check

RACGP CPD solution

Unit 603
April/May 2023

Travel health

RACGP

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We acknowledge the Traditional Custodians of the lands and seas on which we work and live, and pay our respects to Elders, past, present and future.

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Travel health

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The five domains of general practice

- Communication skills and the patient–doctor relationship
- Applied professional knowledge and skills
- Population health and the context of general practice
- Professional and ethical role
- Organisational and legal dimensions

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twinrix
combined hepatitis A and hepatitis B vaccine

GSK

The only combined hepatitis A and B vaccine[1,2]

Don't assume travellers aged 36+ are not at risk!*

*** Most Australians aged 36 years + are not likely to be vaccinated against hepatitis B. Routine infant vaccination began nationally in 2000 and funding for adolescent vaccination ran from 1996 to 2013.[3,4]**

For travellers to hepatitis A and B endemic areas, TWINRIX:[1]

- Provides **long-term protection in only 3 doses**.§
  - For non-immune individuals aged ≥16 years, a three dose standard schedule consists of 0, 1 and 6 months^
- Offers a **4-dose rapid schedule**.ǂ
  - For non-immune individuals aged ≥16 years, a four dose rapid schedule consists of 0, 7, 21 days and 12 months
- Is **generally well tolerated**. Commonly reported adverse events were injection site reactions (pain, redness and swelling), headache, fatigue, malaise, gastrointestinal symptoms (such as diarrhoea, nausea, vomiting) and viral infection.‖

TWINRIX (720/20) is indicated for active immunisation against hepatitis A and hepatitis B virus infection in individuals from 1 year of age.[1]

TWINRIX should be administered intramuscularly into the deltoid region of the upper arm in adults and older children. TWINRIX should never be administered intravenously.

§ Long-term clinical studies have demonstrated persistence of anti-hepatitis A virus (anti-HAV) and anti-hepatitis B surface antigen (anti-HB) antibodies 15 years after immunisation with TWINRIX.[1]
^ For paediatric dosing schedule please see the full product information.[1]
ǂ The rapid schedule is used in exceptional circumstances in adults when more rapid protection is required, e.g. in travellers commencing vaccination within one month of departure.[1]
‖ Adverse events classed as very common (≥1/10) and common: ≥ 1/100 and < 1/10 , based on data from clinical trials where Twinrix was administered to >6,000 subjects who received either the standard 0,1, 6 month schedule or the accelerated 0, 7, 21 days schedule of TWINRIX (720/20).[1]

PBS Information: This product is not listed on the National Immunisation Program (NIP) or the PBS.

Please review full Product Information before prescribing. Product Information can be accessed at www.gsk.com.au/twinrix or by scanning the QR code

References: 1. TWINRIX Approved Product Information. **2.** Australian Government Department of Health. Therapeutic Goods Administration (TGA). Product Information. Available at: www.ebs.tga.gov.au (Accessed March 2023). **3.** Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook, Australian Government Department of Health, Canberra, 2022. Available at: immunisationhandbook.health.gov.au (Accessed March 2023). **4.** National Centre for Immunisation Research and Surveillance (NCIRS). History of immunisation in Australia. Hepatitis B. Available at: www.ncirs.edu.au/provider-resources/vaccination-history/ (Accessed March 2023).

ACTIVITY ID 448934

Travel health

This unit of *check* is approved for 10 hours of CPD Activity (two hours per case). The 10 hours, when completed, including the online questions, comprise five hours' Education and five hours' Reviewing Performance.

To complete this unit as a CPD Activity, you should carefully read all cases, complete the questions for each case (hard copy or online), answer the linked multiple-choice questions online and score >80%, and complete the evaluation form online.

All doctors also need to do a minimum five hours' Measuring Outcomes CPD each year, and you can do this by completing one Mini-Audit each year. You can do a Mini-Audit based on this unit, or any other unit of *check*, or on any topic that is relevant to your practice.

To do a Mini-Audit on this unit's topic, select the last five relevant patients you managed. Review their records, summarise your management and findings, and indicate in writing (for yourself) where your management and patient outcomes could have been improved, based on what you have learned following your completion of this *check* unit.

You can access all online resources here: https://mycpd.racgp.org.au

For any technical issues, including guides and templates for a Mini-Audit, contact us on 1800 284 789. To purchase this unit if you are not an RACGP member, please call 1800 284 789.

About this activity

International travel can pose various health risks to travellers, and it is important that travellers adequately prepare for potential health risks that they can be exposed to while travelling, including animal/insect bites, exposure to blood/other bodily fluids, environmental changes (eg altitude, temperature), food- and water-borne disease, available medical services, injuries and psychological health.[1]

People planning to travel should seek advice about how to best protect their health and reduce their risk of acquiring disease, some of which, but not all, can be prevented by vaccinations.[2,3]

The following factors should be considered when determining the health risks of international travel:[1]

- mode of transport
- destination
- duration and season of travel
- purpose of travels
- accommodation standard, food hygiene, sanitation
- underlying health issues.

The Australian Government's smartraveller website provides travel advice for all Australians, including a pre-travel checklist, and advice on how to take care of your health while you are away and how the Australian Government can help Australians overseas.[4]

This edition of *check* considers the management of patients considering overseas travel and the investigation and management of health risks following travel.

References

1. World Health Organization. Travel and health. WHO, 2023. Available at www.who.int/health-topics/travel-and-health#tab=tab_2 [Accessed 1 June 2023].
2. healthdirect. Travel health advice. healthdirect. Available at www.healthdirect.gov.au/travel-health-advice [Accessed 1 June 2023].
3. Australian Government Department of Health and Aged Care. Immunisation for travel. Australian Government Department of Health and Aged Care, 2022. Available at www.health.gov.au/topics/immunisation/when-to-get-vaccinated/immunisation-for-travel#vaccines-needed-for-travel [Accessed 1 June 2023].
4. smartraveller. Taking care of your health. Smartraveller, 2021. Available at www.smartraveller.gov.au/before-you-go/health [Accessed 1 June 2023].

Learning outcomes

At the end of this activity, participants will be able to:

- discuss preventive measures for people wanting to travel overseas
- explain the benefits of vaccination prior to travel and communicate that vaccination does not protect against all infectious diseases
- outline the health risks for people with existing conditions wanting to travel overseas
- identify appropriate investigations for people returning overseas who present with symptoms
- outline the differential diagnoses for people presenting with symptoms after returning from overseas.

Authors

Case 1

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Case 2

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Cases 3 and 4

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Case 5

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Peer reviewers

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Abbreviations

AIR	Australian Immunisation Register
ASHM	Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
CDNA	Communicable Diseases Network Australia
DEET	N,N-diethyl-m-toluamide
EBV	Epstein–Barr virus
G6PD	glucose-6-phosphate dehydrogenase
HCT	haematocrit
Hib	Haemophilus influenza type b
HRIg	human rabies immunoglobulin
Ig	immunoglobulin
IHR	International Health Regulation
IPV	inactivated polio vaccine
NIP	National Immunisation Program
NSAIDs	nonsteroidal anti-inflammatory drugs
OPV	oral poliovirus vaccine
PEP	post-exposure prophylaxis
RPR	rapid plasma reagin
STI	sexually transmitted infection
WHO	World Health Organization
YEL-AND	yellow fever vaccine-associated neurological disease
YEL-AVD	yellow fever vaccine-associated viscerotropic disease
YF	yellow fever

CASE

1 Marina presents for travel health advice

Marina, aged 25 years, presents for pre-travel health advice six weeks before a planned trip to Cambodia. She is particularly keen to get your advice on which vaccines she should receive pre-travel, and what else she could do to reduce her risk of health issues during travel.

Question 1

What further history would be helpful when assessing Marina?

Further information

Marina reports a history of splenectomy following a motor vehicle accident when she was aged 19 years. She is otherwise fit and well. She does not take any regular medications and has no drug allergies. She lives alone and works as a receptionist at a local veterinary clinic. She is a non-smoker and does not drink alcohol. She identifies as heterosexual, does not have a regular sex partner and reports two casual sex partners in the past 12 months. She has an etonogestrel contraceptive implant (Implanon NXT).

Marina was born in Australia and has previously travelled to New Zealand and Western Europe (UK, France, Italy and Germany). She does not recall receiving any vaccines before her previous overseas trips and has not previously taken malaria chemoprophylaxis. She reports no previous travel-related illness. Her Australian Immunisation Register (AIR) statement indicates that she is up to date with all routine vaccines according to the National Immunisation Program (NIP), including additional vaccines funded for asplenic/hyposplenic individuals (meningococcal B, meningococcal ACWY, pneumococcal and Haemophilus influenza type b [Hib]). She has also received four COVID-19 vaccine doses and this year's annual influenza vaccine.

Marina is planning to travel to Cambodia in June/July (during the wet season) for five weeks. She will be travelling alone. She has booked flights in and out of Phnom Penh and plans to travel overland by bus to Siem Reap, where she will spend a few days exploring the temple complex of Angkor Wat. Following this, she will travel several hours by car to an animal sanctuary in the Cambodian jungle, where she will work as a volunteer for four weeks. Volunteer activities will include participating in animal care and research and upkeep of the sanctuary. Her planned accommodation includes hostels in Phnom Penh and Angkor Wat and a traditional bungalow at the elephant sanctuary.

Question 2

What health risks might Marina face during this trip?

Question 3

What additional travel health risks might Marina face given her history of splenectomy?

Further information

You determine that Marina's itinerary and planned activities put her at risk for potential exposure to a number of infectious diseases, including hepatitis A, hepatitis B, dengue fever, influenza, Japanese encephalitis, measles, leptospirosis, malaria, rabies, scrub and murine typhus, traveller's diarrhoea, tuberculosis and typhoid fever. You note that malaria is present throughout most of Cambodia and that the predominant species is *Plasmodium vivax*. You determine that medical care is extremely limited throughout the country and that outside of Phnom Penh there are almost no facilities that can deal with medical emergencies. You note that Cambodia's maximum elevation is <2000 m, so altitude illness is not a relevant concern.

Question 4

How would you approach the discussion of vaccines in a pre-travel consultation?

Question 5

Which vaccines would you recommend that Marina should receive prior to her trip?

Question 6

What advice would you give Marina regarding malaria prevention?

Question 7

What would you recommend to Marina regarding malaria chemoprophylaxis?

Question 8

What advice would you give to Marina in relation to her history of splenectomy?

Question 9

What advice would you give to Marina in relation to traveller's diarrhoea prevention and management?

CASE 1 Answers

Answer 1

Marina presents for pre-travel health advice prior to a planned overseas trip to Cambodia. Key objectives of a pre-travel consultation are to:

- conduct an individual risk assessment that considers the traveller's health and background and details of the planned trip
- communicate anticipated health risks to the traveller
- provide advice and recommendations on measures to reduce risk (eg vaccines, medications, repellents).

History-taking should focus on aspects of the traveller's health, travel background and planned trip that will inform an individual risk assessment (Table 1).

Table 1. History relevant to individual risk assessment[1]

Host factors (traveller)	Destination factors (itinerary)	Exposure factors (travel style and activities)
• Age • Sex • Medical history • Immune status • Pregnancy/ breastfeeding • Allergies • Medications • Vaccine history/ serology • Travel history (eg past travel-related illness, use of malaria chemoprophylaxis, travel to altitude)	• Health risks present in countries/ regions to be visited • Current outbreaks at destination • Rural or urban travel • Season of travel • Trip duration	• Type of accommodation • Large gatherings (eg pilgrimage) • Travel to high altitude • Water-based activities (eg rafting, diving) • Cave-based activities • Cycling, skiing or extreme sports • Anticipated interactions with animals • Anticipated sexual encounters

The typical pre-travel consultation does not include a physical examination; in some cases, a separate appointment with the same or a different provider may be necessary to assess a person's fitness to travel. An effective pre-travel consultation takes time, effort and commitment. General practitioners should work within their abilities and refer complex cases to travel medicine specialists.[2]

Answer 2

Travellers may encounter a range of health risks, with frequency and severity varying according to individual health and trip characteristics (Table 2). Although infections are an important cause of illness, non-infectious health risks, such as trauma and illnesses relating to changes in altitude, air quality and/or temperature, are important to consider. Travellers with underlying health conditions might experience disease flares or complications during travel.

Marina is travelling to Cambodia, a lower-middle income country in Southeast Asia. Important health risks to discuss with travellers to this country include:

- food- and water-borne diseases, such as traveller's diarrhoea, hepatitis A and typhoid
- respiratory infections, such as influenza and COVID-19
- vector-borne diseases, such as malaria, dengue fever and Japanese encephalitis
- rabies (animal bites).

Marina is planning to undertake outdoor activities in rural areas, which puts her at increased risk of exposure to disease-transmitting vectors and diseases associated with environmental exposures (such as leptospirosis and schistosomiasis [ie bilharzia]). Solo travel, single marital status and a history of casual sex at home are all factors associated with an increased likelihood of casual sex while abroad; therefore, sexually transmitted infections should also be discussed. It is also worth discussing non-infectious risks, such as trauma and injury.

