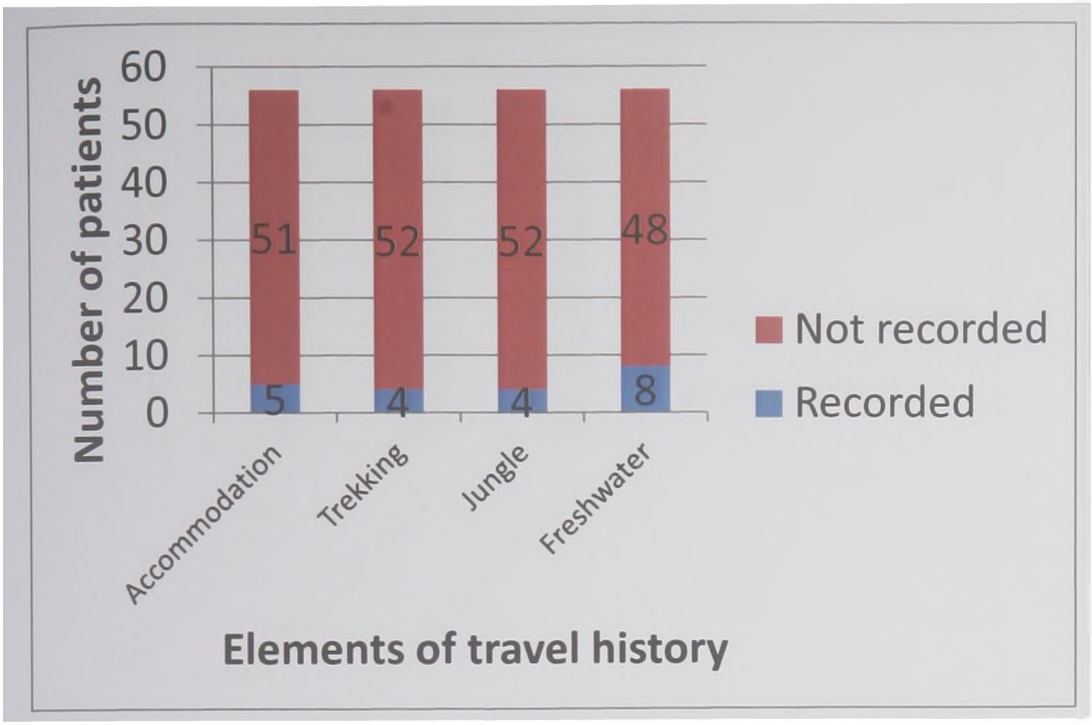

Figure 5.12.ii Documentation of elements of travel history relating to itinerary

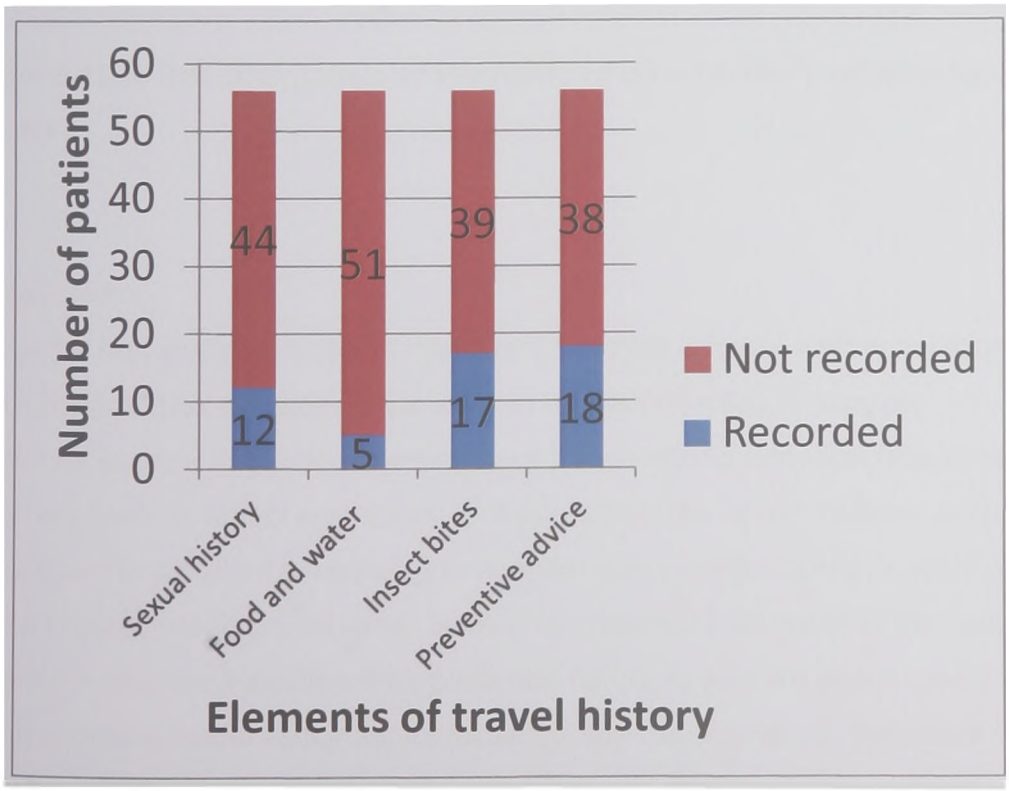

Figure 5.12.iii Documentation of elements of travel history relating to exposures

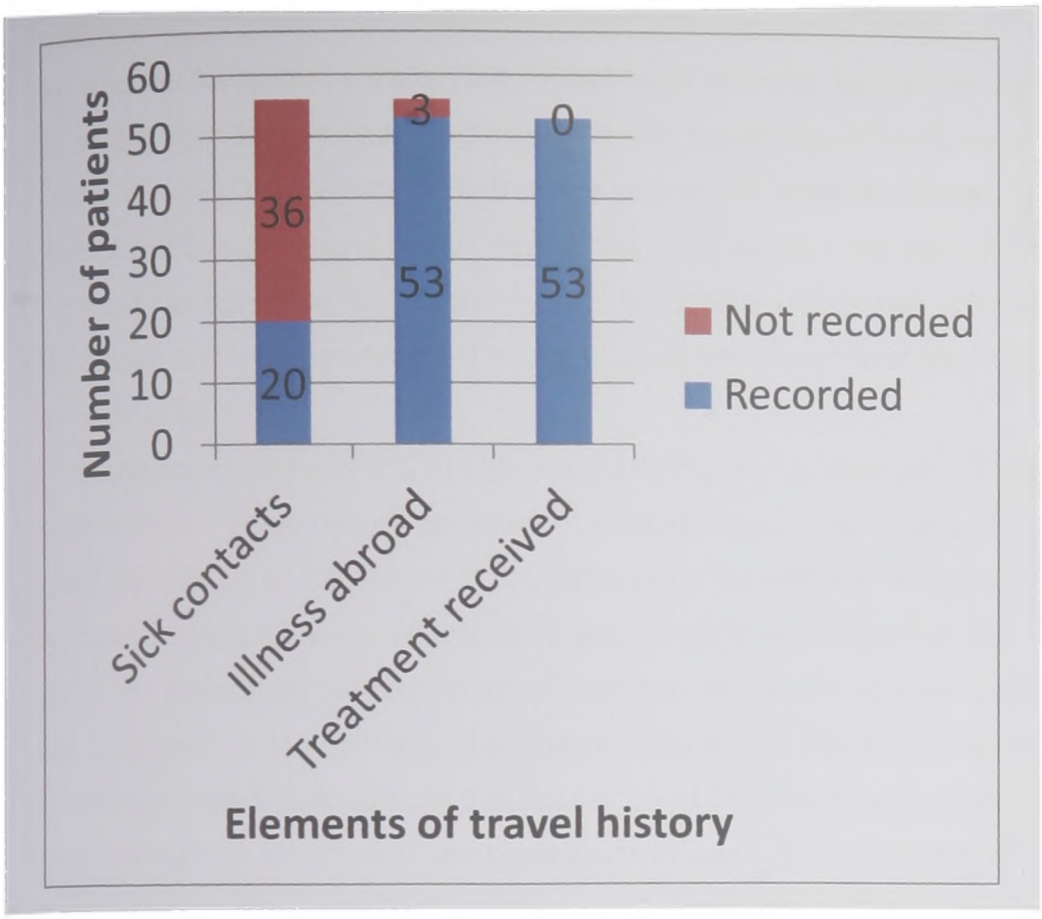

Figure 5.12.iv Documentation of elements of travel history relating to illness abroad

Discussion

This is the first study to evaluate the extent to which a travel history is included in the clerking admission notes of patients in an Irish hospital. It exposes considerable gaps in the documentation of travel-related historical questions which are likely to reflect a generally prevalent practice of not routinely enquiring about travel in a patient presenting to hospital with symptoms which could result from a tropical infectious disease. Travel histories were recorded in the vast minority of returned travellers with particular failure to enquire about pre-travel health advice or travel vaccinations received, the travel itinerary, exposure to contaminated food and water, travel sexual history, and exposure to ill travelling companions. While some of these items may assume greater or lesser importance in individual presenting complaints, it seems reasonable that they form part of a routine screening post-travel history.

