

# Caring for the vulnerable elderly global traveller

Elderly people can now be found exploring the Amazon, visiting polar regions, climbing to high altitude and adventuring into remote parts. They indulge in active leisure time activity and participate in white water rafting, para-gliding, snorkelling, horse riding and sailing while abroad. Moderate physical impairment does not deprive elderly people of the right to venture afar or indulge in active sports, but they should do so aware of potential risk to well-being.

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Elderly people constitute an enlarging proportion of Britain's population. With increasing life expectancy, they lead prolonged, relatively healthy lives. Motivated to expand personal horizons, they consider themselves fit to travel and have time and affluence for this purpose. Many seize the opportunity for extensive overseas ventures. This group fills cruise ships, travels by land and air to distant parts of the globe and makes world-wide journeys. A window of opportunity exists for 65 to 85 year olds to undertake international travel, before passing time brings declining health and physical disability. The majority visit distant family and fulfil world travel dreams, without mishap. A minority succumb to travel related illness and ill health while abroad.

In a community study of people over 65 years old, 33% had travelled from the UK within the past year and 35% of 75–80 year olds had participated in foreign travel in the preceding three year period.<sup>1</sup> Budget airline access has increased this cohort. The healthy

and less well, depart from Britain on intercontinental journeys, often with scant consideration of risk to health that world travel can bring. They travel to undeveloped countries and remote parts, where conventional emergency medical support is limited. Many venture forth, undeterred by pre-existing, chronic illness and on medication and may put their lives at risk. Few consider availability and quality of local medical resources and repatriation possibilities, when embarking on global journeys and cruises.

They depend on travel medical insurance cover for emergency protection, but this may be restrictive, environment and facility dependent. Insurers are rigorously selective with seniors who are now travelling with limited or no health insurance protection. In medical emergency, immediate first aid may be delayed, local health resources inadequate, evacuation protracted and hospitalisation unsatisfactory, with resultant chronic morbidity and mortality. Many elderly travellers do not appreciate the

limitations and high cost of health support overseas.

Vulnerable older travellers who become ill abroad, require local medical services, evacuation and repatriation. Some will never return to good health after acquiring travel induced illness. The experience will prove physically and psychologically traumatic. Involved health professionals have a responsibility to apprise them of health hazards encountered abroad. Pre-travel consultations with intending travellers provide opportunity to meet this challenge with efforts to minimise the risk and optimise protection.

Awareness of the effects of advancing age is a prerequisite for enlightened risk assessment. The fittest and most healthy older traveller has not the physical integrity or endurance of those in the prime of life. Reduction in immune, renal, cardiac and pulmonary function and declining glucose tolerance and physiological stress response place the elderly at higher risk. Pre-existing disease, plus the effects of senescence,

**Box 1:** Case history

A 78 year old man with a history of myocardial infarction and transient ischaemic attack was determined to continue a Caribbean winter cruise ship voyage although travel health insurance cover for his cardiac condition and stroke disease was unobtainable. He opted to travel uninsured and suffered a severe stroke on board ship. Disembarked by the ship doctor at the next port of call on the American, St. Thomas and transferred to hospital in the US the payment of medical and nursing care fees bankrupted him. The endeavour to meet fees and care for her husband precipitated depressive and physical illness in the spouse, who required hospitalisation herself when the patient finally returned to UK.

make seniors vulnerable to travel induced illness. Mild mental and memory impairment can precipitate confusion in stressful travel situations.

## Health status and risk

In terms of health risk, the potential older traveller can be categorised) as:

### 1. Low risk—the “young” old includes those:

- Travelling to low risk destinations
- On short-haul journeys
- Free from any pre-disposing illness.

### 2. Medium risk:

- Group 1, where travel involves environmental extremes, or tropical countries
- The “frail old”
- Those with pre-existing illness.

### 3. High risk:

- Terminally ill
- Pre-existing illness and travelling to high-risk countries
- Pre-existing illness and visiting tropical countries<sup>2</sup> environmental extremes.

Age alone is not the arbiter of fitness to travel abroad, however the over 65 years age group differ from the younger general population with adverse effects on global travel. These are:

- Heterogeneity of health status
- Age-related physiological changes
- Increased incidence of comorbidity
- Atypical disease presentations
- Increased incidence of iatrogenic illness
- Higher need of social support
- Functional disability.