Answer 3

The primary functions of the spleen are to:[4]

- filter the blood and remove old or damaged red blood cells
- support the immune system by removing microorganisms from the blood stream
- store red blood cells and platelets.

Patients such as Marina who are living without a functioning spleen (ie asplenic and hyposplenic individuals) face a lifelong risk of serious infections caused by encapsulated bacteria. These include *Streptococcus pneumoniae* (pneumococcus), *Neisseria meningitidis* (meningococcus), Hib and *Capnocytophaga canimorsus* (an infection associated with bites or scratches from animals, such as cats and dogs). They are also at increased risk of severe disease due to parasites that infect red blood cells, namely malaria (spread by mosquitoes) and babesiosis (spread by certain ticks). Infection can progress very rapidly (within hours) and, if untreated, might lead to serious impairment or death.

Spleen Australia is an organisation that provides support to Australians without a functioning spleen. Medical recommendations for adults and children with asplenia/ hyposplenism, including the number and timing of vaccine doses, are available on the Spleen Australia website (https://spleen.org.au/).[5]

Table 2. Travel health risks commonly discussed in a pre-travel consultation[3]

Category	Disease/syndrome	Factors that may increase risk or *disease severity*
Food- and water-borne diseases	Traveller's diarrhoea	Younger age Adventurous dietary habits Travel to less developed destinations Proton-pump inhibitor use *Pregnancy, extremes of age*
	Hepatitis A	Travellers visiting friends and relatives Travel to less-developed destinations Men who have sex with men *Older age, chronic liver disease*
	Typhoid	Region of travel (highest risk in travellers to South Asia) Travellers visiting friends and relatives Younger age
	Cholera	Humanitarian aid workers responding to emergencies or working in refugee camps
Respiratory diseases	Influenza	Cruise travel Mass gatherings (eg pilgrimages) *Pregnancy, extremes of age, underlying conditions*
	COVID-19	Pregnancy, older age, underlying conditions
	Tuberculosis	Long-term and expatriate travellers *Children aged <5 years, HIV, tumour necrosis factor-alpha inhibitor therapy*
Vector-borne diseases (vector)	Malaria (transmitted by *Anopheles* mosquitoes)	Travellers visiting friends and relatives Long-term and expatriate travellers Travel during peak transmission season Region of travel (highest risk in travellers to Sub-Saharan Africa and parts of Oceania, such as Papua New Guinea) *Pregnancy, children aged <5 years, splenectomy*
	Dengue fever (transmitted by *Aedes* mosquitoes)	Region of travel (found in tropical and subtropical climates worldwide, mostly in urban and semi-urban areas) Travel during peak transmission season
	Japanese encephalitis (transmitted by *Culex* mosquitoes)	Region (Asia) and season of travel Travel to rural/peri-urban agricultural areas Outdoor activities
	Yellow fever (transmitted by *Aedes* mosquitoes)	Outdoor activities in endemic areas
	Rickettsial diseases, such as scrub typhus (transmitted by mites), murine typhus (transmitted by fleas) and African tick bite fever (transmitted by ticks)	Outdoor activities in endemic areas
Sexually transmitted diseases	HIV, chlamydia, gonorrhoea etc	Younger age, travelling alone Long-term and expatriate travellers Contact with commercial sex workers
Diseases associated with animal/ environmental exposures	Rabies (animal bites)	Children (more curious, closer to the ground) Contact with animals
	Schistosomiasis	Freshwater exposure in endemic areas
	Leptospirosis	Outdoor activities involving water or wet soil (eg rafting, kayaking), particularly after heavy rainfall/flooding
Non-infectious health risks	Altitude illness	Travel to altitudes >2500 m Prior history of altitude illness Rapid ascents and high sleeping altitudes
	Jet lag	Crossing multiple time zones
	Physical trauma (eg motor vehicle accidents)	Lack of helmet/seatbelt use in cycling/driving Adventure sports, mountaineering, trekking Alcohol consumption/drug use
	Venous thromboembolism	Flights longer than four hours Underlying risk factors (eg pregnancy, malignancy, inherited thrombophilias)

Answer 4

There are three categories of vaccines relevant to travellers:

- routine vaccines (recommended regardless of travel)
- required vaccines (for entry into specific countries)
- vaccines recommended according to risk.

Routine vaccines are those listed in the NIP, including vaccines funded for all Australians (such as hepatitis B, measles, tetanus, and polio vaccines) and vaccines funded for specific high-risk groups, such as people with asplenia/hyposplenia.

Some countries require proof of vaccination for travellers wishing to enter or exit the country. A list of vaccine requirements is maintained by the World Health Organization (www.who.int/publications/m/item/vaccination-requirements-and-recommendations-for-international-travellers-and-malaria-situation-per-country-2021-edition), but rules can change quickly. Travellers should be advised to contact the nearest embassy or consulate of the country they plan to visit to confirm what (if any) proof of vaccination is required.

Other vaccine recommendations should be based on a risk assessment approach that considers a traveller's health and trip characteristics. Providers should weigh up disease risks and impacts and protective benefits from vaccination against potential adverse effects and the financial and non-financial costs of vaccination.[6] Most 'travel vaccines' are not funded under the NIP and cost might be a barrier to uptake. However, for patients planning to travel again in the future, vaccines (especially those providing longer-term protection) can often be viewed as an investment for future travel health.

Answer 5

Marina's AIR statement indicates that she is up to date with all routine vaccines on the NIP, including the funded vaccines for people with asplenia/hyposplenia. She has already received this year's influenza vaccine.

There are no current vaccine requirements for travellers to Cambodia.

Additional recommended vaccines are listed in Table 3. Hepatitis A vaccine is recommended for all travellers to Cambodia. Typhoid vaccine is recommended to most travellers, especially those such as Marina who are travelling for longer durations and to smaller cities or rural areas. As Marina is planning to travel to Cambodia for more than one month and will be travelling to rural areas during the wet season, Japanese encephalitis vaccine should be recommended. Rabies vaccination (pre-exposure prophylaxis) should also be recommended, as Cambodia is a rabies-endemic country in which access to post-exposure prophylaxis is limited and Marina's planned trip includes several factors that make her more likely to encounter rabid animals such as rural travel, outdoor activities and volunteer work with animals.[7]

Answer 6

Malaria prevention is particularly important in this case, as Marina's history of splenectomy puts her at increased risk for severe disease. A helpful abbreviation for remembering malaria risk reduction measures is ABCD:

- Awareness (of risk, incubation period, key symptoms)
- Bite prevention (measures to avoid mosquito bites)

Table 3. Vaccine recommendations for Australian travellers[6]

Vaccine	Australian immunisation handbook recommendations
Hepatitis A vaccine	Recommended for people aged ≥1 year travelling to moderately to highly endemic areas for hepatitis A
Typhoid vaccine	Recommended for people aged ≥2 years travelling to endemic regions: • where food hygiene may be suboptimal and drinking water may not be properly treated • to visit friends and relatives
	Revaccination is recommended if a person has continued exposure to *Salmonella typhi*, such as by travelling for a long time or living in an endemic region
Japanese encephalitis vaccine	Recommended for travellers spending one month or more in endemic areas in Asia and Papua New Guinea during the Japanese encephalitis virus transmission season (this includes people who will be based in urban areas, but are likely to visit endemic rural or agricultural areas)
	Vaccination should be considered for shorter-term travellers, particularly if: • the travel is during the wet season • there may be ongoing travel to at-risk areas • there is considerable outdoor activity during the travel • the traveller is staying in accommodation without air-conditioning, screens or bed nets
Rabies	Travellers to rabies-enzootic regions are recommended to have a risk assessment to guide vaccination decision making. People likely to be exposed to potentially rabid terrestrial animals in rabies-enzootic areas should receive pre-exposure prophylaxis

- Chemoprophylaxis (antimalarial drugs to suppress infection)
- Diagnosis (seeking urgent diagnosis/treatment in the event of symptoms).

Bite prevention is an important risk reduction measure for all vector-borne diseases. Patients should be advised to:

- use an insect repellent containing one of the following active ingredients: N,N-diethyl-m-toluamide (known as DEET), picaridin or p-menthane-3,8-diol, also known as oil of lemon eucalyptus (OLE)
- sleep in screened accommodation or under a bed net
- wear clothes that cover most of the body
- treat clothes and/or bed nets with permethrin for additional protection.

Travellers should be actively involved in decision making around chemoprophylaxis. If indicated, the advantages and disadvantages of the different options, including side effects and contraindications (Table 4) should be discussed.[6] Consider the possibility of drug–drug interactions with other medications and any drug allergies.

Malaria symptoms can develop as early as seven days after being bitten by an infected mosquito and as late as several months or more after exposure. Patients should be advised that if fever develops, they should seek medical care urgently, report their travel history, get tested for malaria and get treated promptly if infection is confirmed.

Answer 7

Marina should be advised to take malaria chemoprophylaxis on the basis of exposure risk and increased risk of severe disease. No antimalarial drug is 100% protective, and chemoprophylaxis should always be combined with advice about bite prevention measures and seeking medical care in the event of fever. Mefloquine is not recommended for prophylaxis in travellers to the Greater Mekong subregion (which includes Cambodia) due to resistance.[8] Marina's options are therefore atovaquone/proguanil, doxycycline or tafenoquine. There is no one 'correct' choice and the decision on which to prescribe should consider Marina's individual preferences and budgetary constraints.

Atovaquone/proguanil is expensive (especially for longer trips), but generally well tolerated. Tafenoquine is also expensive but offers protection against *P. vivax* relapses (due to its activity against hypnozoites) which may make it an appealing option for countries where *P. vivax* malaria is common, such as Cambodia. Quantitative glucose-6-phosphate dehydrogenase (G6PD) testing is required prior to prescribing tafenoquine to exclude G6PD deficiency,[8] but

Table 4. Malaria chemoprophylaxis options in Australia[8,9]*

Drug	Adult dosing regimen	Start (time before entering malarious area)	Cease (time after leaving malarious area)	Contraindications
Atovaquone/ proguanil	250/100 mg daily	1–2 days	7 days	Pregnancy (category B2 in the prescribing medicines in pregnancy database) Weight <11 kg
Doxycycline	100 mg daily	1–2 days	4 weeks	Pregnancy (category D in the prescribing medicines in pregnancy database) Age <8 years
Mefloquine	250 mg weekly	1–3 weeks	4 weeks	First trimester of pregnancy (category B3 in the prescribing medicines in pregnancy database) Epilepsy Psychiatric history Cardiac conduction disorders Body weight <5 kg Travel to Greater Mekong Subregion‡ (where resistance to this drug has developed)
Tafenoquine†	200 mg daily for three days (loading dose), then 200 mg weekly (starting seven days after the last loading dose)	3 days	Final weekly dose given in week after leaving malarious area	Glucose-6-phosphate dehydrogenase (G6PD) deficiency Pregnancy (category C in the prescribing medicines in pregnancy database) Age <18 years

*Chloroquine, an antimalarial used for prophylaxis in other countries, is not available in Australia; hydroxychloroquine can be used as an alternative but widespread Plasmodium falciparum resistance limits its use.

†Quantitative G6PD testing is required prior to tafenoquine use.[9]

‡Thailand, Vietnam, Cambodia, Laos and Myanmar.

this only needs to be performed once. Doxycycline is the cheapest option but needs to be taken for the longest duration. However, it does offer protection against some other tropical diseases (rickettsial infections and leptospirosis) that Marina may be exposed to. Gastrointestinal side effects (eg nausea, vomiting) have been reported with all three drugs and they should be taken with food; doxycycline might also be associated with photosensitivity and vaginal candidiasis.

Answer 8

People without a functioning spleen are at increased risk of serious bacterial and parasitic infections. Antibiotic prophylaxis is recommended for at least three years following splenectomy in otherwise healthy patients; lifelong antibiotic prophylaxis is recommended for immunocompromised people without a functioning spleen. All people without a functioning spleen should carry an emergency supply of antibiotics in case medical review is not immediately available. The recommended drug is amoxicillin 2 g immediately (four 500 mg capsules), followed by 1 g every eight hours until medical review.[5] Marina should be advised to seek urgent medical attention if she develops signs and symptoms of an infection, and to take her emergency antibiotic supply if review is delayed.

Measures to prevent parasitic infections (malaria and babesiosis) should be discussed. In addition to the bite prevention measures described for malaria prevention, Marina should be advised to keep to the centre of cleared paths in tick-infested areas and inspect her clothes and skin for ticks at the end of each day.

Answer 9

Traveller's diarrhoea is the most commonly reported travel-related illness, affecting between 10–40% of travellers to less-developed destinations.[10] Marina should be offered advice on ways to reduce her risk of traveller's diarrhoea, and what to do in the event of traveller's diarrhoea symptoms.