In a study of patient attendees at an acute medical unit in England, Price and co-workers found that a travel history had been recorded by the clerking doctor in less than 20% of patients presenting with symptoms of fever, rash, diarrhoea, vomiting or jaundice.[517] In the vast majority of cases there was no mention of whether pre-travel health advice had been obtained by the traveller or not. The authors conclude that there needs to be greater awareness of travel-related illness and the importance of taking a comprehensive travel history in an acute medical setting.

Smith found that only 2% of patients attending an Accident and Emergency department had a travel history recorded[518], thus increasing the likelihood that an imported disease could be missed in the emergency department. In the current study, it was found that, where a tropical disease had been diagnosed, the doctors caring for the patient did not document at least that preventive advice had been offered to the patient to avoid a similar illness in the future. Since malaria was the most common imported disease in this cohort, good practice would mandate that the patient would be informed of the importance of wearing long sleeves when outdoors between dusk and dawn, using an insect repellent on exposed skin, and complying with malaria chemoprophylaxis. Further studies should investigate the priority given to the travel history in different clinical settings, including the primary care environment.

Conclusion

This study reveals significant deficiencies in the quality of the travel history recorded by doctors practising in an Irish hospital when presented with travellers returning from the tropics with symptoms suggestive of tropical diseases. The findings of the study reinforce the need to improve education in travel medicine among hospital physicians.

Acknowledgements

I am grateful to Dr. Ryan Gately for assisting with the data collection and Dr. Catherine Fleming for her advice in designing this study.

5.3. Pathophysiology and Prevention of Jet Lag (Minor Review)[5]

Introduction

The syndrome of jet lag or circadian dyschronism emerged with the advent of long-haul air travel[519] which allowed multiple time zones to be rapidly traversed. Travellers affected by jet lag report disturbed sleep during night-time at their destination, including delayed sleep onset after eastward flights or early awakening after westward flights. Fatigue, irritability, decreased ability to concentrate, a feeling of disorientation (personal observation), gastrointestinal disturbances, and decreased enjoyment of meals contribute to the relative misery of the jet-lagged traveller. Waterhouse and co-workers[520] have produced the Liverpool jet lag questionnaire (Appendix 8) in which participants are asked to respond to 15 items on a variable scale from 0 to 10 or -5 to +5 on several occasions in a given day.

Jet lag can be distinguished from travel fatigue because, unlike the latter, the symptoms of jet lag do not resolve after a good night's sleep[521] and are not associated with long-distance flights to the north or south.[522] The symptoms of jet lag can be reproduced in the laboratory when effects due to the difficulties associated with travel and disruption of one's normal routine are eliminated. With the ever increasing number of international travellers, many of them conducting important business abroad, the phenomenon of jet lag constitutes a significant public health problem which deserves the attention of every physician.

Epidemiology

The extent to which individual travellers experience jet lag varies widely. In general, the severity of jet lag symptoms increases with the age of the traveller and the number of time zones crossed.[523] Eastward travel produces more pronounced symptoms than westward travel[524], since it is easier to lengthen than to shorten the period of the circadian cycle which is approximately 25 hours. After

[5] Adapted, with the permission of the co-author, from: G Flaherty, T O'Brien. Jet lag: Novel Insights and Preventive Strategies. Modern Medicine 2008:15-19.

flights to the east the traveller finds it difficult to get to sleep at the new bedtime, whereas after westward flights the jetlagged traveller awakens prematurely. It appears that jet lag symptoms are more commonly reported after arrival home than arrival at one's away destination.[525] This may be because people tend to pay less attention to symptoms when they are distracted by external stimuli in a new and exciting environment. Sleep patterns are also disrupted in aircrew, suggesting that previous experience with time-zone transitions does not confer protection against future symptoms.[526]

The importance of jet lag symptoms varies with the nature of the journey and the itinerary involved. Thus, holiday-makers may fail to enjoy the first few days of their vacation; businessmen might be subject to costly errors, and athletes might suffer a decrement in their performance levels, subjective mood and motivation to train. Previous work has demonstrated an increased time taken for both a sprint and middle-distance run after an eastward flight crossing six time zones.[527] Studies involving pilots on long-haul flights have found that, particularly with nocturnal flights in an easterly direction, pilot fatigue reached levels that could make them prone to serious errors.[528] Repeated long-haul flights produce irregularities in the menstrual cycle due to altered patterns of melatonin secretion.[529] An increased incidence of psychotic and major affective disorders has also been described in chronically jet lagged subjects.[530]

Part of the idiosyncrasy in people's experience of jet lag effects may be due to their individual chronotype (i.e., whether their circadian rhythms are phased earlier or later than average). One study revealed that travellers who had rigid sleeping habits had more jet lag symptoms than did those with less rigid sleep patterns.[531] Elderly travellers have greater difficulty in coping with jet lag, no doubt due in part to their less regular circadian rhythms, and lower amplitude, phase-advanced body temperature rhythms.[532]

Understanding the body clock

Jet lag arises when a dissociation arises between the environmental and internal times due to a shift of the external light-dark cycle occurring after a time-zone transition. The so-called body clock comprises paired groups of cells on either side of the midline at the base of the hypothalamus. These suprachiasmatic nuclei

have receptors for melatonin[533] and receive information about the level of light in the environment via the retinohypothalamic tract.[534] Information about physical activity and general excitement levels are conveyed to the nuclei via the intergeniculate leaflet.

The timing of the body clock is adjusted to the solar day by rhythmic cues in the environment called *Zeitgebers*, or time-givers. A *Zeitgeber* can cause a phase advance, phase delay, or no phase shift, depending on its time of presentation. The principal *Zeitgebers* are the light-dark cycle and the rhythmic secretion of the hormone melatonin which is released by the pineal gland during nocturnal sleep. According to the feeding hypothesis a high-protein breakfast raises plasma tyrosine levels thus promoting the synthesis of the excitatory neurotransmitters dopamine and norepinephrine, while a high-carbohydrate evening meal leads to a rise in plasma tryptophan concentrations, promoting the synthesis of serotonin, a precursor of melatonin.[535] This hypothesis has not been supported by research findings to date, however. Circadian rhythms in core temperature, plasma hormone concentrations, and the sleep-wake cycle are controlled by the body clock. Were it not for the fact that the body clock is relatively resistant to the phase shifting effects of external factors such as time-zone transitions, jet lag would not arise.

Melatonin secretion normally starts at about 2100 h and ends at about 0800 h.[536] Bright light suppresses melatonin secretion such that bright light presented early in the morning just after the body temperature nadir prevents the phase-delaying effect that melatonin would otherwise exert at this time.[537] After flying westwards, travellers feel tired during the new evening at their destination and yet find themselves waking prematurely because of rising core temperature and falling melatonin secretion produced by the unadjusted body clock. Travellers who have flown in an easterly direction do not feel tired at midnight by local time as their body clock is still adjusted to daytime. However, they become sleepy as the new day dawns.

Prevention of jet lag

It is generally agreed that adjustment of the body clock is not possible or desirable for short stays of 3 days or less in a new time zone. If possible, travellers should schedule their arrival in the new time zone well in advance of an important event at that destination. As a general rule, it takes most travellers a number of days to recover from jet lag equal to two-thirds of the number of time zones crossed in the case of an eastward flight and half the number of time zones crossed following a westward flight.[520]

Stopovers of a day or so should be encouraged since jet lag simulation studies have found that less jet lag is experienced when the total time-zone transition is divided into multiple parts.[538] It is worth balancing this benefit with the added difficulties due to baggage transportation, multiple check-ins, passport controls and accommodation seeking. Travel fatigue should be minimised by keeping well hydrated and avoiding alcohol or caffeine. Static exercises and frequent walks down the cabin aisle are effective when the traveller wishes to remain awake in an effort to adjust to a new time zone.

The role of sleep on long-haul flights is difficult to evaluate since shutting the eyelids introduces a light-dark cycle. If adjustment of the body clock is the goal, the traveller should avoid sleep that does not coincide with night-time at the destination unless they have been significantly sleep-deprived during transit. Zolpidem may be preferable to temazepam as a sedative-hypnotic as it has a shorter half-life and affects short-term memory to a lesser extent. It is unclear if benzodiazepines exert a true chronobiotic effect by shifting the body clock but GABA type A receptors have been demonstrated in the suprachiasmatic nuclei. One study found that temazepam had no effect on travellers' sleep or jet lag symptoms when taken for 3 days after a long-haul westward flight.[539] Amphetamines, caffeine, pemoline and modafanil improve mental performance and reduce the ability to sustain sleep and may be useful in promoting alertness in the new time zone.[523]

Melatonin (N-acetyl-5-methoxytryptamine) has a soporific effect, possibly related to its body temperature-lowering effect. A recent Cochrane review concluded that melatonin is effective in reducing subjective symptoms of jet lag after flights in both easterly and westerly directions.[540] The hormone should be taken in the early evening at about 2000 h on the new local time, irrespective of

the direction of travel and number of time zones crossed. Interestingly, ingestion of melatonin at 2000 h local time with eastward flights in excess of 9 h causes phase delays rather than the expected phase advances.[541] When a phase advance in the body clock is required, such as with eastward flights, melatonin should be taken 1 h earlier each day until 1500 h is reached, at which stage it can be stopped. For westward flights, melatonin should be taken 1 h later each day until 0600 h is reached. Results suggest that any sleep-promoting effects of exogenous melatonin are not carried over to the next day. Taking melatonin prior to the day of travel does not accelerate adaptation to the destination time zone and is not currently recommended. No differences have been detected between daily doses of 0.5mg and 5mg of melatonin, except that onset of sleep is faster with the higher dose.[542] Curiously, taking 2mg of the slow-release preparation is largely ineffective, suggesting that a pulse of melatonin works more effectively.[542] No trials combining melatonin and a benzodiazepine hypnotic have been published to date.