## Pre-existing or chronic illness

The impact of relocation, international transit, environmental factors en route and at destination, medical risk factors of transit mode, destination, itinerary, local environment and local medical facilities require consideration by the consulting health professional.

## Effects of the ageing process

Changes occur in:

- Renal function
- Water and sodium regulation
- Temperature regulation
- Cardio-pulmonary function
- Gastro-intestinal function
- Cell-mediated immune response
- Neurological function
- Metabolic response.

These affect the older world traveller and physiological baseline should be considered by health professionals, so that advice can be given on relative health risks ie. there is 60% loss of renal function by age 65 years with decreased sodium conservation and ability to conserve water. Sweating ability and ventilatory response to hypoxia is decreased and there is increased cardiac load.<sup>3-6</sup>

Psychological factors also require consideration. The effects of stress in airports and transit can have deleterious health effects in elderly people and tip the vulnerable into cardiac failure or arrest.<sup>4</sup> Potential adverse effects of sun over-exposure, tropical infection, high altitude and environmental effects are also relevant, Some can be neutralised by advance planning by traveller and travel health professional.<sup>7</sup>

### Age

Ageing organs progressively lose function. Most have reserve ability to function beyond routine needs, but travel brings additional physiological demands eg. change in physical activity and exposure to high altitude can produce extra cardiac load.

### Ageing heart

The ageing process reduces heart muscle strength so pumping power declines, systolic blood pressure rises and maximal heart

rate decreases. The older heart—even in the very fit—is no match for a younger one during exercise or stress. During physical activity the heart must pump more blood to working muscles. In the young it increases heart rate and squeezing harder during contractions, sends more blood with each beat. With ageing, heart rate still rises, but not as high. The force of contraction during vigorous exercise increases, but not as much in older people as in the young and cardiovascular reserve diminishes. An 80 year old can increase cardiac output during exercise to two times over resting levels, however during vigorous exercise the older heart still pumps less blood overall because it cannot beat as fast as a young heart.<sup>5,8,9</sup>

### Ageing lungs

There is progressive decline of pulmonary function due to:

- Dilatation of airspaces
- Loss of elastin fibres and elastic recoil
- Diminished diffusion capacity.

Reduction of respiratory reserve with ageing often increases the risk and severity of pulmonary infections. Changes in lung and chest wall compliance are primarily responsible for age-related decreases in ventilation and corresponding decreases in gas distribution that result from collapse of small airways. Diffusing capacity declines from middle age onward, it declines at a rate of about 17% per decade in men and 15% in women. The loss of alveolar-capillary surface area decreases venous blood oxygenation, particularly under conditions of high pulmonary blood flow (eg. exercise). Partial pressure of arterial oxygen (PaO<sub>2</sub>) declines linearly with

ageing (about 0.3%/year) until age 75 years.<sup>10</sup>

### Autonomic response

Heart rate and ventilatory responses to hypoxia and hypercapnia diminish with ageing, because peripheral and central chemoreceptor responses diminish. Ventilatory response to hypoxia is reduced by 51% in healthy men aged 64 to 73 years compared with healthy men aged 22 to 30 years. Ventilatory response to hypercapnia is reduced by 41%.

### Blood and circulation

Ageing causes reduction in total body water and less fluid in the bloodstream, with decreased blood volume. Red blood cells are reduced, contributing to fatigue. Blood vessels lose elasticity and respond more slowly to change in body position with resultant postural hypotension, dizziness and falls.

### Body temperature

Temperature regulation is more difficult. Loss of subcutaneous fat makes it harder to maintain body heat. Skin changes include reduced ability to sweat. Older people find it more difficult to tell when they are becoming overheated and are at greater risk from hyperthermia or heat stroke.<sup>8</sup>

### Immunity

There is decline in immunity, with immuno-senescence, associated with increased vulnerability to infectious agents. Progressive atrophy of the thymus gland affects ability to generate cell-mediated immune response. The thymus, where T lymphocyte (“T cell”) immune cells mature atrophies and by middle age is 15% of adolescence size. T cell function decreases, causing weakening of the parts of the

immune system controlled by them. Elderly people produce fewer helper T cells and the ones they do have are less effective.

These changes bring slow, steady decrease in immunity. When the body is exposed to bacteria or micro-organisms by actual exposure or by immunisation, fewer protective antibodies may be formed, or form slower. Diminution of cell-mediated immune response leads to a progressive reduction in antigen-driven lymphocyte proliferation, a common deficit in elderly individuals.