Prevention generally centres around careful food and drink choices and observing good hand hygiene. There is insufficient evidence to recommend the use of commercially prebiotics or probiotics or over-the-counter agents containing bovine colostrum.[11,12] There is also insufficient evidence that the oral cholera vaccine protects against traveller's diarrhoea caused by enterotoxigenic *Escherichia coli* and it is not licensed for this indication in Australia.[13] Antibiotic prophylaxis should only be considered in travellers at risk of severe disease (eg immunocompromised patients) and patients should seek expert advice.[13]

Rehydration is the first step in management and is essential in young children.[13] Most traveller's diarrhoea is mild (tolerable, not distressing and does not interfere with planned activities) and can be managed symptomatically with rehydration and/or over-the-counter anti-motility agents such as loperamide.[12] In patients with moderate to severe diarrhoea (distressing or incapacitating and interferes with or prevents planned activities; includes all dysentery), self-treatment with an antibiotic may shorten the duration and reduce the severity of symptoms; azithromycin is the preferred agent due to increasing resistance to fluoroquinolones.[12]

Resources for doctors

Australian immunisation handbook: Vaccination for international travellers, https://immunisationhandbook.health.gov.au/contents/vaccination-for-special-risk-groups/vaccination-for-international-travellers

Resources for patients

Spleen Australia, https://spleen.org.au/patientinfo

Australian Government Department of Foreign Affairs and Trade Smartraveller website, www.smartraveller.gov.au

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CASE

2 Sam has a fever following a holiday abroad

Sam, aged 40 years, is a software engineer. He presents with fever, which he has had for three days. He has recently returned from a holiday in India and Sri Lanka. He spent one week in India followed by three weeks in Sri Lanka, where he visited the capital city and rural areas in the north and south of the country before returning to Australia. He migrated to Australia seven years earlier. He has no history of any significant medical problems and is not on any regular medications. He lives in his own apartment.

Question 1

What questions would you ask Sam to help you in forming a diagnosis?

Further information

Sam visited a wildlife sanctuary while he was in India, where he spent five nights camping and river bathing. He mostly had his meals from roadside cafes and drank bottled water. He was travelling alone. He had no animal bites. He used mosquito repellents. He was not on malaria prophylaxis. He had received all routine vaccinations as well as hepatitis A and typhoid vaccines before travelling. In Sri Lanka, he visited a couple of night clubs in the capital city. Sam informs you that, while on holiday, he smoked three to four cigarettes a couple of times a week and drank mostly beer (five to six drinks over the course of two to three nights). He tells you he did not have any high-risk sexual encounters. Other than a few cuts and bruises, he was well during his entire trip.

Sam returned to Australia five days earlier and developed a fever, headache, myalgia and arthralgia over the past three days. His body temperature measurements were around 39°C during this time. His temperature came down with paracetamol but spiked after four hours. He noticed red spots all over his body since yesterday. He has no respiratory, genitourinary or bowel symptoms. His appetite is reduced and has been mostly on fluids since feeling unwell. He has noted a slight reduction in passing urine.

Question 2

What are your working differential diagnoses?

Question 3

What do you need to examine in Sam to evaluate his problem?

Further information

Sam's body temperature is 38.5°C, his resting heart rate is 96 beats/minute and his blood pressure is 110/70 mmHg, with no postural drop. Sam's respiratory rate is 14 breaths/minute, and his oxygen saturation level is 98%.

Sam is conscious and alert. He looks ill but is not pale and no jaundice is noted. He has no neck stiffness. A generalised blanching maculopapular rash is noted but no other skin lesions are seen other than healed skin cuts and abrasions. His mucus

membranes are slightly dry. No lymphadenopathy is detected and his ear, nose and throat examination is unremarkable.

Tenderness is noted over the right hypochondriac area. The liver is palpable 1 cm below the right costal margin. He has no splenomegaly and no leg oedema.

Respiratory, cardiovascular and neurological system examination is unremarkable. Urine dipstick is negative.

Question 4

What investigations should you consider for Sam?

Further information

Sam's vital signs were normal except for a temperature of 38.5°C. His physical examination revealed right hypochondrial tenderness and a generalised blanching maculopapular rash on the torso and limbs with facial flushing.

Question 5

What is the most likely diagnosis?

Table 3. Sam's pathology results

	Sam's result	Reference range
Haemoglobin	140 g/L	110–160 g/L
White blood cell count	2.4 x 10^9/L	4.0–11.0 x 10^9/L
Differential counts		
Neutrophils	53.78%	25–75%
Lymphocytes	41.5%	15–55%
Monocytes	5.08%	2–8%
Red blood cell count	5.870 x 10^{12}/L	4.5–6.5 × 10^{12}/L
Haematocrit	48.3%	38.0–50.0%
Mean cell volume	90 fL	85–100 fL
Mean corpuscular haemoglobin	25.70 pg	27.0–33.0 pg
Mean corpuscular haemoglobin concentration	33.10 g/dL	33.00–35.00 g/dL
Red cell distribution width	41 fL	39–46 fL
Platelets	120 × 10^9/L	150–400 × 10^9/L
Sodium	141 mmol/L	135–145 mmol/L
Potassium	4.2 mmol/L	3.5–5.5 mmol/L
Chloride	107 mmol/L	95–110 mmol/L
Bicarbonate	26 mmol/L	20–32 mmol/L
Urea	3.8 mmol/L	3.8–8.5 mmol/L
Creatinine	70 µmol/L	59–104 µmol/L
Estimated glomerular filtration rate	>90 mL/min/1.73 m^2	>90 mL/min/1.73 m^2
Random glucose	5.1 mmol/L	3.6–7.7 mmol/L
Total protein	66 g/L	63–80 g/L
Albumin	40 g/L	32–44 g/L
Total bilirubin	14 µmol/L	<16 µmol/L
Alkaline phosphatase	379 U/L	30–115 U/L
Aspartate aminotransferase	110 U/L	10–35 U/L
Alanine aminotransferase	90 U/L	5–30 U/L
Gamma-glutamyl transferase	30 U/L	5–35 U/L
C-reactive protein	18 mg/L	<5 mg/L
Blood smears for malaria	Negative	
Urinalysis	Normal	

Question 6

What investigations would you consider carrying out next to support the above diagnosis?

Further information

Further tests confirm dengue infection.

Question 7

Would you consider admitting Sam to hospital? What are the criteria for hospital admission of patients with dengue fever?

Further information

Sam does not fulfil the criteria for hospital admission.

Question 8

What is your approach to management?

CASE 2 Answers

Answer 1

When presented with a fever without a focus, a detailed and structured history is key to the diagnosis (Table 1).[1]

Answer 2

Possible differential diagnoses might include:

- dengue fever
- chikungunya
- leptospirosis
- malaria
- rickettsial infections
- HIV seroconversion
- secondary syphilis
- measles
- chicken pox
- enteric fever (typhoid or paratyphoid)

Some diagnoses may be disregarded if there has been no exposure or characteristic symptoms have been excluded. For example:

- enteric fever is less likely in the absence of diarrhoea
- measles, chicken pox and other vaccine-preventable diseases are less likely if a patient is up to date with routine vaccinations
- acute HIV and secondary syphilis if sexual encounters can be ruled out. Acute HIV presents with influenza-like symptoms, including fever, malaise and a generalised rash.[2] In cases of secondary syphilis, the rash can mimic the rash of measles, acute HIV or infectious mononucleosis and is classically seen on the palms and soles of the feet. Syphilitic rash itself contains bacteria so the infection can be passed on through skin-to-skin contact alone. Widespread lymphadenopathy and wart-like lesions (condylomata lata) on the genitals are other associated symptoms.[3]

Inclusion of a comprehensive list of differential diagnoses serves as a reminder of some of the more important and common infections.

Other causes of fever, such as urinary tract infections, pneumonia and viral infections (eg influenza, infectious mononucleosis and viral exanthems), should also be considered in returning travellers.

Dengue fever

The dengue flavivirus is transmitted through two vectors, the *Aedes aegypti* and *Aedes albopictus* mosquitoes (known as dengue mosquito in Queensland), and is a common cause of fever in the tropics in large cities. There are four serotypes of dengue virus, all producing a similar clinical syndrome.

Table 1. Key elements of structured history-taking

Symptoms. Clarify the symptoms the patient is experiencing and the severity of illness.	
Fever	Establish whether there are any patterns to the fever (eg is the fever intermittent, remittent or continuous?) Has the patient measured their temperature? Is it low-grade (37.1°C [98.8°F] or 38°C [100.3°F]) or high-grade (39.4°C [103°F] or above) fever?
Relevant systemic enquiry	**Respiratory.** Does the patient have a cough? Is the patient experiencing shortness of breath, haemoptysis or chest pain? **Abdominal.** Is the patient experiencing abdominal pain/cramps, diarrhoea, vomiting, constipation or hepatosplenomegaly? **Genitourinary.** Does the patient have any pelvic pain, dysuria, haematuria, urethral/vaginal discharge? Has the patient noted any changes in frequency of urination? **Neurological.** Has the patient experienced any neck stiffness, headaches or seizures? **Skin.** Does the patient have a localised rash, erythema or limb swelling? **Ear, nose and throat.** Does the patient have earache, a sore throat, difficulty swallowing, postnasal drip or nasal congestion?
Other important symptoms	Check for/ask the patient about: • a generalised rash. Is this blanching/non-blanching, maculopapular, petechial or purpuric? • cervical lymphadenopathy • myalgia, arthralgia, arthritis • weight loss • night sweats • bleeding, including gum bleeding
Timing of the symptoms. This is extremely important. The probability of certain infectious diseases occurring can be assessed based on incubation periods. Most viral infections occur within a couple of days to weeks of returning home.	
Incubation period of less than 2 weeks	Traveller's diarrhoea, dengue fever, other arboviral infections, leptospirosis, influenza
Incubation periods of 2–6 weeks	Malaria, typhoid fever, acute HIV, viral hepatitis, leishmaniasis
Incubation periods of several months	Malaria, schistosomiasis (also known as bilharzia), leishmaniasis, tuberculosis
Onset	When did the symptoms start? How long after returning home did they appear?
Course of the illness	For example, is it prodrome, relapsing or progressive? What is the duration of the symptoms?
Travel itinerary. The exposures to various infections will be different depending on a person's reason for travel (eg a healthcare worker who works in a healthcare setting versus a tourist returning after a holiday).	
Reasons for travel	Leisure, visiting friends and relatives, business, missionary/volunteer work, health worker
Countries visited and duration of stay	All countries visited or transited through, including dates of entry and departure
Locations visited	Urban/rural environment. Certain infectious diseases are endemic to specific locations (eg cities versus rural villages)
Type of accommodation	Hostel, camping, resort
Risk factors. Other possible risk factors need to be explored.	
Sexual	Did the patient have unprotected sexual intercourse or have high-risk sexual encounters while on holiday?
Procedures	Did the patient: • undergo any hospitalisation while on holiday? For example, did they receive any blood products or vascular access lines? • have any tattoos or piercings carried out while on holiday? • use recreational/illicit drugs while on holiday?
Animal contacts	Was the patient bitten while away on holiday (eg by animals or insects, such as mosquitoes, ticks, sandflies)? Was the patient in close contact with household birds or pets?
Human contacts	Was the patient in contact with any sick individuals? Were any other members of the travel party unwell?
Food and drink	Did the patient eat raw produce, undercooked meat, unpasteurised milk or seafood? What was the source of the patient's drinking water?