Just as individuals differ in the degree to which they experience jet lag symptoms, there may be individual differences in the effectiveness of melatonin. Melatonin is unlicensed in Europe or Australia but is available as an over-the-counter food supplement in pharmacies and health food stores in certain countries including the United States, Thailand and Singapore. One study found that four out of six melatonin products purchased in health food stores in the USA were found to contain unidentified impurities.[542] No studies on the effects of long-term administration of melatonin have been carried out to date. Such studies are unlikely to be funded by pharmaceutical companies since the substance is not patentable. Young people and pregnant women have been advised against the use of melatonin[543] and studies have advocated caution in using the substance in patients with epilepsy or in those taking anticoagulants.[540] Promising results with melatonin analogues are now appearing in the literature, however.[544]

Another approach to adjustment of the body clock is exposure to and avoidance of bright light in the new time zone. Published tables can be consulted which recommend times for the use of bright light on the first day after arriving in a new time zone.[520] Portable light sources are becoming available for this purpose but it is interesting to note that, although much weaker than natural daylight, even artificial domestic lighting can still act as a *Zeitgeber*. The times of exposure

Future research

It is understandable why no pharmaceutical company is willing to pay for the toxicological studies and the data assembly required to obtain a product licence for melatonin as they cannot claim any exclusivity over the substance. Use of this drug is clearly in the public interest and would be of great benefit to holiday-makers, business people, diplomats, government officials, international athletes, the armed forces and air crew. Additional research is needed into the molecular changes associated with time-zone transitions, with a view to designing novel body clock-adjusting therapies.

CHAPTER 6
Education and Training in Travel Medicine

6.1. Special Study Modules in Travel Medicine

Lofty Thoughts – Introducing Medical Students to High Altitude Medicine

Introduction

Recent years have witnessed increased opportunities to study high altitude medicine with the advent of the UIAA Diploma in Mountain Medicine.[546] A significant number of doctors in Europe have received instruction in mountain medicine through participating in various medical education programs.[547] High altitude medicine has traditionally received little coverage in the undergraduate medical curriculum, however. Increasingly, medical graduates are participating in high altitude treks, either for recreation or as volunteer or paid expedition doctors, with little or no prior training in this highly specialised branch of travel medicine.

The concept of special study modules (SSMs) arose as a response to the recommendations of the General Medical Council[548] to medical schools in the UK. Optional modules which allow the student to spend more time studying subjects of particular interest to them in more depth represent "the most exciting and significant development in medical education thinking in recent years".[549] The author set out to develop an SSM in high altitude medicine in an effort to address the educational deficit in this field.

Learning objectives

The learning objectives of the SSM in high altitude medicine are presented in Table 6.1, so that by the end of the module the student is expected to be able to:

Table 6.1 Learning objectives of SSM in high altitude medicine

1. Appreciate historical aspects of high altitude medical expeditions
2. Understand genetic adaptations of Tibetan and Andean populations
3. Demonstrate knowledge of physiological effects of high altitude exposure
4. Understand the process of altitude acclimatisation
5. Discuss the effects of high altitude on sleep
6. Describe the pathophysiology of acute mountain sickness, high altitude cerebral oedema and high altitude pulmonary oedema
7. Recognise the clinical presentation of high altitude illness
8. Discuss the management of high altitude illness
9. Understand the indications and contraindications for the use of acetazolamide, dexamethasone and nifedipine in the management of high altitude illness
10. Discuss the aetiology and clinical features of chronic mountain sickness
11. Advise patients with pre-existing illness on safe travel to high altitude
12. Discuss the complications of commercial air travel

Pedagogical approach

A 10-week SSM requiring a minimum of 50 hours of notional student learning time was designed. Students were required to submit a testimonial outlining their previous experience of high altitude environments and their motivation for pursuing this SSM. Twenty-two students were selected in the first year of the programme on the basis of their applications. They were provided with an e-handbook posted on Blackboard® which gave details of the learning objectives, teaching methods, assessments, practical sessions, web resources and a recommended reading list.

Students received a minimum of 2 hours of contact time with their supervisor per week. Scheduled sessions included lectures, case discussions, and

a practical class demonstrating use of a portable hyperbaric chamber. Students selected 2 assignment topics from a list of 20, one written in essay format, and the other in an alternative format such as an information leaflet. A 10-minute viva voce examination assessed the remaining learning objectives. To conclude the SSM the students participated in a team-building field trip to a local mountain in the West of Ireland in testing weather conditions.

Module evaluation

Seventy-eight percent (n=17) of the students had never travelled to high-altitude destinations previously. 83% (n=18) of students rated their knowledge of high altitude illness as "poor" or "very poor" prior to completing the SSM. All of the students believed that the SSM provided them with the knowledge necessary to recognise high altitude illness, while 94% (n=21) believed that the SSM equipped them with the skills necessary to manage high altitude illness in a wilderness environment. Fifty percent (n=11) of the students identified the case studies sessions as the most beneficial element of the module. Forty four percent (n=10) of students stated that high altitude medicine should have a presence for all students in the core undergraduate curriculum. Overall, 94% (n=21) of students expressed an increased interest in high altitude medicine as a result of the SSM. The student who achieved the highest mark in the SSM was awarded a scholarship to attend an Expedition Medicine course in the UK.

Author's note

The SSM in high altitude medicine has been delivered to over 60 first year medical students at the School of Medicine, National University of Ireland, Galway, since it was first designed, and the content has evolved to incorporate weekly student-led presentations on the health risks associated with travel to a variety of mountains at very high or extreme altitude, a student-led journal club, a visit to an altitude training hypoxic centre at the University of Limerick[550], and delivery of the first student-led Medical Grand Rounds presentation on the subject of high altitude illness at Galway University Hospitals.

A novel SSM in Travel Medicine has also been designed which introduces students to the general health risks associated with international travel as well as discussing specific regional travel health risks. The students are supervised in organising a travel health awareness day on the University campus, and they are guided in the development of research proposals on a wide range of topics, to focus their minds on research priorities in travel medicine. Furthermore, each student is enrolled as a student member of the Travel Medicine Society of Ireland and is invited to attend its regional educational seminars, thus seeding the Society with the next generation of travel medicine specialists.

Conclusion

The use of special study modules is a flexible and educationally desirable tool for introducing undergraduate medical students to travel medicine and its subspecialties, including high altitude medicine. There is scope for extending this educational initiative to embrace interdisciplinary learning in travel health which includes nursing and pharmacy students, and for designing a common European undergraduate curriculum in travel medicine, in partnership with the Faculty of Travel Medicine in Scotland and the steering group of the Northern European Conference on Travel Medicine. Efforts are underway to achieve these objectives.

6.2. Development of a novel educational format in travel medicine

As Chair of the scientific committee for the 4th Northern European Conference on Travel Medicine (NECTM4), hosted by the Travel Medicine Society of Ireland in Dublin in 2012, I designed and piloted a novel workshop format which aimed to promote greater access to a diverse range of learning opportunities for delegates and to facilitate greater levels of interaction between expert and non-expert delegates. The format was successfully adopted at NECTM in Dublin, Ireland in 2012 (Table 6.2), and in Bergen, Norway in 2014. The scientific committee for the 2016 NECTM, to be held in London, England, has also included the original OSKE format in their scientific programme.[551] In an effort to introduce the format to the 12 NECTM partner societies, invited contributors and delegates, I drafted the following set of frequently asked questions.

Frequently asked questions for OSKE workshops (NECTM4, 2012)

1. ***What does "OSKE" stand for?***

OSKE stands for "Objective Structured Knowledge Exchange". It is a novel concept developed by the scientific committee of NECTM4 as an alternative to the traditional workshop found in many conference programmes. Medical educators (and students) will already be very familiar with the term OSCE which stands for "Objective Structured Clinical Examination" and upon which the format for the OSKE is based.

2. ***What is the aim of the OSKE at NECTM4?***

The OSKE aims to provide delegates with an opportunity to learn from passionate healthcare professionals with a special interest in their topic and to interact with these "facilitators" in a fun and friendly small group context. Conventional workshops often do not allow this level of interaction as the groups are usually

much larger. Delegates should leave their OSKE session stimulated and updated on a range of relevant travel health topics.

3. *How many OSKE sessions will there be?*

In order to accommodate up to 900 delegates NECTM4 will have 4 OSKE sessions, 1 on Wednesday June 6th 2012, 2 on Thursday June 7th 2012, and 1 on Friday June 8th 2012. Topics will be different at each OSKE session, with the exception of day 3 when each of the 3 parallel OSKE circuits will cover continental travel health risks, albeit delivered by different facilitators.