Antibody responses to some vaccines (eg. pneumococcal, influenza) decline with increased age. Cellular immunity also declines. Immunisations eg. influenza may be less effective, and protection may not last as long. The immune system also becomes less able to detect foreign particles, and infection risk is greater.<sup>11</sup>

### Ageing kidney

The number of nephrons is reduced and overall amount of kidney tissue is diminished. Blood vessels become hardened and kidneys filter blood more slowly. Changes lead to:

- Decline in glomerular filtration rate
- Decreased urinary concentration
- Decrease in diluting ability
- Diminished urinary acidification
- Impaired potassium clearance
- Proneness to drug toxicity
- Fluid and electrolyte imbalance, especially when dehydrated.<sup>12,13</sup>

Kidneys have a built-in extra capacity. However, decreased efficiency occurs with increased workload from illness, medications, and dehydration. Dehydration can occur more readily compounded by decreased thirst sense and awareness

of over-heating. Bladder wall changes with elastic tissue replacing tough fibrous tissue make the organ less distensible. The bladder may not empty completely when urinating with continence problems.

### Skin:

Thinning occurs as rate of cell production slows in epidermis. The dermis may also become thinner with vulnerability to sunburn. Older skin has fewer sweat and oil glands, with reduced ability to sweat. Loss

of subcutaneous fat makes it harder to maintain body heat.

### Ageing brain

Two thirds of older people eventually experience some significant loss of mental lucidity with ageing.

#### Prescribing information (UK) ▼ JENTADUETO® 5 mg film-coated tablets

Film-coated tablets containing 5 mg Inagliptin. **Indication:** Jentaduo is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as monotherapy - in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment; as combination therapy - in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control - in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. **Dose and Administration:** 5 mg once daily, if added to metformin, the dose of metformin should be maintained and inagliptin administered concomitantly. When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. Patients with renal impairment: no dose adjustment required. Pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking. Elderly: no dose adjustment is necessary based on age however, clinical experience in patients > 75 years of age is limited. The safety and efficacy of inagliptin in children and adolescents has not yet been established. No data are available. Jentaduo can be taken with or without a meal at any time of the day if a dose is missed, it should be taken as soon as possible but a double dose should not be taken on the same day. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions:** Jentaduo should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Caution is advised when inagliptin is used in combination with a sulphonylurea; a dose reduction of the sulphonylurea may be considered. **Interactions:** Inagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isoenzyme CYP2C8, but does not inhibit other CYP isoenzymes. It is not an inducer of CYP isoenzymes. Inagliptin is a P-glycoprotein substrate and inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on these results and *in vivo* interaction studies, inagliptin is considered unlikely to cause interactions with other P-gp substrates. The risk for clinically meaningful interactions by other medicinal products on inagliptin is low and in clinical studies inagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glyburide, simvastatin, warfarin, digoxin or oral contraceptives (please refer to Summary of Product Characteristics for information on clinical data). **Fertility, pregnancy and lactation:** Avoid use during pregnancy. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Jentaduo therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. No studies on the effect on human fertility have been conducted for Jentaduo. **Undesirable effects:** Adverse reactions reported in patients who received inagliptin 5 mg daily as monotherapy or as add-on therapies (pooled analysis of placebo-controlled studies). The adverse reactions are listed by absolute frequency. Frequencies are defined as very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), or very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data). Very common: hypoglycaemia (combination with add-on to metformin and sulphonylurea). Uncommon: nasopharyngitis (monotherapy; combination with add-on to metformin); hypersensitivity (combination with add-on to metformin); cough (monotherapy; combination with add-on to metformin). Not known: nasopharyngitis (combination with add-on to metformin and sulphonylurea); hypersensitivity (monotherapy; combination with add-on to metformin and sulphonylurea); cough (combination with add-on to metformin and sulphonylurea); pancreatitis (monotherapy; combination with add-on to metformin; combination with add-on to metformin and sulphonylurea). Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** 28 tablets £33.20. **Legal category:** POM. **MA number:** EU/1/11/707/003. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. Prepared in September 2011.