Table 1. Key elements of structured history-taking

Recreational activities	Did the patient: • swim in natural lakes/rivers, pools, tubs? • undertake other activities involving water (eg white water rafting, boating, canoeing, paddy fields) where the patient could have been exposed to muddy water (this could potentially suggest leptospirosis)? • go scuba diving in the ocean? Was the patient exposed to marine life? • go on safari or hiking? This might expose people to tick- and mosquito-borne infections
Precautions. These measures do not guarantee protection.	
Vaccinations	Pre-travel vaccination (eg hepatitis A and B, typhoid, paratyphoid, Japanese encephalitis) Routine vaccination (eg measles, COVID-19 vaccinations)
Prophylaxis	Use of malarial prophylaxis and compliance
Insect bite prevention	Use of effective insect repellents and bed nets
Additional information	
	Find out more about the patient's physical and lifestyle health, including: • whether the patient smokes, drinks alcohol or uses illicit drugs • information about past medical conditions • family medical history

Asymptomatic infections are common. Prodromal illness of two days with malaise and headache is followed by fever (lasting 2–7 days), backache, arthralgias, incapacitating body aches and pains (breakbone fever), pain on eye movement, nausea, vomiting, anorexia etc.[4]

Leptospirosis

Leptospirosis, a zoonotic disease caused by *Leptospira interrogans*, is transmitted through direct contact with infected animals or soil or water contaminated by the urine of infected animals.[5] In tropical climates, outbreaks occur with flooding during the monsoon season. Most cases of leptospirosis are mild, manifest as self-limited febrile illness or are asymptomatic, while some may be severe and fatal. Two phases of the illness are described:

- the acute bacteraemic phase occurs 3–9 days from the onset of symptoms and manifests as a sudden onset of fever, severe myalgia (calf, abdomen, paraspinal muscles) and headache associated with other non-specific symptoms, such as anorexia, nausea, vomiting, abdominal pain, dizziness, lethargy, arthralgia, eye pain and photophobia
- conjunctival suffusion developing on the third to fourth day is a characteristic finding
- immune-mediated multi-organ damage occurs after more than seven days from the onset of symptoms in the second phase of illness with development of jaundice, acute kidney injury and other serious organ dysfunction.[6]

Malaria

Malaria is caused by *Plasmodium falciparum*, *P. vivax*, *P. ovale* and *P. malariae*.[7] It is transmitted by *Anopheles* mosquitoes and occurs throughout the tropics and subtropics. Malaria should be suspected in any febrile individual with unexplained fever, a history of recent travel (within one year) to a malaria-endemic country (especially India, Pakistan, Haiti and African countries) and belonging to high-risk groups (eg businessmen, overseas workers, migrants, refugees, asylum seekers and security forces returning from peace-keeping missions). Immigrants returning to their country of origin after a long residence in Australia are also at high risk, as they have lost their partial immunity and do not realise that they should be taking malaria prophylaxis.[8]

P. falciparum is the most dangerous of the malarias, causing a severe form of disease and usually presents within one month after a mosquito bite. The onset is insidious, with non-specific symptoms, such as malaise, headache, vomiting, cough and mild diarrhoea, and could be mistaken for influenza. The fever has no pattern, unlike other forms of malaria. *P. vivax* and *P. ovale* have a long incubation period and can present weeks to months after travel with continued fever before the development of classical bouts of high-grade fever on alternate days associated with chills and rigor. The hot or flush phase begins about 0.5–1 hour after the onset of the fever. This lasts for several hours and gives way to profuse sweating and the gradual fall of temperature. This cycle is repeated 48 hours later. Relapses are common in the first two years after leaving a malarious area. *P. malariae* is usually associated with mild symptoms and bouts of fever every third day. Parasitaemia may persist for many years.[7]

Rickettsial infection

Rickettsial diseases are the most common tick-borne infection transmitted through bites or contact with ticks, lice or fleas or infected saliva of biting vectors, such as rats. Rickettsiae are intracellular Gram-negative organisms. The two main groups of rickettsial diseases are spotted fever group and typhus group. Patients present acutely with a headache, which is often retro-orbital in nature, fever, rash and, sometimes, neurological symptoms.

Scrub typhus and the African tick typhus are most likely to be present in travellers returning from the tropics, and the incubation period of 5–14 days coincides with a return from holiday. Infections are commonly seen in travellers on safari or trekking, or those who have visited rural areas. Scrub typhus is endemic in the Southeast Asia and parts of South Asia, while African tick typhus is endemic in Southern and Central Africa.

Answer 3

Physical examination should include all systems. Important clinical features to look for include jaundice, anaemia, skin rash (rose spots, maculopapular, petechial, purpuric, vesicles), lymphadenopathy, hepatomegaly, splenomegaly, skin lesions (eschar), muscle or joint involvement, neck stiffness, photophobia, conjunctivitis, neurological signs or evidence of bleeding (Table 2). Urine should be examined by dipstick initially for blood and glucose.[4,7,9]

Table 2. Clinical findings suggestive of the cause of a fever[10]

Physical signs	Possible infection
Jaundice	Hepatitis, malaria, leptospirosis
Maculopapular rash	Dengue fever, chicken pox, measles, acute HIV, syphilis, typhoid, typhus, chikungunya, leptospirosis
Petechial rash	Rickettsia, meningococcal, viral hemorrhagic fever, leptospirosis
Eschar	Scrub typhus, tick bite fever, spider bites
Ulcers	Leishmaniasis, mycobacteria
Lymphadenopathy	Leishmaniasis, rickettsia, brucellosis, toxoplasmosis, HIV, syphilis
Hepatomegaly	Hepatitis, leptospirosis, enteric fever, dengue fever, schistosomiasis, liver abscess
Splenomegaly	Malaria, visceral leishmaniasis, typhus, dengue fever, typhus, brucellosis, schistosomiasis, trypanosomiasis

Dengue fever

Dengue fever presents as a mild to severe flu-like illness with or without an erythematous generalised blanching maculopapular rash (Figures 1 and 2), with posterior cervical lymphadenopathy. After a few days the liver is often enlarged and tender. Leucopenia is the earliest abnormality in the full blood count, which indicates a high probability of dengue.

Petechiae and mucosal membrane bleeding (eg nose and gums), massive vaginal bleeding and gastrointestinal bleeding occur in dengue haemorrhagic fever.

The severe form of the illness, dengue shock syndrome, is characterised by a high respiratory rate, right hypochondrial tenderness, mucosal bleeding and pleural effusion and ascites; if these signs are found, the patient should be urgently admitted to hospital.

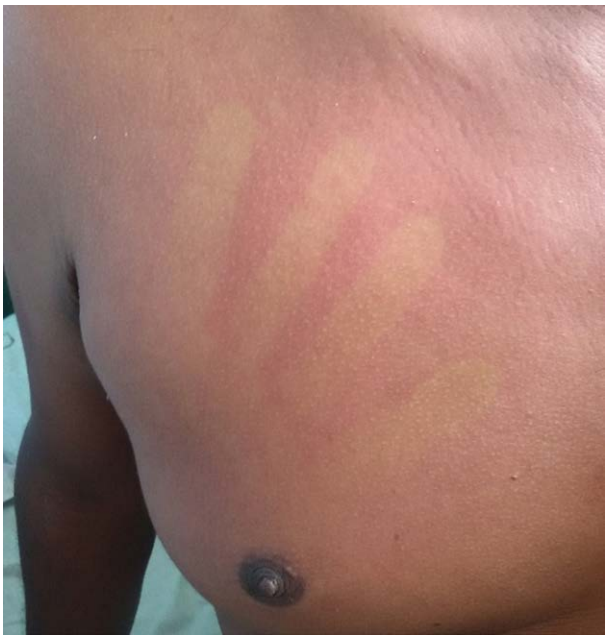

Figure 1. Dengue maculopapular rash in early phase.

Image reproduced from Wikimedia Commons with permission (https://commons.wikimedia.org/wiki/File:Early_Dengue_Fever_Rash_2014.jpg).

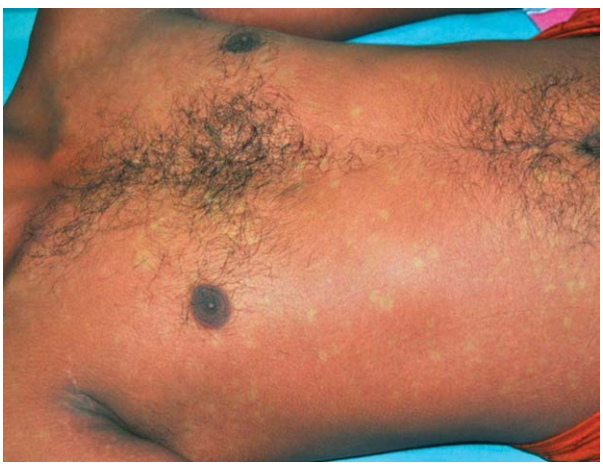

Figure 2. Dengue rash in recovery phase (white islands in red sea).

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Leptospirosis

In cases of leptospirosis, conjunctival hyperaemia ('suffusion'), pharyngitis, calf and muscle tenderness, splenomegaly, lymphadenopathy and hepatomegaly are seen. Skin rash typically lasts for 1–2 days and may be maculopapular or petechial in nature. 'Weil's disease' is a severe form of leptospirosis, and is described as a classic triad of fever, jaundice and renal failure. Neurological complications, meningitis, encephalitis, convulsions,

Guillain–Barré syndrome, transverse myelitis and ocular complications, such as subconjunctival and retinal haemorrhages, optic neuritis and chronic uveitis, might be involved.[5]

Malaria

The main effects of malaria are haemolytic anaemia. With *P. falciparum*, jaundice is common due to haemolysis and hepatic dysfunction. The liver and spleen become tender. Anaemia develops rapidly. Cerebral malaria and renal impairment are associated complications.[7]

Rickettsial infection

Fever, central macular rash with eschar (crusted necrotic sore at the site of a bite due to vasculitis following an immune response) and regional lymphadenopathy are seen in all types of rickettsial infection. In the case of scrub typhus, an erythematous or maculopapular rash often appears in addition to these symptoms on the fifth to seventh day, and spreads to the trunk, face, limbs, palms and soles of the feet with generalised painless lymphadenopathy. The rash fades by the 14th day. The temperature continues as remittent fever with sweating. Hepatosplenomegaly, myocarditis, confusion, pneumonia, renal failure, haemorrhage and deafness are possible complications. Convalescence is slow and tachycardia might persist for weeks. African tick typhus is a milder illness.[7]

Chicken pox

The rash in chicken pox is generalised and itchy. It progresses rapidly from macular to papular to vesicular lesions before crusting. Lesions are typically present in all stages of development at the same time. The rash appears on the face, chest and back, and then spreads to the rest of the body.[11]

Measles

Prodromal illness of one to three days, after which fever, upper respiratory symptoms, conjunctivitis and Koplik spots on the internal buccal mucosa (small white spots surrounded by erythema) are pathognomonic for measles and precede the rash. Maculopapular rash appears, lasting five to six days and gradually fades, staining pale skin. Generalised lymphadenopathy and diarrhoea are common and can be complicated with pneumonia and convulsions.[12]

Answer 4

Initial screening of an undifferentiated fever should include:[7]

- full blood count, liver function tests, urea, electrolytes and creatinine
- C-reactive protein
- urinanalysis
- thick and thin blood smears for malaria or rapid diagnostic tests over two days
- HIV test, if indicated
- chest X-ray, and ultrasound of liver and spleen, if indicated.

Further investigations should follow once a diagnosis is suspected. While some of these tests are diagnostic, the results of others should be interpreted in combination with clinical features, which would help in making a definitive diagnosis.

Answer 5

Dengue fever

Dengue fever is a clinical diagnosis and should be suspected in patients with spiking fevers, low platelet count and leucopoenia who have visited dengue-endemic areas, such as India and Sri Lanka.[9]

Basic investigations, together with clinical features may point to a diagnosis. A study on febrile returned travellers noted that:[7]

- malaria was predicted by splenomegaly, thrombocytopenia (platelet count <150 x 10^9/L
- dengue fever was predicted by rash, thrombocytopenia and leucopoenia (leucocyte count <4 x 10^9/mL)
- acute schistosomiasis was predicted by an eosinophil count of ≥0.5 x 10^9/mL
- enteric fever was predicted by splenomegaly and elevated liver transaminases.

All patients with fever must be investigated for malaria if they have been to a malarious region within the past year. Three malaria blood tests over 2–3 days are recommended to rule out malaria with confidence as parasitaemia fluctuates.[13] Malaria can take time to be detected, which is why more than one test is recommended.[14]

Malaria can be diagnosed by microscopy of a blood film, which is the gold standard, or by using a rapid diagnostic antigen test.[15]

Serology testing for tropical infections, including rickettsial infections, Q fever, leptospirosis, brucellosis and arbovirus infections (eg dengue fever, chikungunya), should be carried out if these conditions are suspected. Contact the public health unit of each state/territory for advice.

Many patients infected with dengue virus remain asymptomatic. Others, after an incubation period of 4–7 (range: 3–14) days, develop a febrile illness, which could progress to be one of the following:

- undifferentiated fever
- dengue fever
- dengue haemorrhagic fever.

A simple fever indistinguishable from other viral infections is self-limiting and can be managed as any other viral fever with symptomatic treatment.

Dengue fever is characterised by a sudden-onset high fever lasting 5–7 days, with severe headache, myalgia, arthralgia, facial flushing/diffuse blanching erythematous maculopapular rash. Haemorrhagic manifestation, such as petechial haemorrhages, mucosal bleeding or epistaxis, may

be associated. Bleeding may be heavy in patients taking aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), steroids or long-term anti-platelet drugs. It is difficult to differentiate dengue fever from dengue haemorrhagic fever in the early (febrile) phase of the illness.

Dengue fever and dengue haemorrhagic fever are considered two clinical entities. Plasma leakage, which occurs soon after the end of the febrile phase, is the hallmark of dengue haemorrhagic fever. There is a tendency to develop hypovolaemic shock (dengue shock syndrome) due to plasma leakage. Warning signs include severe abdominal pain, persistent vomiting, lethargy or restlessness, hepatomegaly, reduced oral intake, oliguria, postural hypotension and mucosal bleeding.