4. *What is the duration of each OSKE session?*

Each OSKE session comprises 3 parallel circuits held in different rooms. Each circuit includes 4 stations of 15 minutes duration each. A whistle will sound when delegates have spent 15 minutes at each station. A further 3 minutes will be allowed between stations to enable groups of delegates to move around the OSKE circuit.

5. *How many delegates will attend each OSKE session?*

The scientific committee has capped each OSKE group at 20, which means that each circuit will have 4 groups of 20 delegates occupying the four corners of a large room. On day 3 each OSKE will comprise 3 stations of 25 minutes duration each. Since there are three parallel circuits, 240 delegates will participate in each OSKE session (180 on day 3). As there will be 4 OSKE sessions at NECTM4, we can accommodate up to 900 delegates. The number of delegates per group may vary depending on the number of delegates who register for NECTM4.

6. ***How do delegates choose which OSKE to attend?***

Upon registration at www.nectm.com delegates are invited to select ONE OSKE session from the four available. Within this session the delegate must choose ONE circuit only, i.e. everyone will learn about 4 topics of interest (or 3 topics if they choose OSKE session 4 on day 3). When 20 delegates have chosen an individual circuit, that circuit will be marked as FULL on the website registration page and delegates will be asked to choose an alternative circuit. The earlier a delegate registers the more likely he/she is to secure a place in their preferred circuit.

7. ***Will delegates not be frustrated if they cannot attend their preferred OSKE session?***

Possibly, but we think that all of the OSKE circuits are interesting and there is something to suit all delegates. With traditional workshops it has never been possible to accommodate every delegate's first preferences.

8. ***Why include so many OSKE topics?***

Travel medicine encompasses many diverse themes which it is not possible to address comprehensively in a 3 day conference. We hope that the OSKE will be of educational value to delegates and that it will complement the core scientific programme to the satisfaction of delegates.

9. ***What is the format of each OSKE session?***

When delegates receive their conference bag and name badge at the registration desk they will find details of the day, time and room for their chosen OSKE circuit on their badge. When delegates arrive for their OSKE a list on the room door will direct them to a start station where they will join up to 19 other delegates.

Invigilators will be on hand to provide orientation as necessary. A whistle will sound to signal the beginning of the session. Delegates will stand (with the option of sitting) at each of the 4 stations where a facilitator will present useful information and encourage group participation. Delegates will proceed in clockwise fashion to the next station (numbered I-IV) when a second whistle blows, and so on, until they have completed all 4 stations in a 75 minute session.

10. How have OSKE facilitators been selected for NECTM4?

The scientific committee recruited OSKE facilitators following the results of a survey sent to all of the NECTM partner organisations in which colleagues were asked to express a preference for a range of topics which had been previously agreed by members of the scientific committee. In addition, where the scientific committee was aware of individuals with special expertise and/or teaching ability, these colleagues were contacted directly and invited to participate.

11. Is there a 'one size fits all' approach to OSKE stations?

We encourage facilitators to be creative and original and not to be constrained by too rigid a formula for their OSKE. The purpose is to stimulate, transmit knowledge in a memorable fashion and encourage interaction and the exchange of knowledge between members of each OSKE group. Different OSKE topics will favour a different approach and different facilitators will have their own style of presentation. This is perfectly acceptable. We expect that there will be a good deal of post-OSKE discussion where delegates will compare their educational experiences in different circuits.

12. What is expected of each OSKE facilitator?

You should prepare well for your OSKE station. You should be in command of your topic. You should be fully up to date and you should be willing to discuss

controversial aspects of your topic with a well informed audience. It is an advantage if you can entertain your group, but at the least we hope that you will leave your group feeling invigorated and enthused. Above all else, try to communicate your passion for your subject for this is one of the hallmarks of an effective teacher.

13. Can you give us an example of how we might construct a typical OSKE station?

I will personally be facilitating three OSKE stations. For the "Travelling with Diabetes" station, I plan to introduce the delegates to a case study taken from a diabetes clinic involving a type 1 diabetic travelling with a complex itinerary. The group will then be invited to suggest how this traveller's pre-travel consultation should proceed. I will make reference to the recent literature in this subject and I will quote some guidelines. Delegates will be asked to share their most challenging experiences with diabetic travellers. I will end by pointing to gaps in the relevant travel medicine literature. All of this will be delivered in 15 minutes. It is just as well that learners have short attention spans.

14. Can I use slides or props at my station?

We would ask that you try to avoid where possible the need for a laptop so as not to slip into a didactic lecture mode. You may wish to show laminated images or laboratory test results which the group could pass around or you may wish to use a poster design to present your topic. In some cases you may use physical props, such as insect repellents or mosquito bed nets to illustrate your points. If you have special audiovisual or equipment needs for your station, please inform our conference secretary at least a month before the conference so that we can make the necessary arrangements.

15. Will I not get bored saying the same thing to four groups of delegates?

If you have a passionate interest in your topic and if you succeed in capturing your audience's attention, then you (and they) should be far from bored. Do not expect to have to repeat the same thing to all four groups. Depending on your interaction with the groups, you might choose to shift your focus from group to group. We have kept the format as flexible as possible in this regard.

16. What if my groups have recognised experts in my topic?

It is likely that delegates will not choose circuits containing topics in which they are expert but even if they do, do not worry as this will give you an exciting opportunity to generate group discussion by involving the expert delegate, who should be more than willing to share his/her experience and wisdom.

17. Do I need to have my OSKE station approved by the scientific committee?

No, but please do contact our conference secretary if you have specific requests or useful suggestions. The secretary will pass on your communication to the chair of the scientific committee as appropriate.

18. Will the OSKE format be used in future NECTM conferences?

This will depend on the success of this format at NECTM4 and upon your dedication in facilitating a fascinating and well informed discussion at your station.

Table 6.2 OSKE topics delivered at NECTM4, Dublin 2012

Publishing in travel medicine
Preparing the VFR traveller
Travel related sexually transmitted infections
Travelling with diabetes
Faculty of Travel Medicine Glasgow
Ticks and travellers
Probiotics and travellers' diarrhoea
Remote dentistry
Tropical dermatology
Solar damage in travellers
Traveller security
Medico-legal aspects of travel medicine practice
Preparing athletes for international travel
Risks of adventure sports travel
Schistosomiasis
Acetazolamide at altitude
Assessing the returned traveller
Insect repellents
Cruise-ship medicine
Diploma in Travel Medicine RCPS (Glasgow)
Asylum seekers' healthcare
Running a travel medicine clinic
TB in travellers
Aviation medicine
Global travel trends
Medical tourism
Preparing the elderly traveller
The pregnant or breast-feeding traveller
Snow tourism
Emerging tropical infectious diseases
Managing needle phobias in travel clinics
Rabies prophylaxis
Towards a curriculum in global international health
Update on dengue Infection
Using a portable hyperbaric chamber at altitude
Travel to South America
Travel to the Indian Subcontinent
Travel to Africa

6.3. Travel Medicine in Latin America

The following short article arose from a research project I invited Brazilian medical student scholars on the Science without Borders programme at the National University of Ireland, Galway to complete in the summer of 2014. I wish to acknowledge their assistance in retrieving and translating research articles published in the Portuguese language. The article attempts to compare the practice of travel medicine in Europe (specifically the British Isles), with that in Latin America (specifically Brazil), and it summarises the extent to which travel medicine, or emporiatrics, has already developed as a medical specialism.

Travel Medicine Practice, Education and Research in Brazil – Current State and Future Perspectives

Introduction

International travel from developed countries has increased rapidly in recent decades. The World Tourist Organization estimates that international tourist arrivals will reach 1.8 billion by 2030.[552] International tourist arrivals in the emerging economy destinations of Latin America, Asia, and Africa will grow twice as rapidly as those of developed economy destinations. Leisure is the most common reason for travelling overseas from the British Isles. Other reasons for travel include business trips, international sports activities, medical tourism, and humanitarian aid-work. Accidental injury is the commonest cause of travel-related death in younger age groups, while cardiovascular disease accounts for most of the illness occurring in older travellers. Vaccine-preventable diseases cause a relatively minor proportion of travel-related mortality but are responsible for significant morbidity.