#### UK Prescribing information ▼ JENTADUETO® (inagliptin and metformin hydrochloride) 2.5 mg/850 mg film-coated tablets and 2.5 mg/1,000 mg film-coated tablets

Film-coated tablets containing 2.5 mg inagliptin and 850 mg metformin hydrochloride or 2.5 mg inagliptin and 1,000 mg metformin hydrochloride. **Indication:** Treatment of adult patients with type 2 diabetes mellitus: as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of inagliptin and

metformin; in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea. **Dose and Administration:** The dose of Jentaduo should be individualised based on the patient's current regimen, effectiveness and tolerability, not exceeding the maximum recommended daily dose of 5 mg inagliptin plus 2,000 mg of metformin hydrochloride. For patients inadequately controlled on maximal tolerated dose of metformin monotherapy: the usual starting dose of Jentaduo should provide inagliptin 2.5 mg twice daily (5 mg total daily dose) plus the current dose of metformin. For patients switching from co-administration of inagliptin and metformin initiate Jentaduo at the dose of inagliptin and metformin already being taken. For patients inadequately controlled on dual combination of the maximal tolerated dose of metformin and a sulphonylurea: The dose of Jentaduo should provide inagliptin 2.5 mg twice daily (5 mg total daily dose) and a dose of metformin similar to the dose already being taken. When inagliptin plus metformin hydrochloride is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia. Elderly: As metformin is excreted by the kidney, Jentaduo should be used with caution as age increases. Monitoring of renal function is necessary. Clinical experience with patients > 60 years of age is limited and caution should be exercised. **Renal impairment:** Jentaduo must not be used in patients with moderate or severe renal impairment (creatinine clearance < 60 ml/min) due to metformin. Hepatic impairment: Jentaduo is not recommended in patients with hepatic impairment due to metformin. Clinical experience with Jentaduo in patients with hepatic impairment is lacking. **Pediatric population:** The safety and efficacy of Jentaduo in children and adolescents (aged 8 to 18 years) have not been established. No data are available. Jentaduo should be taken twice daily with meals. All patients should continue their diet with an adequate distribution of carbohydrate intake during the day. Overweight patients should combine their energy-restricted diet. If a dose is missed, it should be taken as soon as the patient remembers. However, a double dose should not be taken at the same time (the missed dose should be skipped). **Contraindications:** Hypersensitivity to the active substances or to any of the excipients; diabetic ketoacidosis, diabetic keto-acidosis, renal failure or renal dysfunction (creatinine clearance < 60 ml/min); acute conditions with the potential to alter renal function such as dehydration, severe infection, shock, acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock; hepatic impairment, acute alcohol intoxication, alcoholism. **Warnings and Precautions:** Jentaduo should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Caution is advised when Jentaduo is used in combination with a sulphonylurea due to increased incidence of hypoglycaemia. Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin hydrochloride accumulation. Reported cases have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors. As metformin hydrochloride is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter. Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired. As Jentaduo contains metformin hydrochloride the treatment must be discontinued 48 hours before elective surgery with general, spinal or epidural anaesthesia, or prior to, or at the time of intravascular administration of iodinated contrast agents in radiologic studies and therapy with Jentaduo should usually not be resumed earlier than 48 hours following surgery or test and only after renal function has been re-evaluated and found to be normal. The use of Jentaduo in combination with insulin has not been adequately studied. Caution should be exercised when treating patients 80 years and older. As Jentaduo contains metformin, a patient with previously well controlled type 2 diabetes on Jentaduo who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. If acidosis of either form occurs, Jentaduo must be stopped immediately and other appropriate corrective measures initiated. In post-marketing experience of inagliptin there have been sporadically reported adverse reactions of acute pancreatitis. If pancreatitis is suspected, Jentaduo should be discontinued. **Interactions:** Combination requiring precautions: Air Use: glucocorticoids (given by systemic and local routes), beta-2-agonists, and diuretics. More frequent blood glucose monitoring should be performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of Jentaduo should be adjusted during therapy with the other medicinal product and on its discontinuation. **Contraindications not recommended:** There is increased risk of lactic acidosis