Dengue virus is not endemic in Australia, but outbreaks can still occur each year in north and central Queensland as a result of imported cases. To prevent the breeding of dengue mosquitoes on their property, residents should remain vigilant.[16]

Severe dengue, although less common in Australia as it is associated with repeated infections by different serotypes, may be seen in migrants who have had primary infections and have returned from an endemic area with a secondary infection by the same serotype. Long-lasting immunity usually develops following an infection with a particular type of dengue virus, but susceptiblilty to infection with other types of dengue virus remains.

The clinical course of dengue haemorrhagic fever comprises three stages:

- febrile phase
- critical phase (leakage phase)
- recovery phase.

The early febrile phase is indistinguishable from dengue fever. Dengue haemorrhagic fever is characterised by a continuing high fever lasting for 2–7 days. Some patients may have a sore throat, injected pharynx, conjunctival injection and diarrhoea. Leucopoenia (white blood cell count of $<5 \times 10^9$/L and mild thrombocytopenia ($<150 \times 10^9$/L) are common in the late febrile phase. The presence of tender hepatomegaly may point to a diagnosis of dengue haemorrhagic fever. Liver transaminases may be elevated in dengue fever and dengue haemorrhagic fever.

Critical phase (leakage phase) usually occurs towards the late febrile phase, around the third to fifth day of illness with defervescence (settling of fever). Plasma leakage is selective (ascites and pleural effusion) and transient, usually lasting for 24–48 hours and is due to immune mediators causing increased capillary permeability. This results in haemoconcentration shown with a rising haematocrit (HCT). A 20% rise in the HCT from the baseline indicates significant plasma leakage. However, a rise in HCT during the early febrile phase indicates dehydration. A daily clinical review and blood count is recommended until recovery from the critical period.

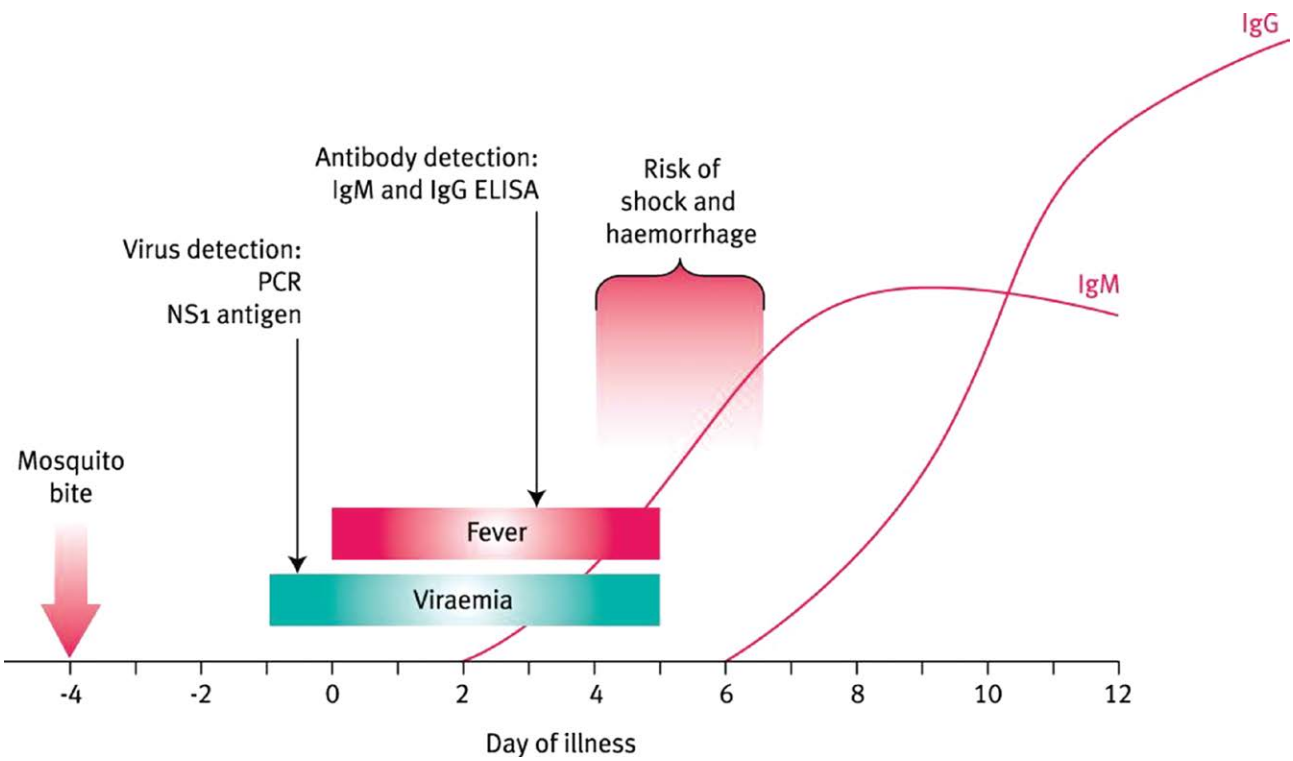

Figure 3. Timing of serology tests and high-risk period in primary dengue.

Reproduced from Queensland Dengue Management Plan 2015–2020 with permission (www.health.qld.gov.au/__data/assets/pdf_file/0022/444433/dengue-mgt-plan.pdf).[17]

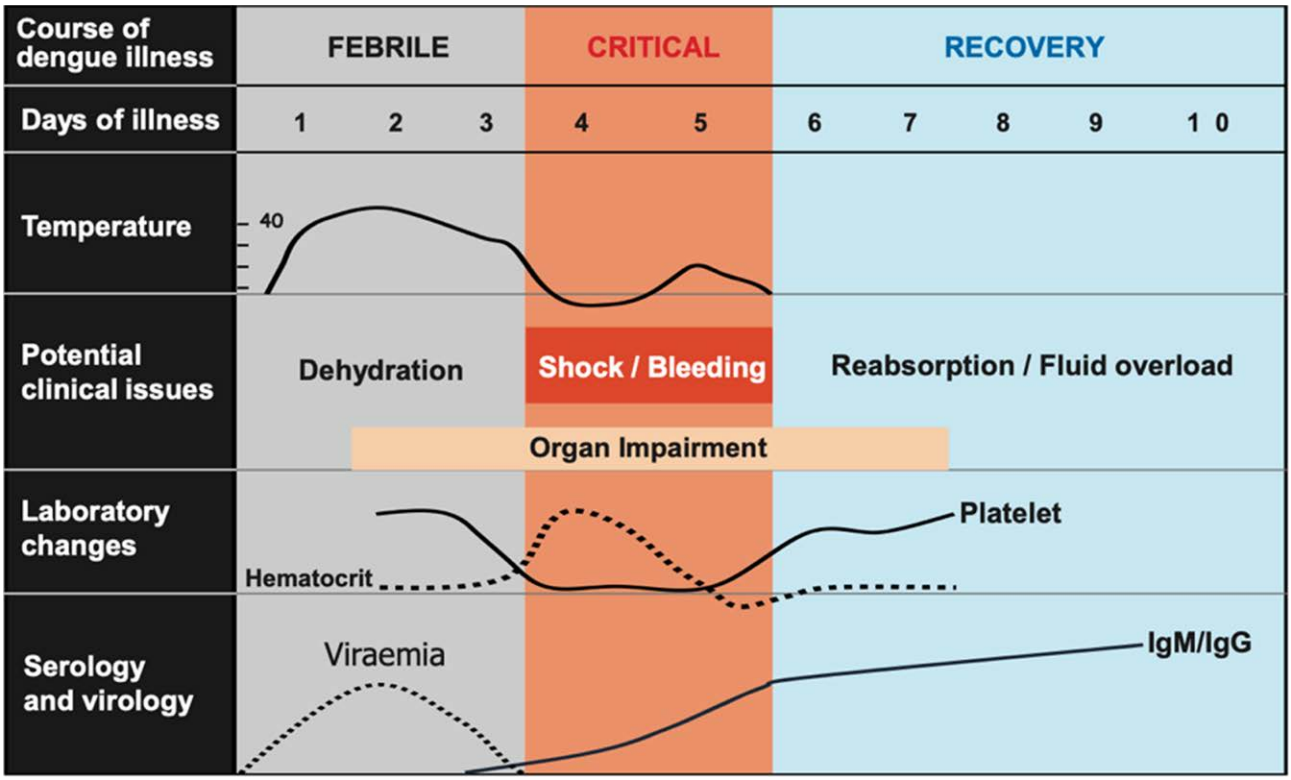

Figure 4. Clinical course of dengue haemorrhagic fever.

Reproduced with permission from Malaysia Health Technology Assessment Section (MaHTAS), *Management of dengue infection in adults (3rd edition).*

During the recovery phase, there will be reabsorption of leaked fluid. Features associated with this phase include improved appetite, convalescent rash, generalised itching, bradycardia, diuresis, and a rise in the white blood cell count followed by platelets. However, if excessive fluids have been given intravenously during the critical phase this could lead to fluid overload in this phase resulting in pulmonary oedema.[18]

Answer 6

Non-structural protein-1 antigen testing can be carried out from the onset of illness up to nine days following the onset of fever, but is not readily available in most states in Australia and takes several days to get results.[17] Polymerase chain reaction testing for early diagnosis (within five days of the onset of illness) can also be carried out. Immunoglobulin (Ig) M detection can be used for later diagnosis (five or more days after illness onset). Positive serological testing (enzyme-linked immunosorbent assay) for dengue virus IgM supports a recent infection while a positive IgG supports past infections.[4]

Answer 7

Clinical features indicating early admission to hospital are:[9,18]

- a platelet count of ≤100 x $10^{9/L}$
- persisting abdominal pain or tenderness
- pleural effusion or ascites
- mucosal bleeding
- lethargy
- enlarged liver >2 cm.

Answer 8

The following treatment measures are recommended for patients who do not need admission to hospital:[9]

- adequate oral fluid intake of around 2500 mL for 24 hours (if the body weight is less than 50 kg, give fluids at 50 mL/kg for 24 hours). This should consist of oral rehydration fluid, fruit juices or soup, rather than plain water. Exclude red and brown drinks, which could cause confusion with haematemesis or coffee ground vomitus
- adequate physical rest
- supportive treatment with paracetamol for fever, antiemetics and histamine type 2 receptor blockers, if necessary
- avoid all NSAIDs
- withhold antiplatelet medications in patients who take these long term
- clinical monitoring and a full blood count should be carried out daily.
- a normal full blood count or a count suggestive of bacterial infection on the first day of illness does not exclude dengue illness. Therefore, follow-up full blood counts are essential.

Prognosis and secondary prevention

Despite the use of chemoprophylaxis, bed nets and insect repellent, malaria should be ruled out in febrile patients with a history of travel to malaria-endemic regions.

In the UK, malaria was detected four times more in those who had visited friends and family overseas than tourists who had visited the same region. This group was less likely to take precautions against mosquito bites, seek advice prior to travel and take chemoprophylaxis.[19]

Conclusion

Sam was reviewed daily with a full blood count. On day five, Sam's platelet count dropped to 105 x 10^9/L and the fever subsided. Platelet count on day six had risen to 125 x 10^9/L, and on day seven to 135 x 10^9/L. By day eight, Sam's symptoms had resolved and the results of his laboratory tests were normal.

The patient improved clinically with conservative management. Dengue virus infection is a 'routine' notifiable condition and must be notified by medical practitioners and pathology services in writing within five days of diagnosis. This is a Victorian statutory requirement.[17] Dengue virus infection is a nationally notifiable disease and both confirmed cases and probable cases should be notified.[20]

To identify potential areas of low-risk transmission and prevent the spread of infection, public health units investigate each case to determine the source of the infection. For information about the public health response, contact the state public health unit.

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CASE

3 Lily has been bitten by a dog while on holiday abroad

Lily, aged 23 years, presents the day after returning from a holiday in Bali. She was there with her partner for a short holiday. On the second day of their holiday, they went to a restaurant for lunch and, while Lily was playing with the restaurant owner's dog, the dog jumped up and bit her on the forearm. She went to a medical clinic later that afternoon, where she was given a dose of Rabivax. It has been four days since these events took place.

Question 1

What further history should you take?

Further information

Lily states that the bite was quite small but broke the skin and bled a little. The clinic in Bali cleaned the wound and applied a simple dressing. Lily shows you the vaccination card she received in Bali, which documents one dose of Rabivax given intramuscularly on the same day that she was bitten.

The bite had been playful and the dog had not acted in an aggressive way. Lily does not know if the dog had been vaccinated against rabies.

Currently, the wound site does not feel sore or numb, and Lily does not feel unwell in any other way.

Lily has no other medical conditions and takes the oral contraceptive pill but no other regular medications. She has no known allergies and, more specifically, is not allergic to eggs. She had all her routine childhood vaccinations but cannot remember when she last had a tetanus vaccination. She had not received any vaccinations against rabies prior to the dose given in Bali.