Scope of travel medicine

The travel health-care provider requires knowledge of the epidemiology, recognition and prevention of travel-related infectious diseases, including tropical infectious diseases; the indications, contraindications and administration of travel vaccinations; the prevention and management of non-infectious travel health risks including those which may affect the traveller with pre-existing medical conditions; and the identification of disease in returned travellers. The quality of pre-travel health-care depends on conducting a comprehensive and individualised risk assessment of the proposed travel itinerary taking account of the traveller's medical history, concurrent medications, allergies and immunisation history (Figure 6.1). Consideration should be given to seasonality, mode of travel, planned activities, type of accommodation, and duration of travel. Preventive advice is tailored to the specific needs of the individual traveller but generally includes a discussion of the nature of vaccine-preventable travel-associated illness, prevention and self-treatment of travellers' diarrhoea, and the prevention of malaria through mosquito bite avoidance measures and prescription of malaria chemoprophylaxis.[553]

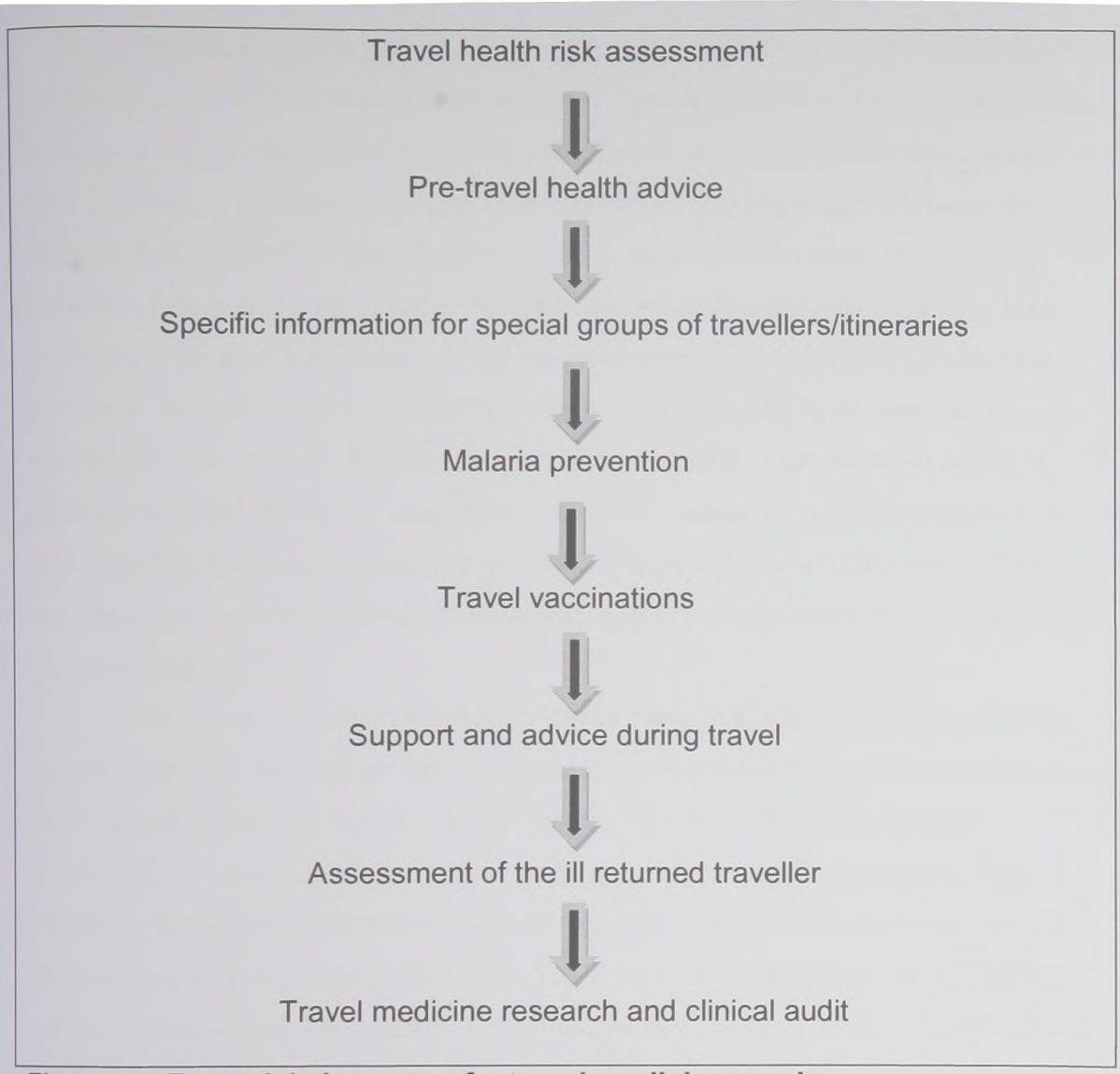

Figure 6.1 Essential elements of a travel medicine service

Attention is given to personal safety and security precautions, the risks of sex tourism and the avoidance of sexually transmitted infections. Environmental illness, including heat and cold-related injury, high-altitude illness, barotrauma associated with scuba-diving, and drowning risks associated with rip currents and jellyfish envenomations, must also be addressed. For some travellers, advice on minimising jet lag, travel-related deep vein thrombosis and motion sickness will also be indicated. Most pre-travel consultations will include the provision of

detailed verbal information on the avoidance and management of potentially fatal rabies exposure.

Some travellers will be advised to bring travel medical kits when travelling for prolonged periods in resource-poor settings. Travel health and medical evacuation insurance will be recommended to all travellers and specific guidance provided on how to access competent medical care overseas. The International Association for Medical Assistance to Travellers provides an excellent service to travel health professionals giving such advice. Some travel medicine providers may provide emergency contact information in the event of a medical emergency occurring overseas. Special groups of travellers will benefit from highly specialised advice derived from a detailed knowledge, both of the traveller's pre-existing medical condition and the effects of travel thereon. Such groups include the pregnant and breastfeeding traveller, the elderly traveller, the traveller with diabetes mellitus, families travelling with children, the immunocompromised traveller, and the disabled traveller.[554]

A relatively new phenomenon in travel medicine is that of medical tourism, whereby patients travel from developed to developing countries to receive medical care, including surgery and stem cell therapy[555], before returning to their homeland. In some cases, the travel medicine specialist will accompany the travellers, for example as team physician, health-care worker accompanying a pilgrimage group or working for a non-governmental organisation, or expedition doctor. Considerable knowledge of the health-care capacity and limitations of the host country is required in such cases. A planned post-travel assessment may be conducted in selected travellers, for example in aid workers or expatriates. The non-specialist travel medicine practitioner will be required to assess returned travellers and refer appropriately to infectious diseases experts as well as alerting public health officials where a suspected disease outbreak may be imminent. Psychological debriefing will be required for some returned travellers, including those travellers who have had to be repatriated owing to psychiatric reasons.

Travellers are also recognised as the means by which many new and emerging infectious diseases circumnavigate the globe. The introduction of novel pathogens may have both profound consequences for the health systems of receiving countries and detrimental long term economic effects. Examples from the last 20 years include HIV/AIDS, the spread of multi-drug resistant bacteria,

and the recent outbreaks of Ebola viral disease in West Africa. In the last decade we have witnessed significant public health problems associated with travellers who imported SARS and, more recently, H1N1 influenza and MERS-CoVe viral infections.

Travel medicine in the British Isles

In the British Isles, medical practitioners who practise travel medicine are drawn from a diverse range of professional backgrounds, including General Practitioners, Consultant Physicians specialising in Infectious Diseases or Tropical Medicine, Consultants in Public Health, and specialists in Occupational Medicine. Nurse Practitioners have equally varied backgrounds, and the Royal College of Nursing in the United Kingdom has published standards for practice in travel health.[556] In 2012 the Faculty of Travel Medicine at the Royal College of Physicians and Surgeons of Glasgow in the UK published its standards for the practice of travel medicine in the British Isles.[557]

The Diploma in Travel Medicine offered by the Royal College of Physicians and Surgeons of Glasgow was the first academic training programme leading to a recognised qualification in travel medicine. Entry to the Membership of the Faculty of Travel Medicine examination occurs through the Diploma in Travel Medicine examination or the International Society of Travel Medicine Body of Knowledge Certificate examination (Table 6.3). Elsewhere in the UK, both the London and Liverpool Schools of Tropical Medicine and Hygiene offer Diploma and Masters courses in tropical medicine.

Table 6.3 Body of knowledge of the International Society of Travel Medicine[558]

Epidemiology
Immunology/Vaccinology
Pretravel assessment/Consultation
Patient evaluation
Special populations
Special itineraries
Prevention and self-treatment
Diseases contracted during travel
Diseases associated with:
Vectors
Person-to-person contact
Ingestion of food and water
Bites and stings
Water/environmental contact
Other clinical conditions associated with travel
Occurring during or immediately following travel
Associated with environmental factors
Threats to personal security
Psychological and psycho-social issues
Post-travel assessment
Screening
Triage
Diagnosis
Management
Administrative and general travel medicine issues
Medical care abroad
Travel clinic management
Travel medicine information/resources

Within the United Kingdom, authoritative websites dealing with travel health issues include those administered by the National Travel Health Network and Centre of the Department of Health, and Travax administered by Health Protection Scotland. The Foreign and Commonwealth Office gives guidance with respect to wider travel-related issues that impact on health such as personal security, country-specific information on travel risks, and consular advice. The British Global and Travel Health Association aims to promote a multi-disciplinary approach to travel health for the various disciplines involved in promoting the health of travellers by providing a forum for discussion, information exchange and education, as well as stimulating research on travel health issues. The Travel Medicine Society of Ireland has a similar role in the Republic of Ireland.

Travel medicine in Brazil

Travel medicine has only recently been established as a scientific discipline in Latin America.[559] While travel medicine practice in Brazil began in 1997, there are few reports in the literature on travel health issues affecting outward Brazilian travellers. Significant attention has been given to the preparation of inward visitors to Brazil attending major international sporting events.[560] The purpose of the current study was to explore the origins and development of travel medicine practice in Brazil, to compare travel medicine in Brazil with that in the British Isles, and to anticipate the future potential for travel medicine delivery, education and research in this large Latin American nation.