in acute alcohol intoxication. Consumption of alcohol and medicinal products containing alcohol. Cationic substances that are eliminated by renal tubular secretion (e.g. cimetidine). The intravascular administration of iodinated contrast agents in radiological studies may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis (see above). **Fertility, pregnancy and lactation:** Jentaduo should not be used during pregnancy, if the patient plans to become pregnant, or if pregnancy occurs. Treatment with Jentaduo should be discontinued and switched to insulin treatment as soon as possible in order to lower the risk of fetal malformations associated with abnormal blood glucose levels. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Jentaduo therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. No studies on the effect on human fertility have been conducted for Jentaduo. **Undesirable effects:** Adverse reactions reported with the fixed dose combination: Adverse reactions reported in all clinical trials with Jentaduo. Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ): nasopharyngitis; hypersensitivity; cough; decreased appetite; diarrhoea; nausea; vomiting; pruritus; blood amylase increased. Not known (cannot be estimated from the available data): pancreatitis. Adverse reactions known to occur with each active substance given singly but which have not been seen in clinical trials with Jentaduo, may occur during treatment with this medicinal product. Adverse reactions reported when inagliptin and metformin were combined with sulphonylurea: additional adverse reaction very common ( $\geq 1/10$ ): hypoglycaemia. **Additional information on individual components:** Adverse reactions previously reported with one of the individual active substances may be potential adverse reactions with Jentaduo, even if not observed in clinical trials with the medicinal product. Inagliptin: All identified adverse reactions of inagliptin monotherapy are also described for Jentaduo. Metformin: Known adverse reactions that were not reported in patients who received Jentaduo. Very common ( $\geq 1/10$ ): abdominal pain. Common ( $\geq 1/100$  to  $< 1/10$ ): taste disturbance. Very rare ( $< 1/10,000$ ): lactic acidosis; vitamin B12 deficiency; liver function disorders; hepatitis; skin reactions. Post-marketing experience: additional adverse reactions from post-marketing experience for inagliptin: rare ( $\geq 1/10,000$  to  $< 1/1,000$ ): angioedema; urticaria (frequency estimates are based on the pooled analysis of the placebo-controlled trials). Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** 2.5 mg/850 mg 56 tablets £33.20; 2.5 mg/1,000 mg 56 tablets £33.20. **Legal category:** POM. **MA number:** 2.5 mg/1,000 mg (56 tablets) EU/1/12/780/005; 2.5 mg/850 mg (56 tablets) EU/1/12/780/019. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. Prepared in August 2012.

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Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

Individuals 60 years and older often experience some measure of cognitive decline including impairment in memory, loss of concentration, decreased clarity of thought, impairment in judgment. Factors that impair normal memory function are, stress, alcohol use, lack of sleep, all elements associated with international travel.

### Bone

Coupled bone formation is affected by reduction of osteoblast differentiation and activity. Resultant osteoporosis can bring fracture from minor travel-falls.<sup>14</sup>

### Sensorial change

At age 70 years, 30% people have some impairment of vision and hearing. Failing visual acuity creates difficulties in reading instructions and locomotion particularly in low light situations. Presbycusis affects up to half of people over 75 with loss of auditory acuity creating difficulty hearing public address systems.<sup>15,16,17</sup>

### Environmental factors

Relocation and international travel are stressors. Elderly people with more rigid thought processes can be slow to adapt and find coping strategies and have slower reaction times in emergency situations.<sup>18-20</sup>

### The effects of existing disease

Illness, or recent surgery can further weaken the immune system, increasing susceptibility to infections. Diabetes can further decrease immunity. Reductions in ventilatory response increase risks of developing hypoxia and hypercapnia, if elderly people acquire disorders that produce low O<sub>2</sub> levels (eg. pneumonia, COPD). Chronically low oxygen levels, reduce tolerance to illness,

decrease exercise tolerance and increase risk of lung infections such as pneumonia or bronchitis.

Urinary disorders increase risk of acute and chronic renal failure. Bladder infections and urinary tract infections are common in seniors in part, related to incomplete bladder emptying. Urinary retention occurs with the urethra blocked by an enlarged prostate gland. In women, weakened muscles can allow the bladder or vagina to prolapse, causing blockage and urinary difficulties. These are serious considerations for older travellers, facing restricted access to toilets in world travel.

### Medication

Long term medication can add to health risk with potential effect on prophylaxis and from failed compliance.

### Management plan

1. Identify health hazards
2. Analyse risk
3. Advise on health hazards, prophylaxis and vaccination
4. Provide clinical valuation for high risk, very frail old
5. Create customised management plan.<sup>21,22</sup>

### Conclusion

Aged world travellers are vulnerable to travel related disorder but risk appraisal, professional advice to minimise risk, prophylaxis and vaccination can ensure older world travellers return in good health.

**Conflict of interest: none**

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