On examination, Lily looks well. She is afebrile and her pulse and blood pressure are within normal limits. She has a wound on her right proximal forearm that is 5 mm long and 2–3 mm deep, with signs of healing. There is no erythema, tenderness or evidence of paraesthesia.

Question 2

What is your assessment of Lily for her risk of rabies?

Further information

You check Lily's Australian Immunisation Register (AIR) record and confirm that she has not had a tetanus vaccination since she was aged 12 years.

Question 3

What management is required for Lily?

Question 4

How would you organise for Lily to receive the required management?

Further information

You counsel Lily about the recommendation of rabies post-exposure prophylaxis and tetanus vaccination, and Lily consents to receiving this. You then call your local public health unit, which advises you they will urgently courier HRIg and a second dose of rabies vaccine to your practice. They also assist in determining when the third and fourth doses of the vaccine should be given to complete the vaccine course. You encourage Lily to keep her wound clean and dry, monitor it for any redness, pain or discharge, and present for review if she notices these features or feels otherwise unwell.

Lily comments that her brother is about to go to Bali and wonders if he should be vaccinated against rabies before he travels.

Question 5

What is your advice?

CASE 3 Answers

Answer 1

Lily has potentially been exposed to rabies virus. History-taking should focus on the risk of the exposure, considering:

- type of exposure. Obtain details about the bite (or scratch), particularly whether the bite broke the skin and whether there was bleeding
- animal source. Exposure to classical rabies virus can occur from terrestrial animals and other mammals in rabies-enzootic countries. Bats anywhere in the world (including Australia) are a potential source of lyssaviruses. Consider whether the animal was behaving abnormally and whether it is known to have been vaccinated
- immune status. Other medical history, including immunocompromising conditions and/or immunosuppressive medications
- previous vaccination history. Consider any rabies vaccines given in the past (eg for travel, or after a previous incident) as this may impact the post-exposure protocol.

In addition, gather information to determine the required post-exposure prophylaxis schedule in Australia by:

- obtaining details of vaccines or immunoglobulin given overseas, including date, brand, dose and route of administration. Original records should be sighted if possible
- confirming details of any allergies, including egg allergy.

Assessment of the patient should also consider the risk of non-rabies infections by:

- confirming the patient's tetanus vaccination status
- determining whether the patient has any current symptoms of either localised or systemic infection.

Answer 2

A rabies exposure is defined in the Communicable Diseases Network Australia (CDNA) National Guidelines for Public Health Units as any bite or scratch from, or mucous membrane or broken skin contact with, the saliva or neural tissues of:

- a bat in Australia or elsewhere in the world
- a wild or domestic terrestrial mammal in a rabies-enzootic country
- a wild or domestic terrestrial mammal in Australia, where there is laboratory confirmation of infection with any lyssavirus.[1]

For exposures due to direct contact with bats in situations where bites or scratches might not be apparent as some bats have small teeth and claws, refer to the *Australian immunisation handbook* for further details on unknown bat exposures.[2]

Public Health England maintains a list of rabies risk in terrestrial animals by country.[3] However, if there is any concern, you can discuss the potential exposure with your local public health unit.

Indonesia is a 'high-risk' country and, as such, Lily should be considered at risk of developing rabies. Rabies is almost always fatal, and early initiation of post-exposure prophylaxis (PEP) is up to 100% effective in preventing rabies-related deaths.[1]

Answer 3

Rabies PEP is urgent and consists of:

- immediate and thorough washing of the wound with copious soap and water, and an application of a viricidal preparation such as povidone-iodine solution[1]
- a course of rabies vaccine. For immunocompetent people who have not been vaccinated in the past, doses are given on days zero, three, seven and 14.[2] However, this schedule varies with immunocompromise, past vaccination and when PEP has been commenced overseas. Refer to the *Australian immunisation handbook* and contact the local public health unit for advice.[2]

Infiltration of the wound with human rabies immunoglobulin (HRIg) is also required in every case where there has been the possibility of broken skin or mucous membrane involvement (ie category III). HRIg provides immediate protection, while the rabies vaccine takes at least one week to mount an immune response. Rabies virus can spread from the bite site to nerve endings immediately, hence the urgency. One week after the vaccine has been administered, the HRIg might be redundant due to the vaccine response, but it can also impair the vaccine

response, so should not be given after that time.[2] In cases where HRIg has not been given overseas, the patient should be urgently assessed for HRIg eligibility following their return to Australia.

Lily did not receive HRIg in Bali, which means she should receive it today, as it is within seven days of her first vaccine dose.

Vaccination that has been initiated overseas with an approved vaccine can be completed in Australia with Australian-registered vaccines. The *Australian immunisation handbook* maintains a list of rabies vaccine available globally, and their compatibility with vaccines registered in Australia.[4]

Rabivax is considered compatible with Australian-registered vaccines; therefore, Lily's first vaccination given on day zero is valid. It is important to note that day zero is the date of the first vaccine dose, which might not be the same as the date of the bite. Lily has missed her day three vaccination so she should receive her missed vaccine dose today (day four). Contact your local public health unit for assistance in realigning the rest of the vaccine schedule for Lily.

Recommendations for completion of PEP in Australia where varying PEP regimens have been commenced overseas is available in the *Australian immunisation handbook*.[5] Advice can be obtained from your local public health unit.

As this is also a tetanus-prone wound, and it has been more than 10 years since Lily's last tetanus vaccination, it is also recommended that Lily should be vaccinated against tetanus.[6]

Antibiotic therapy is required for bites that are infected or in cases where there are other risk factors present (eg puncture wound; cat bite; bite on the hands, feet or face – see the Therapeutic Guidelines for the full list).[7] As Lily's wound has no evidence of infection and she is otherwise healthy, antibiotics are not automatically indicated. Lily should be counselled to present again for review if the wound becomes red, painful or produces discharge.

Answer 4

Clinicians should contact their local public health unit or Department of Health to urgently obtain rabies vaccine and immunoglobulin.

Answer 5

Pre-exposure rabies vaccination is available, and generally recommended for:

- people who might receive bites or scratches from bats, including in Australia
- people travelling to or living in rabies-enzootic areas after a risk assessment that considers the likelihood that the person will interact with animals and their access to emergency medical attention
- laboratory workers working with any live lyssavirus.[2]

A vaccinated person who is exposed to rabies would need fewer doses (two instead of four) of rabies vaccine in the post-exposure phase, and they would not need HRIg unless they are severely immunocompromised.[8]

Lily's brother is taking a surfing trip to Bali and is not planning any activities involving animals. As with all travellers to rabies-enzootic areas, he should be advised to avoid close contact with any animals, even animals in areas where there may be many people interacting with the animals.[1]

Resources for doctors

- Australian immunisation handbook, https://immunisationhandbook.health.gov.au/
- Local public health unit
- Local state and territory health departments, www.health.gov.au/about-us/contact-us/local-state-and-territory-health-departments

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CASE

4 Jacob has a rash all over

Jacob, aged 24 years, is a patient known to you and your practice. He presents with a new rash 'all over' that he first noticed about four days earlier. It is not itchy. He has been feeling otherwise well; he has not had any febrile, coryzal, respiratory or other symptoms. He has not had contact with anyone that he knows of who has had a rash or been unwell. He tells you that he has recently returned home to Australia after 12 months in the UK on a working holiday.

Question 1

What further history would you take from the patient?

Further information

Jacob has no significant medical history and does not recall having had a rash like this previously. He has not taken any medications, supplements or recreational drugs in the past 1–2 weeks. He did not have a pre-travel consultation but has had all routine childhood vaccinations. He has no known allergies.

Jacob had been in the UK on a working holiday, backpacking around different cities and working in hostels and bars for the past 12 months. He took occasional weekend trips to Europe, visiting places in France, Spain, Italy, Germany and the Czech Republic. His return flight to Australia stopped in Dubai for a few hours.

He is currently staying at his parents' house in the metropolitan area until he is able to secure rental accommodation. Since returning, he has mostly been home resting, job searching online and updating his resume. There are no pets in the household. He is not aware of any specific exposures that could have led to a reaction.

He travelled to the UK alone. While travelling, he had multiple casual sexual partners. Jacob states that he has sex with women and not men, and that sometimes he has unprotected sex.

Question 2

What do you look for on examination?

Further information

Jacob is afebrile and his vital signs are within normal limits. Examination of the skin reveals rough reddish plaques affecting the trunk, limbs, palms and soles of his feet. Your systems examination reveals cervical and inguinal lymphadenopathy, but is otherwise unremarkable.

Question 3

What are the differential diagnoses?

Question 4

What investigations would you request?

Further information

Jacob's full blood picture, urea and electrolytes, liver function tests and inflammatory markers are all within normal ranges. HIV serology is negative, and polymerase chain reaction tests for chlamydia and gonorrhoea are negative. Syphilis serology detects *Treponema pallidum* immunoglobulin G antibodies and a rapid plasma reagin (RPR) test returns a result of 32.

Question 5

What is your interpretation of the syphilis serology?

Question 6

How would you manage Jacob?

Further information

Once you receive Jacob's results, your practice nurse contacts Jacob urgently for another appointment, and Jacob agrees to come in the following day.

At the review appointment, you explain Jacob's diagnosis and treatment to him. You also explain the importance of contact tracing and ask Jacob about the people he has had sex with in the past six months. He does not have contact details for any of his sexual contacts from overseas. However, since returning home, he met up with an ex-girlfriend and they had unprotected sexual intercourse a week earlier.

Question 7

What further management is required?

CASE 4 Answers

Answer 1

A history aimed at exploring differential diagnoses for a new rash includes:

- onset and progression of the rash
- medical history, including other medical conditions and previous history of rash
- recent use of medications (including over-the-counter medications), supplements and recreational drugs
- immunisation history
- allergies
- exposure to potential allergens through diet or the physical environment.[1]

As Jacob has recently returned from travel, it is important to find out where he has travelled and what kind of activities he has undertaken. If Jacob had travelled to tropical and subtropical regions, for instance, he could potentially be at risk of certain vector-borne infections.

A high proportion of travellers engage in unprotected casual sex while overseas.[2] The UK experienced an outbreak of mpox in 2022, and there have also been rising cases of syphilis since the turn of the century.[3] These diseases and HIV can also cause a non-specific rash.

Answer 2

Examination should include:

- measurement of body temperature and other vital signs
- an evaluation of the characteristics and distribution of the rash
- a review of the skin across the whole body, including the palms and soles of the feet, scalp, oropharynx and conjunctivae
- a systems-based assessment, including a review of the lymphopoietic system.[1]

Answer 3

Differential diagnoses include:

- pityriasis rosea
- secondary syphilis
- other viral and infective exanthems, including Epstein–Barr virus (EBV) and HIV
- psoriasis and other autoimmune causes
- a drug reaction
- atopic or contact dermatitis.[4]

Although the clinical picture is less typical for mpox and measles, these differential diagnoses should also be considered in a recently returned traveller.

Answer 4

Where the diagnosis is not obvious on clinical examination, the following investigations should be considered to assess the differential diagnoses listed above:

- full blood picture and inflammatory markers
- urea and electrolytes, liver function tests
- EBV and other viral serology depending on the clinical assessment
- syphilis serology
- HIV serology.[4]

Pityriasis rosea is a clinical diagnosis that often does not require further investigations, but as it uncommonly affects the palms and soles of the feet,[5] further investigations in this setting would be appropriate.

In view of the patient's history of unprotected sex, it would also be appropriate to encourage a full screen for sexually transmitted infections (ie chlamydia, gonorrhoea, hepatitis B serology if the patient is not known to be immune) in addition to the syphilis and HIV serology recommended.[6]

Answer 5

A positive syphilis antibody result means that Jacob has been infected with syphilis at some point. The RPR of 32 indicates current disease activity. In the clinical setting of a rash, Jacob has evidence of secondary syphilis.

Answer 6

The treatment for infectious syphilis (primary, secondary and early latent phases) is benzathine benzylpenicillin 2.4 MU given intramuscularly. Benzathine benzylpenicillin is not readily available at community pharmacies but is available from the prescriber bag, so it is recommended that practices always keep it in stock as this avoids unnecessary delays to treatment. It is a long-acting form of penicillin; other formulations of penicillin (such as the similarly named benzylpenicillin) that are short-acting are ineffective in the treatment of syphilis.

Patients being treated for infectious syphilis should be warned that they may develop a Jarisch–Herxheimer reaction 6–12 hours after treatment, causing symptoms such as fever, headache and malaise. The symptoms may last for several hours but are self-limiting and can be managed with analgesics and rest.

Jacob needs to have another RPR test on the day of his treatment, and repeat RPR tests at three, six and (if necessary) 12 months after treatment. Demonstration of a fourfold decrease in RPR confirms successful treatment. This means that if Jacob's RPR has risen to 64 on the day of treatment and drops to 16 or less by six months post-treatment, then he shows evidence of successful treatment.