Original and review articles published in English and Portuguese in the past 10 years and which related to travel medicine in Brazil were accessed in the literature databases PubMed and SciELO, using the keywords "travel medicine in Brazil, *medicina de viagem*, *saúde de viajante*, and traveler health in Brazil". Article reference lists were searched in order to yield other relevant publications. Websites relevant to travel medicine practice in Brazil were also studied. A total of 74 relevant articles were retrieved, 14 of which related directly to travel medicine or travel health.

According to the Brazilian Ministry of Tourism, the number of travellers from Brazil, both domestic and international, increased from 43 million to 50 million between 2007 and 2010.[561] Approximately 15% of Brazilian travellers engage in

international travel. Despite this, few reports exist regarding the health problems occurring in Brazilian travellers. One report described a 13.4% incidence of travellers' diarrhoea among travellers from the North-eastern region of Brazil.[562] Faculty members of a large Brazilian university, travelling mostly for business purposes, had a self-reported incidence of travel-related health problems of 13.6%.[563] Most such health problems related to the occurrence of respiratory tract infections. There was a low awareness of travel health risks, and 30% of the respondents travelled without health insurance protection. The authors advocated the implementation of health advice programs which would raise faculty awareness of the health risks associated with travel.

The first documented travel medicine service developed in Brazil was the Cives Information Center on Health for Travelers (http://www.cives.ufrj.br/), which was established in 1997 at the Faculty of Medicine of the Federal University of Rio de Janeiro.[564] Additional travel medicine services arose at the Emílio Ribas Infectious Diseases Institute in São Paulo, and at the Travelers' Clinic of Hospital das Clínicas, at the University of São Paulo School of Medicine. Lo and colleagues at the Travelers' Clinic of Hospital das Clínicas published a profile of travellers attending their clinic for pre-travel medical advice.[565] The median age of travellers was 33.5 years, and the majority (51%) travelled for business purposes. The most frequently visited destinations were Africa (47%), Asia (31.7%), and South America (21.4%). The travel vaccinations which were administered most frequently were typhoid, diphtheria-tetanus, hepatitis A, hepatitis B, and yellow fever.

The 2001 Brazilian Infectious Diseases Congress in Rio de Janeiro and the 2002 Congress of the Brazilian Society of Tropical Medicine both hosted round-table discussions on travel medicine in Brazil. A symposium devoted to travel medicine took place at the Emílio Ribas Infectious Diseases Institute in São Paulo in 2002. The First Conference on Travel Medicine and the inaugural Symposium of the Brazilian Society of Travel Medicine were held in 2008. Rio de Janeiro attracted the Third Latin American Congress of Travel Medicine in 2012. Matos and Barcellos concluded from a literature review of 41 travel health-related articles that a need existed to direct health care policies at tourists, which would include a surveillance and notification system for tourists.[566]

In 2010, new travel medicine clinics appeared at the University of São Paulo at Ribeirão Preto and the University Federal de São Paulo, both of which offer pre-travel health consultations and diagnostic services for returned travellers. Chaves and colleagues highlight examples of disease outbreaks affecting travellers within Brazil, including outbreaks of malaria, Chagas disease, yellow fever, and influenza A (H1N1).[567] The same author reported two cases of imported Chikungunya virus infection in Brazilian travellers returning from Indonesia and India.[568] The specialist travel medicine clinics in São Paulo also provide continuing education in travel medicine and have contributed to the discussions regarding the regulation of travel medicine services throughout Brazil. Table 6.4 summarises the organisations involved in travel medicine education and training in the British Isles and Brazil.

Table 6.4 Agencies delivering travel medicine education and training in the British Isles and Brazil

British Isles*	Brazil
Faculty of Travel Medicine	Latin American Society of Travel Medicine
British Global and Travel Health Association	Sociedade Brasileira de Medicina Tropical
Travel Medicine Society of Ireland	Cives Information Center on Health for Travelers
National Travel Health Network and Centre	Emílio Ribas Infectious Diseases Institute
Health Protection Scotland	Travelers' Clinic of Hospital das Clínicas University of São Paulo at Ribeirão Preto
Royal College of Nursing	University Federal de São Paulo
Foreign and Commonwealth Office	

*The designation "British Isles" encompasses the islands of Great Britain, Ireland, and over 6000 smaller isles.

In an editorial in 2003, Igreja argued that travel medicine should be incorporated into the work of the infectious disease specialist in Brazil.[564] Nurses practising in Brazil are already involved in the administration of yellow fever vaccine in accordance with International Health Regulations of the World Health Organization. An expanded role for nurses in the emerging field of travel health, similar to that observed in the British Isles, has been proposed.[569]

Conclusion

The standards of medical care given to travellers, before, during and after travel should be as high as those practised in other branches of medicine and surgery. Internationally accepted standards of best practice, already in existence in the British Isles, should be adopted in Brazil and formal accredited training should become mandatory for all health-care professionals who provide medical advice to travellers. Assurance of the competence of travel medicine providers should be subject to national regulation by a competent authority. The travelling public should also be educated to recognise and minimise the health risks of travel. In the case of a large country such as Brazil, this includes both domestic and international travellers. Brazil has the potential to become one of the global leaders in travel medicine practice, education and research.

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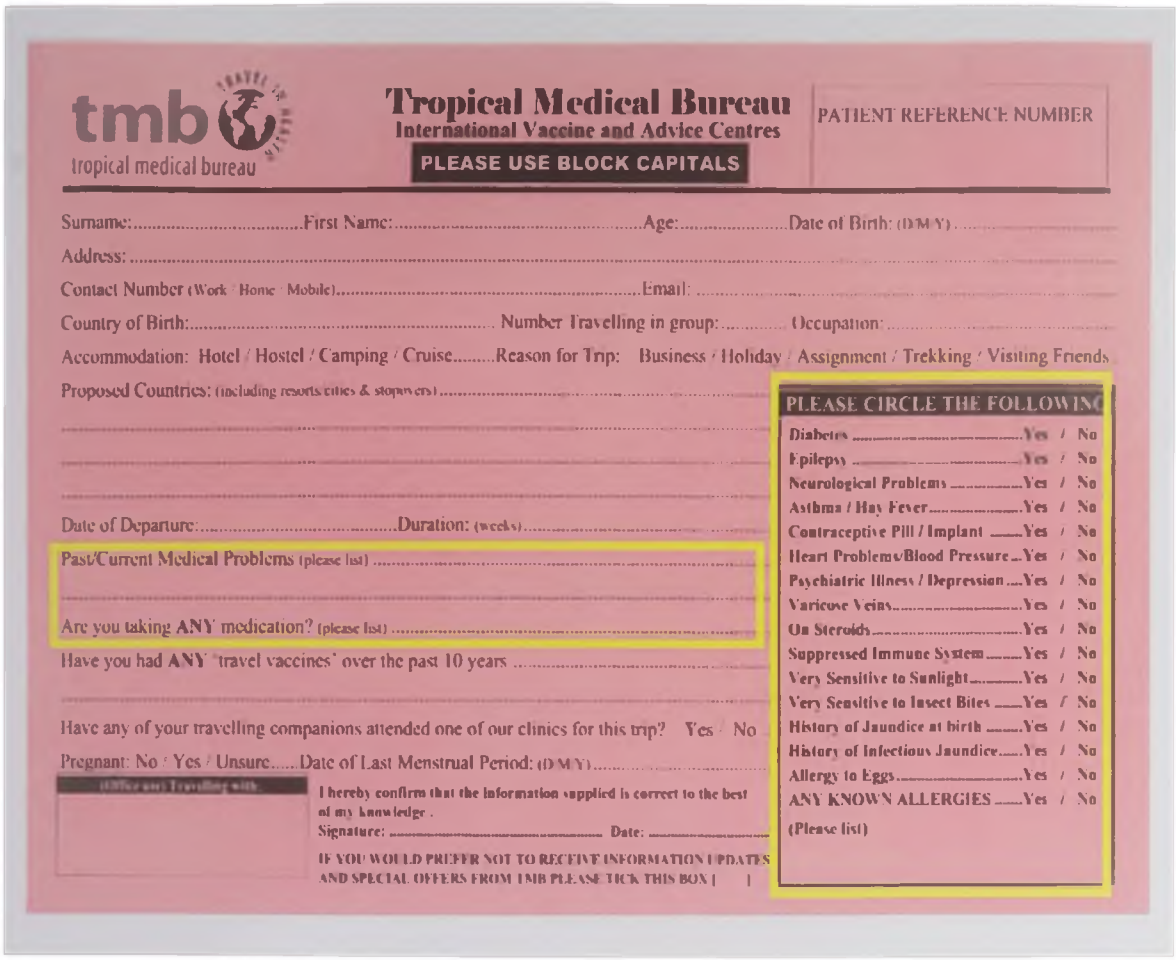
Appendix 1: Pre-travel medical registration card



tmb tropical medical bureau

Tropical Medical Bureau
International Vaccine and Advice Centres
PLEASE USE BLOCK CAPITALS

PATIENT REFERENCE NUMBER

Surname:.....First Name:.....Age:.....Date of Birth: (D/M/Y).....

Address:.....

Contact Number (Work / Home / Mobile).....Email:.....

Country of Birth:..... Number Travelling in group:.....Occupation:.....

Accommodation: Hotel / Hostel / Camping / Cruise.....Reason for Trip: Business / Holiday / Assignment / Trekking / Visiting Friends

Proposed Countries: (including resorts/cities & stopovers).....

.....

.....

.....

Date of Departure:.....Duration: (weeks).....

Past/Current Medical Problems (please list).....

.....

Are you taking ANY medication? (please list).....

Have you had ANY 'travel vaccines' over the past 10 years .....

.....

Have any of your travelling companions attended one of our clinics for this trip? Yes / No

Pregnant: No / Yes / Unsure.....Date of Last Menstrual Period: (D/M/Y).....

(Other) Travelling with:

I hereby confirm that the information supplied is correct to the best of my knowledge .

Signature:..... Date:.....

IF YOU WOULD PREFER NOT TO RECEIVE INFORMATION UPDATES AND SPECIAL OFFERS FROM TMB PLEASE TICK THIS BOX [ ]

PLEASE CIRCLE THE FOLLOWING

Diabetes	Yes / No
Epilepsy	Yes / No
Neurological Problems	Yes / No
Asthma / Hay Fever	Yes / No
Contraceptive Pill / Implant	Yes / No
Heart Problems/Blood Pressure	Yes / No
Psychiatric Illness / Depression	Yes / No
Varicose Veins	Yes / No
On Steroids	Yes / No
Suppressed Immune System	Yes / No
Very Sensitive to Sunlight	Yes / No
Very Sensitive to Insect Bites	Yes / No
History of Jaundice at birth	Yes / No
History of Infectious Jaundice	Yes / No
Allergy to Eggs	Yes / No
ANY KNOWN ALLERGIES	Yes / No

(Please list)

Key sections relating to the traveller's past medical history and medication usage are outlined. Reproduced with the kind permission of Mr. Andrew Lewis, CEO of Tropical Medical Bureau, Ireland.

Appendix 2: The Lake Louise Acute Mountain Sickness Score[†]

Self-report questionnaire

1. Headache	0	No headache
	1	Mild headache
	2	Moderate headache
	3	Severe headache, incapacitating.
2. Gastrointestinal symptoms	0	No gastrointestinal symptoms
	1	Poor appetite or nausea
	2	Moderate nausea or vomiting
	3	Severe nausea and vomiting, incapacitating.
3. Fatigue and/or weakness	0	Not tired or weak
	1	Mild fatigue/weakness
	2	Moderate fatigue/weakness
	3	Severe fatigue/weakness, incapacitating.
4. Dizziness/lightheadedness	0	Not dizzy
	1	Mild dizziness
	2	Moderate dizziness
	3	Severe dizziness, incapacitating.
5. Difficulty sleeping	0	Slept as well as usual
	1	Did not sleep as well as usual
	2	Woke many times, poor night's sleep
	3	Could not sleep at all.

Clinical assessment

6. Change in mental status	0	No change in mental status
	1	Lethargy/lassitude

[†] A score of three points or greater on the acute mountain sickness self-report questionnaire alone, or in combination with the clinical assessment score, constitutes acute mountain sickness.

2 Disoriented/confused
3 Stupor/semi-consciousness
4 Coma.

7. Ataxia (heel-to-toe walking) 0 No ataxia
1 Manoeuvres to maintain balance
2 Steps off line
3 Falls down
4 Can't stand.

8. Peripheral oedema 0 No peripheral oedema
1 Peripheral oedema at one location
2 Peripheral oedema at two or more locations.

Functional score

Overall, if you had any symptoms, how did they affect your activity?

0 No reduction in activity
1 Mild reduction in activity
2 Moderate reduction in activity
3 Severe reduction in activity (e.g. bed rest).

Appendix 3: Altitude health risks questionnaire

Gender: Male / Female

Age Group: <20 20-25 26-30 31-35 36-40 >40

1. **How many weeks until you depart?**
   <1 wk 1-2 wks 2-3 wks >3wks

2. **Destination(s):** Alps Kilimanjaro Inca Trail Himalayas Other _____

3. **Duration of trip**: <2 wks 2-3 wks 3-4 wks >4 wks

4. **Number of people in group**: <55-10 11-15 >15 Don't know (DK)

5. **Is the trek guided?** Yes / No / DK

6. **Do you have travel insurance?** Yes / No / DK

7. **What is the maximum altitude you intend to reach during the trek?**

   <10,000ft 10,000-15,000ft 15,000-20,000ft >20,000ft DK

8. **How many days will it take you to reach this altitude?** <2 2-4 >4 DK

9. **Will the expedition involve technical climbing?** Yes / No / DK

10. **Have you experienced high altitude before?** Yes / No / DK

11. **If "Yes", did you suffer from high altitude sickness?** Yes / No / DK

12. **What is the maximum altitude you have ever reached?** _____ / DK

13. **To the best of your knowledge, is there a risk of any of the following health problems occurring during your trek?**

Diarrhoea	Yes / No / DK	**Frostbite**	Yes / No / DK
Rabies	Yes / No / DK	**Dehydration**	Yes / No / DK
Malaria	Yes / No / DK	**Blisters**	Yes / No / DK
Sunburn	Yes / No / DK	**Disturbed sleep**	Yes / No / DK

14. Do you know any ways to reduce the risk of altitude sickness? Yes/ No

If "Yes", please give details:

_____

15. Do you know any of the symptoms of altitude sickness? Yes / No

If "Yes", please give details:

_____

16. If a person is unfit, are they more likely to suffer from altitude sickness? Yes / No / DK

17. What are your main sources of information about the health risks of travel to high altitude?

Internet Books Friends GP Travel Medicine Clinic

18. If one of your climbing companions experienced severe altitude sickness, what would you advise? (You can choose more than one option)

Rest Ascend Descend Medication Helicopter evacuation

Thank you for completing this questionnaire. Enjoy your trip!

Appendix 4: Online Educational Resources in High-Altitude Medicine

1. The International Society for Mountain Medicine (www.ismmed.org/) encourages research and the dissemination of practical information about high-altitude medicine.

2. The Wilderness Medical Society (www.wms.org/) aims to improve knowledge in health matters related to wilderness environments.

3. The Himalayan Rescue Association (www.himalayanrescue.com/) is a voluntary organisation that aims to reduce the number of casualties in the Nepalese Himalayas.

4. Medical Expeditions (www.medex.org.uk/) is a research charity dedicated to investigating the mechanisms underlying high-altitude illness.

5. The High Altitude Medicine Guide (www.high-altitude-medicine.com) provides up-to-date information for doctors and laypersons on the prevention, recognition and management of high-altitude illness.

6. The International Mountaineering and Climbing Federation (www.uiaa.ch/) is the governing body for climbing organisations worldwide.

7. The CIWEC clinic (www.ciwec-clinic.com/) provides treatment of high-altitude illness for trekkers in Kathmandu, Nepal.

Appendix 5: Practical use of a portable hyperbaric chamber in the management of severe high altitude illness

Figure A.1 The author's inflated portable hyperbaric chamber

A portable hyperbaric chamber is an air-impermeable, mummy-shaped, acoustically transparent PVC bag (Figure A1) into which we place victims who are suffering from severe acute mountain sickness (AMS), high altitude cerebral oedema (HACE) or high altitude pulmonary oedema (HAPE). Portable hyperbaric chambers effect a physiological descent when they are inflated to a significant pressure above the pressure of the ambient atmosphere. In this way they simulate a lower altitude, thereby increasing the partial pressure of oxygen in the patient's arterial blood and producing clinical improvement. It is essential that as many members as possible of a high altitude trekking party practise inflating and deflating the portable hyperbaric chamber before it is used in a wilderness setting. It is important to remember that use of the portable hyperbaric chamber is NOT a substitute for prompt descent where this is possible. There are several portable hyperbaric chambers available commercially. The video demonstration available at **http://www.youtube.com/watch?v=5D3bgP8ZHyI**, which I prepared with my medical students completing the special study module in high altitude medicine at the National University of Ireland, Galway, uses the portable altitude

chamber or PAC which was developed by Dr. Jim Duff from Australia. The chamber is transported in a light protective bag which also includes a foot pump, connecting hose and repair kit. An external anchor point allows the chamber to be secured on steep ground. The chamber should be rolled out on as flat a surface as possible which should be free from rocks or other sharp objects. The PAC has three valves – an inlet valve, a variable pressure release valve and an auto release valve. One end of the hose is connected to the inlet valve and the other end to the foot pump. The variable pressure release valve is closed. Take care when opening the chamber not to damage the heavy zipper. Open the zipper completely to make it easier for the victim to enter the chamber. To prepare the operating area, sleeping mats should be placed under and inside the chamber. An open sleeping bag should be placed inside the chamber. The chamber should be positioned in the shade during the daytime or covered with sleeping bags at night when temperatures may be below zero at high altitude. A pillow is also placed in the chamber for the victim's comfort. Before the victim is helped into the chamber the operator should explain how the chamber works and how to equalise middle ear pressure by performing the Valsalva manoeuvre. The victim should flex his separated knees and hold the bag off his face as it is being inflated. The victim should wear a hat as the cold incoming air may be uncomfortable. The victim should be given a cloth to wipe the windows from the inside, a water bottle, a urine bottle and a plastic bag in case of vomiting. The operator should maintain eye contact with the victim through the windows of the chamber. An altimeter may be placed into the inside pocket window to confirm that the chamber has been pressurised when inflated. The circumferential chamber zipper is then closed gently by straddling the bag. The chamber is initially inflated rapidly by depressing the pump by hand. When the chamber wall is tensioned the chamber is pumped steadily by foot to pressurise it. A pair of ski poles may be used for balance. When the chamber wall becomes tense the rate of pumping should be slowed to give the victim time to equalise his middle ear pressure. The pumping task should be rotated between different members of the trekking party. It is important to communicate with the victim at all times. If the victim experiences ear pain, the variable pressure release valve is opened by rotating it anticlockwise and pumping stopped until the pain resolves. The variable