HIV serology should also be repeated 12 weeks after the last time he had unprotected sex.

Contact tracing is an important aspect of management to prevent re-infection and reduce onward transmission. Jacob's sexual contacts from the past six months should be tested and treated empirically. How far back contact tracing should extend depends on the stage of syphilis; local public health units or Departments of Health can provide advice and assist with notifying contacts.

Jacob should avoid any sexual contact for seven days following treatment. He should also be counselled that it is possible to be re-infected with syphilis, therefore it is important to use barrier protection with casual partners and seek regular sexually transmitted infection (STI) screening.

More detail about the management of syphilis is available from the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) (https://sti.guidelines.org.au). ASHM has also created a valuable interactive decision-making tool (https://www.ashm.org.au/resources/syphilis-decision-making-tool/).

Note that syphilis is a notifiable disease and clinicians are required to notify their state or territory Department of Health of syphilis diagnoses.

Answer 7

Jacob's ex-girlfriend needs to be notified that she is a contact of syphilis. Jacob may elect for her to be notified in various ways: he may choose to notify her himself or, if he prefers, she can be notified by a third party without his details being divulged.

As a contact of someone with infectious syphilis, she should receive empirical treatment with benzathine benzylpenicillin and be tested at the time of treatment.

As she is of reproductive age, she will also need to have a pregnancy test, as a syphilis diagnosis in pregnancy carries the risk of vertical transmission.

Australia has seen a rise in syphilis cases in recent years, reaching outbreak levels in regions of Queensland, Northern Territory, Western Australia and South Australia. Cases have been increasing in women of reproductive age and, in 2020, Australia recorded the highest number of congenital syphilis cases since 2001.[7]

Resources for doctors

- Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) Decision making in syphilis. STI management guidelines for use in primary care, https://sti.guidelines.org.au

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CASE

5 Amy is pregnant and would like to travel to Kenya and Uganda

Amy, aged 27 years, is a registered nurse and midwife, and is pregnant for the first time. She is 15 weeks pregnant and is planning to visit Kenya and Uganda on an organised tour to visit the gorillas when she is 18 weeks pregnant.

The tour is for 16 days, on an overland truck, and involves camping in tents.

It begins in Nairobi and travels northwest through Lake Nakuru and Eldoret and into Uganda. The tour then goes through Kampala to Kalinzu Forest National Park and Queen Elizabeth National Park in the west of the country. Trekking is required uphill to see the gorillas in both parks. The tour then skirts the top of Lake Victoria, back into Kenya and then to Masai Mara National Reserve for game drives. The tour ends in Nairobi.

Question 1

What history would you seek from Amy?

Further information

Amy has had no problems with her pregnancy so far, her ultrasound scans and other tests have all been normal, and she has no underlying medical issues or allergies. She has done some adventure travel in Nepal previously, including trekking.

Amy is up to date with her vaccinations for diphtheria–tetanus–pertussis and influenza. Her employer has tested her immunity to hepatitis B, measles, mumps, rubella, and varicella (chickenpox). She previously received hepatitis A and typhoid vaccinations for her trip to Nepal five years earlier and has had the booster for hepatitis A.

Question 2

What vaccinations does Amy need for her upcoming trip?

Question 3

What are the risks of giving yellow fever vaccine in pregnancy?

Question 4

What is the risk of Amy contracting yellow fever during her two-week stay?

Question 5

What are the risks if Amy were to get malaria while pregnant?

Question 6

What antimalarial medications can be recommended for pregnant women?

Question 7

What advice would you give to Amy to stay healthy while abroad?

Further information

Despite recommendations from medical professionals, the ultimate decision to travel lies with the patient. In this case, Amy says postponing the trip is not an option: she has already paid for it all and has always wanted to see the gorillas. She adds that once she has the baby it will be years before she will be able to do it. She understands that there is some risk but she has travelled before and knows all the tricks to reduce her risks and notes that lots of women are pregnant in Africa.

Question 8

Is it safe for Amy to travel while pregnant?

CASE 5 Answers

Answer 1

An initial question to ask Amy would be whether she absolutely had to do this trip while she was pregnant and to explain the risks to her and her unborn child if she goes ahead. The advice would be to not go on the trip at this point in time.

It is important to ask Amy:

- whether she has had any problems with her pregnancy
- whether she has any underlying medical issues
- whether she has any allergies
- what previous experience she has in adventure travel.

Answer 2

It is more than three years since Amy's last typhoid vaccine so she will need a booster. In pregnancy, the inactivated injectable vaccination rather than the live oral capsules is used.

Uganda is currently on the World Health Organization's (WHO's) list of polio outbreak countries.[1] The WHO recommends that all travellers to polio-affected areas should be fully vaccinated against polio. Residents from infected areas (and visitors travelling to affected regions for more than four weeks) should receive an additional dose of oral

poliovirus vaccines (OPV) or inactivated polio vaccine (IPV) within four weeks to 12 months of leaving the outbreak country. The *Australian immunisation handbook* recommends vaccination for travellers to areas or countries where polio is epidemic (outbreaks) or endemic.[2] Boosters should be given to all adults visiting these high-risk countries.

Yellow fever is also endemic in Uganda. A yellow fever vaccination certificate is required for all travellers aged one year or more and is mandatory for entry into the country. Yellow fever vaccination is also recommended for travellers aged one year or over travelling to Kenya, which is also endemic, but is not required for entry unless the traveller is coming from a yellow fever endemic country. In Amy's case, this means she does not require yellow fever vaccination to enter Kenya directly from Australia but would need it when entering Kenya from Uganda (as Amy intends to do at the end of her trip), and she will also require a yellow fever vaccination certificate when she come back to Australia. The WHO recommends yellow fever vaccination for both Uganda and Kenya.[3,4]

Answer 3

There are many sources of contraindications and precautions for yellow fever vaccine, which include the Centers for Disease Control and Prevention (CDC) *yellow book*, the *Australian immunisation handbook* and the WHO.[5–7]

In general, precautions to an individual receiving yellow fever vaccination are:

- age >60 years
- HIV infection with a CD4 count >200 cells/mm^3
- pregnancy
- breastfeeding infants aged <nine months
- haemopoietic stem cell recipients (24 months post-transplant).

These sources might have some variation in the list of precautions, but pregnancy is always included in all.

It is important to note here that pregnancy is a precaution, not a contraindication, to yellow fever vaccine.

The Australian Immunisation Register states that yellow fever vaccine (which is a live attenuated viral vaccine) is not recommended for pregnant women. It emphasises that we should advise pregnant women against going to rural areas where yellow fever is endemic, which would be the most responsible way to manage this situation. However, if a pregnant woman insists on travel to a country with a risk of yellow fever virus, she should receive the yellow fever vaccine. Many pregnant women have received the yellow fever vaccine with no adverse outcomes.[6]

If we consider Figure 1, and as discussed previously, the WHO states that both countries are a risk of yellow fever transmission and recommends vaccination for both countries. Uganda requires proof of yellow fever vaccination to enter, as does Kenya to re-enter from Uganda.

We reach the conclusion that we should consider the risk of disease versus the risk of the vaccine for Amy. Please note that because WHO recommends the vaccination for both, a waiver should not be given in this case.

Answer 4

If yellow fever is contracted, approximately 12% of cases progress to severe disease and, of those, 30–60% die.[5]

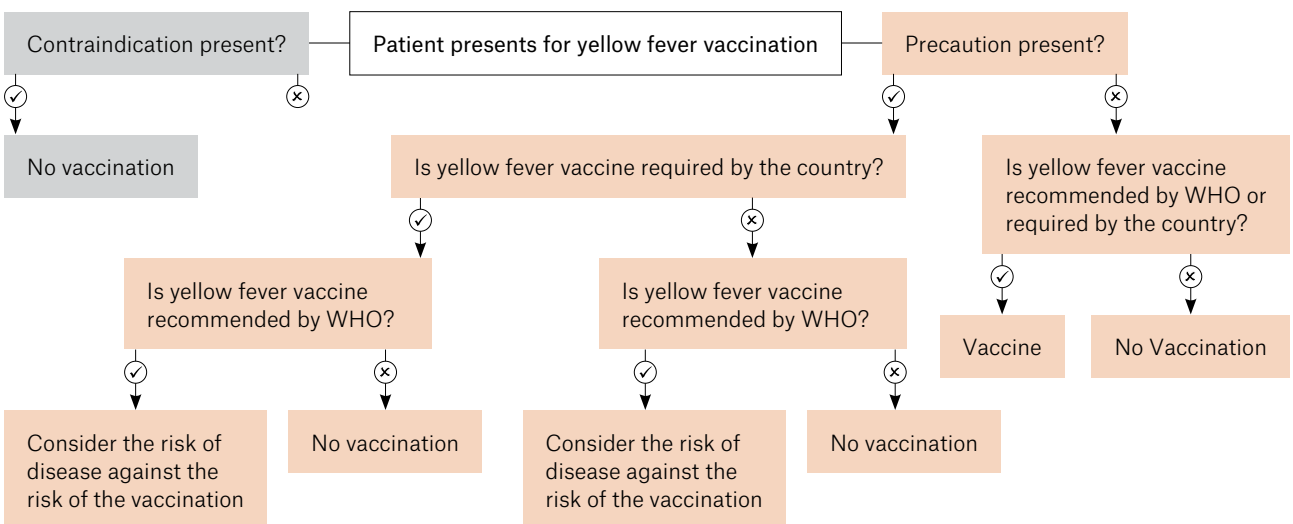

Figure 1. Yellow fever vaccination decision-making tree – Precautions.
WHO, World Health Organization.

The *CDC yellow book notes:*[5]

- The risk of acquiring yellow fever during travel is not absolute. There are variations in ecology influencing virus risk and transmission. Outbreaks might be limited to certain areas of countries. For a two-week stay, the estimated risks for illness and for death due to yellow fever for an unvaccinated traveller visiting a risk area are:
  - in West Africa, 50 per 100,000 and 10 per 100,000, respectively
  - in South America, five per 100,000 and one per 100,000, respectively.

West Africa has a higher risk than East Africa as many of the countries have outbreaks often. There has been an outbreak of yellow fever in Kenya in 2023 in Isiolo province, which is not included in Amy's itinerary.[8] Uganda has also reported some sporadic cases of yellow fever.[9]

Amy's risk of acquiring yellow fever disease in two weeks is approximately 50 in 100,000. The risk of side effects to the yellow fever vaccine is a 10–30% chance of mild systemic adverse events, as it is a live attenuated vaccine, and includes headache, muscle ache and low-grade fever, which will become apparent within 10 days. The risk of immediate hypersensitivity is 1.3/100,000 doses. Yellow fever vaccine can also be associated with the more severe side effects of yellow fever vaccine-associated neurological disease (YEL-AND) or yellow fever vaccine-associated viscerotropic disease (YEL-AVD). The risk of YEL-AND (which is rarely fatal) is 0.8/100,000 doses and the risk of YEL-AVD (48% case fatality ratio) is 0.3/100,000 doses.

As it is a live vaccine, a live vaccine check would be needed to make sure there were no other underlying risk factors for Amy to have this vaccine.

If this information is considered, the risk of having the vaccination is less than the risk of her contracting yellow fever disease. After the pros and cons of having the vaccine have been explained to Amy, the final decision on whether she has the vaccine lies with Amy.

If, after discussion on all of these factors and Amy decides to have the yellow fever vaccination, then the vaccination should be recorded on an International Certificate of Vaccination or Prophylaxis (ICVP).

The International Health Regulations (IHR) 2005 (www.who.int/publications/i/item/9789241580496) allow countries to require proof of yellow fever vaccination documented on an ICVP as a condition of entry for travellers arriving from certain countries, even if only in transit, to prevent importation and indigenous transmission of yellow fever virus. Some countries require evidence of vaccination of all entering travellers (usually over the age of nine months).[5]

The ICVP:[5]

- becomes valid 10 days after the date of vaccination
- on 11 July 2016, the duration of validity of the ICVP for yellow fever changed from 10 years to the 'life of the person vaccinated' following amendment of Annex 7 of the IHR 2005 (www.who.int/publications/i/item/9789241580496).
- Considering the now lifelong validity of the ICVP for yellow fever for life, there are still some situations where a yellow fever booster dose is recommended. Women who were pregnant when receiving their initial vaccination should receive a booster prior to next visiting a yellow fever risk area. This is because immunological function might vary in pregnancy and the proportion of women who become yellow fever immunoglobulin G positive varies from 39% to 98% in various studies.[5]

Both Kenya and Uganda are malaria risk countries and prescription of malaria medication needs to be considered for Amy to protect her whilst travelling. This decision also needs to be considered in the light of the risk of malaria to Amy and her unborn child, compared with the risk of any proposed antimalarial medication given she is pregnant.

Answer 5

Malaria risk is high in almost all parts of Uganda and Kenya. The risk predominantly relates to *Plasmodium falciparum* in both countries. The WHO recommends the use of malaria medication for both countries.[4]

Malaria in pregnancy is associated with heavy parasitaemia, severe anaemia, hypoglycaemia and placental sequestration of the parasite. It is associated with a greatly increased risk of premature delivery, miscarriage, stillbirth and maternal death. Non-immune women, who have not been born in an endemic country and never had malaria, are at risk of more severe malaria and worse outcomes (Figure 2).

Answer 6

It is important to stress that the use of antimalarials and insect bite prevention measures does not eliminate the risk of malaria completely. Any fever experienced seven or more days after entering a malarious area should be considered malaria until proven otherwise. Specific considerations should be borne in mind when prescribing antimalarials to pregnant women.[10]

Mefloquine is categorised as B3 in the prescribing medicines in pregnancy database and is the only antimalarial recommended in pregnancy.[10] Studies carried out in pregnancy have not revealed an increase in teratogenicity or adverse outcomes. Animal studies have revealed embryotoxicity and teratogenicity at levels higher than prophylactic levels. Mefloquine is contraindicated in those with anxiety, depression or previous intolerance to the medication.

Atovaquone/proguanil is categorised as B2 in the prescribing medicines in pregnancy database but as yet is not routinely given in pregnancy.[10] There have been no adverse outcomes with animal testing at levels above those used for prophylaxis. The safety of the drug combination in human pregnancy has not been established. There is no information on the effects of atovaquone administration during human pregnancy. Fetal death and malformation have rarely been reported in association with the use of proguanil.

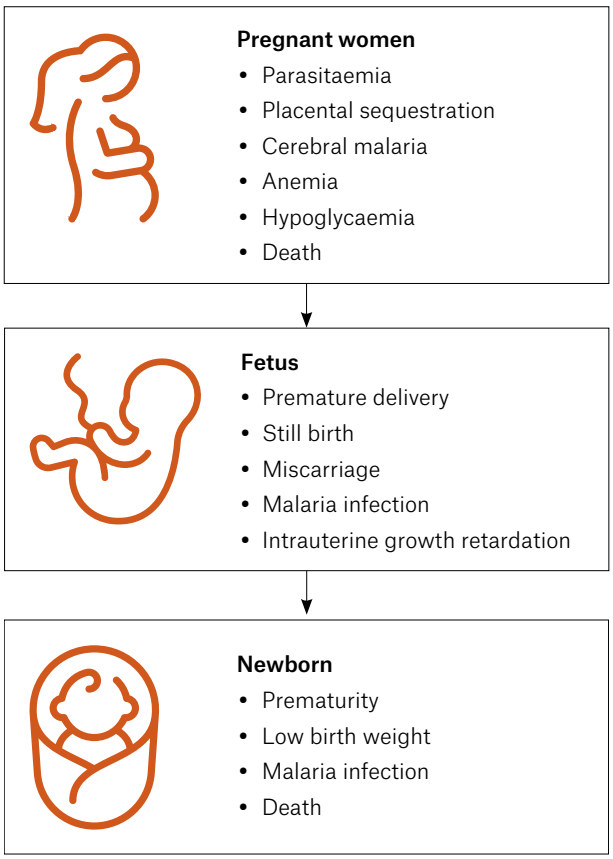

Figure 2. Risks of malaria infection during pregnancy to the pregnant woman, the fetus and newborn.

Mefloquine should be recommended for Amy as it is the only medication currently recommended during pregnancy.

For patients who insist on travelling to a malarious area and mefloquine is contraindicated, referral to a specialist travel medicine centre should be considered for consideration of prescription of atovaquone/proguanil as an option. Sending Amy away with no antimalarial medication at all is not recommended given the high risks to her unborn child and herself if she were to contract malaria.

Answer 7

Amy should be advised to take a medical kit containing medications for the management of diarrhoea and other common infections with her on her trip. For a pregnant patient, we would provide oral rehydration solution, azithromycin, ondansetron and amoxil. Advice would be given to seek medical care first if available. The medications are given under strict counselling for how they should be used. As she will be in very remote areas with little quality medical care they are provided to her if she requires them but is unable to seek medical care. She should also be advised to avoid swimming in inland water catchments due to the risk of schistosomiasis (bilharzia) in Kenya and Uganda.

In addition, Amy should be advised on measures to prevent insect bites to reduce the risk of dengue fever, malaria, tsetse flies, ticks and other insects. This includes:

- using 30–40% DEET insect repellent (okay for use in pregnant women)
- wearing long, light clothing to cover as much of the body as possible
- using mosquito nets where possible (this might be difficult in tents so you could suggest she invests in an impregnated sleep sheet; eg anti-insect anti-bacterial sleeping bag liners, https://www.equip.com.au/products/category.aspx?cid=27)
- minimising the time spent outside at night (when outside at night, she should wear impregnated clothing and insect repellent).

Answer 8

Amy is a midwife, and being a health professional is likely to understand the discussion regarding the risks to herself and her unborn child. We have already recommended that she should reconsider her trip given the risks of vaccines and malaria medications, as well as the risks if she were to contract these diseases. Given she has decided to still travel it is imperative that we cover other really important factors for pregnant women to be aware of, in general, for travel.

In general, pregnant travellers should be advised that:

- it is better to travel in the second trimester as it is the least risky time of pregnancy for complications
- insurers should be made aware of travel plans and extra cover taken out. The unborn child is considered as an individual who is uninsured if there is premature delivery or other complications
- a letter from an obstetrician outlining progress of the pregnancy so far should be taken on the trip so that if medical care is needed overseas, the treating doctor has the information of the pregnancy so far at hand
- medical treatment might be more difficult to access, particularly in remote areas, and might not be of the standard that is available at home
- environmental risks need to be considered, particularly with regard to activities undertaken. For example, in Amy's case, trekking in a tropical environment is not recommended when pregnant
- airlines impose limits on when pregnant women can travel based on gestation[11]
- while it is best to give as few vaccinations as possible during pregnancy, generally many vaccinations (although not live vaccinations) are safe for pregnant women.[12]

There has recently been an outbreak of Ebola virus in Uganda that would need to be considered.[13]

Conclusion

Amy decides that she has to go on the trip and decides to have the polio and typhoid vaccinations. After discussion, she decides to take the yellow fever vaccination and mefloquine for malaria. She also takes a kit for diarrhoea, including a broad-spectrum antibiotic, as well as permethrin for her clothing, a 30–40% DEET insect repellent and a permethrin-impregnated sleep sheet.

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Multiple-choice questions

Case 1 – Abdul

Abdul, aged 25 years, is planning a six-week trip to South Sudan, a malaria-endemic country where he will be visiting friends and relatives. Abdul was born in Australia and is up to date with all vaccinations according to the Australian National Immunisation Program schedule. His Australian immunisation statement also shows that he received parenteral hepatitis A, typhoid, yellow fever and meningococcal ACWY vaccines prior to his last trip to South Sudan four years earlier, and a second dose of hepatitis A vaccine six months later. Abdul has a history of glucose-6-phosphate dehydrogenase (G6PD) deficiency, and depression, for which he takes fluoxetine. During his last trip to South Sudan, he took doxycycline for malaria prophylaxis, but stopped this early due to severe indigestion; he is not keen to take this again.

Question 1

Which of the following vaccines should be recommended to Abdul prior to this trip?

A. Yellow fever

B. Hepatitis A

C. Typhoid

D. Japanese encephalitis

Question 2

Which of the following would be the most appropriate antimalarial chemoprophylaxis option for Abdul?

A. Atovaquone/proguanil

B. Doxycycline

C. Mefloquine

D. Tafenoquine

Case 2 – Shane

Shane, aged 30 years, recently returned from India with fever, malaise, rash all over his body and lymphadenopathy. He was on holiday for one month with friends.

Question 3

Which of the following should be considered in the differential diagnosis?

A. Dengue fever

B. Primary HIV infection

C. Secondary syphilis

D. All of the above

Question 4

Which of the following red flags, if present, indicate hospital admission?

A. Any rise in liver transaminases

B. Persisting right hypochondrial pain

C. Petechial rash

D. Platelet count of 110 x 10^9/L

Question 5

Which of the following statements are true in the management of dengue fever?

A. Daily monitoring of full blood count

B. Ibuprofen for high-grade fever

C. Plenty of fluids

D. All of the above

Case 3 – Julie

Julie, aged 22 years, was bitten by a dog four days earlier while holidaying in Bali. She presents the day after returning home. The dog belonged to the owner of the establishment where she was staying and jumped up and bit Julie on the arm while they were playing. She was given a dose of Rabivax later that day at a medical centre.

Question 6

With regard to rabies post-exposure prophylaxis, what is the next step?

A. Commencement of post-exposure prophylaxis is urgent

B. Even if rabies vaccination has been commenced overseas, it should be recommenced in Australia with TGA-approved vaccines according to the recommended schedule in Australia

C. A person who has been vaccinated against rabies does not require post-exposure prophylaxis (human rabies immunoglobulin [HRIg] and rabies vaccination)

D. Patients should also be assessed for whether they need a tetanus booster

Question 7

With regard to HRIg, which of the following is correct?

A. It is only required for deep wounds that penetrate deeper than the dermis

B. It is required for 48 hours after potential exposure to rabies virus

C. It should not be given from one week post rabies vaccination

D. It works to potentiate the effectiveness of the rabies vaccine

Case 4 – George

George, aged 27 years, presents with a new rash all over his body that is not itchy. He first noticed the rash four days earlier and has been feeling well otherwise with no other symptoms. He advises that he has recently returned home to Australia after 12 months away on a working holiday.

Syphilis serology detects *Treponema pallidum* immunoglobulin G antibodies and a rapid plasma reagin (RPR) test returns a result of 32.

Question 8

The recommended first-line treatment for infectious syphilis is:

A. Phenoxymethylpenicillin 500 mg orally four times a day for seven days

B. Procaine penicillin 1 g intramuscularly immediately

C. Benzathine benzylpenicillin 2.4 MU intramuscularly immediately

D. Benzylpenicillin 300 mg intravenously four times a day for seven days

Case 5 – Amy

Amy, aged 29 years, is 15 weeks pregnant and wants to travel to Kenya and Uganda in Africa.

Question 9

What vaccinations can be recommended for this trip?

A. Typhoid only

B. Typhoid, polio

C. Typhoid, polio, yellow fever

D. She cannot have any vaccines as she is pregnant

Question 10

Which antimalarial would you recommend for Amy?

A. Mefloquine

B. Atovaquone/proguanil

C. Malaria tablets should not be given to pregnant travellers as the risk of side effects and foetal toxicity is too high

D. Chloroquine

twinrix
combined hepatitis A and hepatitis B vaccine

GSK

The only combined hepatitis A and B vaccine[1,2]

Don't assume travellers aged 36+ are not at risk!*

*** Most Australians aged 36 years + are not likely to be vaccinated against hepatitis B. Routine infant vaccination began nationally in 2000 and funding for adolescent vaccination ran from 1996 to 2013.[3,4]**

For travellers to hepatitis A and B endemic areas, TWINRIX:[1]

- Provides **long-term protection in only 3 doses**.§
  - For non-immune individuals aged ≥16 years, a three dose standard schedule consists of 0, 1 and 6 months^
- Offers a **4-dose rapid schedule**.ǂ
  - For non-immune individuals aged ≥16 years, a four dose rapid schedule consists of 0, 7, 21 days and 12 months
- Is **generally well tolerated**. Commonly reported adverse events were injection site reactions (pain, redness and swelling), headache, fatigue, malaise, gastrointestinal symptoms (such as diarrhoea, nausea, vomiting) and viral infection.‖

TWINRIX (720/20) is indicated for active immunisation against hepatitis A and hepatitis B virus infection in individuals from 1 year of age.[1]

TWINRIX should be administered intramuscularly into the deltoid region of the upper arm in adults and older children. TWINRIX should never be administered intravenously.

§ Long-term clinical studies have demonstrated persistence of anti-hepatitis A virus (anti-HAV) and anti-hepatitis B surface antigen (anti-HB) antibodies 15 years after immunisation with TWINRIX.[1]
^ For paediatric dosing schedule please see the full product information.[1]
ǂ The rapid schedule is used in exceptional circumstances in adults when more rapid protection is required, e.g. in travellers commencing vaccination within one month of departure.[1]
‖ Adverse events classed as very common (≥1/10) and common: ≥ 1/100 and < 1/10 , based on data from clinical trials where Twinrix was administered to >6,000 subjects who received either the standard 0,1, 6 month schedule or the accelerated 0, 7, 21 days schedule of TWINRIX (720/20).[1]

PBS Information: This product is not listed on the National Immunisation Program (NIP) or the PBS.

Please review full Product Information before prescribing. Product Information can be accessed at www.gsk.com.au/twinrix or by scanning the QR code

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