pressure release valve must be operated with the fingers only to avoid damaging it. Once the chamber has been fully inflated to a pressure of 2p.s.i., the automatic pressure release valve will begin to hiss like a pressure cooker. Air is felt as it emerges from the chamber. If possible the head of the chamber should be elevated to 30 degrees in cases of HAPE and HACE. If the victim is short, the end of the chamber should have been packed to prevent the victim from slipping to the end of the chamber when it is elevated. Pumping should be continued at the rate of once every 5 seconds until deflation of the chamber begins. Breaks of pumping should not be longer than 60 seconds to avoid an accumulation of carbon dioxide. After the first hour of treatment the patient is removed from the bag and reassessed. Additional cycles of simulated descent and patient reassessment are continued as needed until either the patient's clinical status has improved enough to not require further hyperbaric treatment, or he/she is capable of supervised descent having been previously incapacitated. Guidelines suggest that severe AMS requires at least 1 hour of treatment, HAPE typically requires 2-4 hours of hyperbaric treatment, and HACE may require as many as 4-6 hours of hyperbaric treatment. A simulated pressure descent graph on the side of the PAC displays the actual pressure inside the chamber when it has been fully inflated to 2p.s.i. To deflate the chamber, first cease pumping and open the variable pressure release valve by rotating it clockwise. If the victim complains of ear pain while the chamber is being deflated, the variable pressure release valve must be closed and the chamber re-inflated by pumping it until the pain subsides. The victim should be encouraged to yawn or swallow. Deflation usually takes about 3 minutes. The video clip shows the interior of the chamber from the victim's perspective. When the chamber wall loses most of its tension, the zipper should be opened gently but completely to avoid being damaged as the victim emerges from the chamber. After removing moisture from the inside of the chamber with a towel the chamber should be allowed to air dry. The pump is disconnected from the chamber and the variable pressure release valve closed. The chamber should be zipped up but not completely and rolled up from the front end taking care not to crease the windows. The victim is now ready for descent.

Appendix 6: Rabies awareness study questionnaires

Baseline questionnaire administered by physician

1. Gender:_____
2. Age:_____
3. Occupation:_____
4. Departing in ____ weeks
5. Duration of stay in Rabies endemic countries (weeks):_____
6. Countries to be visited: _____
7. Accommodation:_____
8. Activities:_____
9. Have you heard of rabies before?:_____
10. Can you get rabies in Ireland?:_____
11. How is it spread?:_____
12. What (other) animals can spread it?:_____
13. How would you recognise rabies in an animal?:_____
14. What activities would increase your risk?:_____
15. Do you ever pet dogs or cats in foreign countries?:_____
16. Were you ever bitten by an animal?:_____
17. Where?:_____
18. Are you at risk of Rabies during this trip?:_____
19. Low…moderate…high risk?:_____
20. How does Rabies affect a person?:_____
21. Is it ever fatal?:_____
22. What % of infected persons die?:_____
23. Is there any treatment for Rabies?:_____
24. How effective is that treatment?:_____
25. Can Rabies be prevented?:_____
26. How?:_____
27. Is there a vaccine available?:_____
28. If you were exposed what would you do?:_____

29. If the owner of the animal said the animal was vaccinated would you seek treatment?:_____

30. If you are vaccinated beforehand do you require any further treatment?:___

Vaccine recommended Yes/No Vaccine accepted Yes/No

If vaccine not accepted, give reason(s)_____

Follow-up questionnaire administered by nurse

When a client traveller presents to you for his/her third and final pre-travel booster of Rabies HDCV vaccine, please check if that traveller has been entered into the Rabies Study. Travellers who have participated in the study will have a red sticker on the top left hand corner of their TMB card with a number written on it. Please write the same number on the top left hand corner of this page and ask the traveller the following additional questions without prompting, recording what the traveller says in his/her own words.

1. Do you think you could be exposed to Rabies when you travel to (state name of countries to be visited)? Yes _____ No _____

2. If yes to question 1, how would you rate the extent of your Rabies risk?
   a. Low risk_____
   b. Moderate risk_____
   c. High risk_____

3. In the event of being exposed to Rabies overseas, what practical steps would you take (in sequence)?
   a. _____
   b. _____
   c. _____

Appendix 7: Rabies information leaflet inserted in travel vaccination booklet

PROTECT YOURSELF AGAINST RABIES!

- Rabies is almost invariably fatal. No effective treatment exists.
- Most developing countries are high-risk areas for rabies exposure.
- A bite, scratch or lick from a warm-blooded animal, especially dogs, cats, monkeys and bats, may transmit the rabies virus.
- Bites on the head and neck are particularly dangerous.
- If you are in the company of young children, always suspect an animal exposure if the child is found crying and has been unsupervised in the presence of animals.
- Do not pet animals. Avoid caves where bats often abound.
- Wear trousers if you are hiking or cycling. Be careful jogging in city slums.
- If you have been pre-vaccinated and become exposed to rabies, wash the wound thoroughly with soap and water, apply an antiseptic and seek IMMEDIATE medical advice. It is preferable to visit a specialised centre where possible. The wound should NOT be stitched. Inform the doctor that you have been pre-vaccinated and require 2 further does of cell-culture-derived rabies vaccine on days 0 and 3. You do NOT require rabies immunoglobulin in this situation. If this treatment is delayed it is never too late to receive it.
- If you have not been pre-vaccinated and become exposed to rabies, wash the wound thoroughly with soap and water, apply an antiseptic and seek IMMEDIATE medical advice. It is preferable to visit a specialised centre. The wound should NOT be stitched. You require rabies immunoglobulin and 4 doses of cell-culture-derived rabies vaccine on days 0, 3, 7, 14, and 28. If this treatment is delayed it is never too late to receive it.
- Request a post-exposure treatment certificate from the doctor, detailing the type and quantity of vaccine used, the manufacturer's name, batch number, expiry date, route of administration and date of application.
- The vaccination status of the animal should not be a factor in withholding post-exposure treatment.
- Inform your travel medicine practitioner when you return from your trip.

Appendix 8: The Liverpool Jet Lag Questionnaire

1. Jet lag:

How much jet lag do you have?

2. Last night's sleep. When compared with normal:

a. How easily did you get to sleep?

b. What time did you get to sleep?

c. How well did you sleep?

d. What was your waking time?

e. How alert did you feel 30 min after rising?

3. Fatigue:

In general, compared to normal, how tired do you feel at the moment?

4. Meals. Compared with normal:

a. How hungry did you feel before your meal?

b. How palatable (appetising) was the meal?

c. After your meal, how do you now feel?

5. Mental performance and mood. Compared with normal:

a. How well have you been able to concentrate?

b. How motivated do you feel?

c. How irritable do you feel?

6. Bowel activity today. Compared with normal:

a. How frequent have your bowel motions been?

b. How has the consistency been?

Appendix 9: Clinical Research Ethics Committee Approval Forms

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Merlin Park University Hospital
Ospidéal na h-Ollscoile, Páirc Mheirlinne
GALWAY UNIVERSITY HOSPITALS

Clinical Research Ethics Committee
Block B
Main Administration Building
Merlin Park Hospital
Galway.

3rd August 2007.

Dr. Gerard Flaherty
Department of Medicine
NUI
Galway.

Ref: C.A. 1234 ***Exploring Malaria Awareness In The African Visiting-Friends-And-Relatives (VFR) Population Living In The West Of Ireland***

Dear Dr. Flaherty,

I have considered the above project, and I am happy to grant Chairman's approval to proceed.

Yours sincerely,

p.p. Dr. Shaun T. O'Keeffe
Chairman Clinical Research Ethics Committee.

Merlin Park University Hospital, Ospidéal na h-Ollscoile, Páirc Mheirlinne,
Galway, Ireland. Tel: 00 353 (0)91 757631

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Merlin Park University Hospital
Ospidéal na h-Ollscoile, Páirc Mheirlinne
GALWAY UNIVERSITY HOSPITALS

Clinical Research Ethics Committee
Unit 4
Merlin Park Hospital
Galway.

15th June, 2009.

Dr. Gerard O'Flaherty
Consultant of Infectious Diseases
University College Hospital
Galway.

Ref: C.A. 255 – "Profile of Imported Tropical Illness Presenting to a Tertiary Infectious Diseases Service in the West of Ireland.

Dear Dr. O'Flaherty,

I have considered the above project, and I am happy to grant Chairman's approval for the study to proceed.

Yours sincerely,

Dr. Shaun T. O'Keeffe
Chairman Clinical Research Ethics Committee.

Merlin Park University Hospital, Ospidéal na h-Ollscoile, Páirc Mheirlinne,
Galway, Ireland. Tel: 00 353 (0)91 757631

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Appendix 11: Word Cloud Generated from Thesis