Hepatitis E virus infections in travellers: assessing the threat to the Australian blood supply

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Background. In many developed countries hepatitis E virus (HEV) infections have occurred predominantly in travellers to countries endemic for HEV. HEV is a potential threat to blood safety as the virus is transfusion-transmissible. To minimise this risk in Australia, individuals diagnosed with HEV are deferred. Malarial deferrals, when donors are restricted from donating fresh blood components following travel to an area in which malaria is endemic, probably also decrease the HEV risk, by deferring donors who travel to many countries also endemic for HEV. The aim of this study is to describe overseas-acquired HEV cases in Australia, in order to determine whether infection in travellers poses a risk to Australian blood safety.

Materials and methods. Details of all notified HEV cases in Australia from 2002 to 2014 were accessed, and importation rates estimated. Countries in which HEV was acquired were compared to those for which donations are restricted following travel because of a malaria risk.

Results. Three hundred and thirty-two cases of HEV were acquired overseas. Travel to India accounted for most of these infections, although the importation rate was highest for Nepal and Bangladesh. Countries for which donations are restricted following travel due to malaria risk accounted for 94% of overseas-acquired HEV cases.

Discussion. The vast majority of overseas-acquired HEV infections were in travellers returning from South Asian countries, which are subject to donation-related travel restrictions for malaria. This minimises the risk HEV poses to the Australian blood supply.

Keywords: risk, safety, transfusion, travel, hepatitis.

Introduction

Hepatitis E virus (HEV) is a cause of acute hepatitis[1], associated with large outbreaks of disease in developing countries as a result of faecal-oral transmission[2]. In contrast, in some developed countries, the majority of cases are associated with travellers returning from countries endemic for HEV[2-4]. Autochthonous HEV infection transmitted via the consumption of undercooked contaminated meat or contact with infected animals, has recently emerged as a major route of transmission in developed countries[5-7]. Other modes of transmission include congenital transmission, as well as transmission through infected organs or blood[3,8], which has led to HEV gaining the attention of the transfusion medicine community.

HEV is a single-stranded positive-sense RNA virus. The virus is the only member of the genus of the *Hepeviridae* family[9]. There are four known genotypes (HEV 1, 2, 3 and 4) that infect humans, subdivided into 24 sub-genotypes[9,10], which represent a common serotype[2]. The geographical distribution and mode of transmission of the genotypes differ[11]. Genotypes 1 and 2 only infect humans and are reported in Asia and Africa, whereas genotypes 3 and 4 infect humans and animals and are seen in Europe, and South-east Asia[3]. HEV genotype 3 has also recently been reported in the USA[12]. The route of transmission of genotypes 1 and 2 is faecal-oral, while genotypes 3 and 4 are predominantly transmitted via contact with infected animals or through the consumption of undercooked infected meat (primarily pork, but also deer and wild-boar), but infections can occur via the faecal-oral route[3,4].

In 2005, it was estimated that, globally, there were 20.1 million incident HEV genotype 1 and 2 infections, resulting in 3.4 million symptomatic cases, 70,000 deaths

and 3,000 still births[13]. The mortality rate in pregnant women in developing countries can be up to 25%[2].

Although the majority of HEV infections are asymptomatic, there are differences in asymptomatic rates between developing countries (up to 50% of cases can be asymptomatic) where genotypes 1 and 2 predominate and developed countries (the asymptomatic rate can be 67-98%) where genotypes 3 and 4 predominate[5]. This may be due to the infecting genotype, or the underlying health of the population. The symptoms of HEV infection are similar to those of infection with other hepatitis viruses and include anorexia, vomiting, jaundice and hepatomegaly[2]. Chronic HEV infections, due to genotypes 3 and 4, with a viraemic phase of more than 3 months, have been reported in solid organ transplant recipients and in patients with immunosuppressive disorders[14].

HEV is nationally notifiable in Australia[15]. The seroprevalence of HEV was estimated to be 5.9% among Australian blood donors, with a higher prevalence in donors reporting overseas travel (6.4%) than in donors who had not travelled overseas (3.4%)[16]. HEV cases have been associated with travel to countries endemic for HEV, including India, Sri Lanka, Vietnam and Thailand[17]. Locally acquired HEV infections are also reported in Australia, albeit more rarely. Thirty-five HEV cases were reported between October 2013 and June 2014, from the state of New South Wales, all in subjects with no recent overseas travel history and all linked to the consumption of undercooked infected pork[18]. Eighteen of these cases were associated with an outbreak from a single restaurant[18]. Recently a case of locally acquired HEV was reported in a liver transplant recipient who had also received a blood transfusion[19]. There was insufficient evidence to elucidate the exact route of transmission, however, it was postulated to include contaminated food or the transfusion[19].

There has been increasing concern within the transfusion community about HEV, given the high proportion of asymptomatic infections. HEV RNA has been detected in blood donors in the United Kingdom, Japan, Germany, The Netherlands, Spain and Scotland[1,9]. Moreover, transfusion-transmitted HEV (TT-HEV) has been reported in the United Kingdom, Japan and France[1,20,21], leading to symptomatic disease in some transfusion recipients[21,22]. HEV has also been transmitted via plasma treated with a pathogen inactivation technology, which demonstrates resistance of the virus to that type of pathogen reduction technology[23].

To date there are no published case reports of TT-HEV in Australia. Blood donations are currently not screened for markers of HEV infection in Australia; however, such testing has been proposed in France and the United Kingdom[24,25], and has been implemented in the Hokkaido region of northern Japan[24,26]. The Australian Red Cross Blood Service (Blood Service) manages the risk of TT-HEV through examination of potential donors' medical and travel history via a mandatory pre-donation questionnaire. This results in the total exclusion of individuals diagnosed with an HEV infection for 12 months from the date of their recovery[27]. Moreover, in instances in which a donor notifies the Blood Service of a post-donation infection, fresh components (red blood cells, platelets and fresh frozen plasma) are recalled for up to 2 months prior to the date of the donor becoming ill[27]. Potential donors are also deferred from all types of blood donation if they have had household or sexual/mucosal contact with an infected person[27]. Donors are also excluded from donating fresh components for a minimum of 120 days after travel to countries endemic for malaria and until the donation tests negative on malarial antibody screening[27]. This travel deferral may prevent the risk of collecting an HEV infectious donation as many of these countries are also endemic for HEV.

The aim of this study was to describe overseas-acquired HEV cases notified in Australia in order to determine whether infection in travellers poses a risk to Australian blood supply safety. This will provide evidence in relation to whether the existing Blood Service travel-related exclusion policy for malaria manages the potential risk of TT-HEV from travellers.

Materials and methods

Hepatitis E virus surveillance system in Australia

Hepatitis E is classified as a gastrointestinal disease and there is a requirement for all cases to be notified to state and territory health departments under their public health legislation. States and territories forward de-identified notification data to the Australian Government Department of Health's National Notifiable Diseases Surveillance System (NNDSS)[28]. Only confirmed cases of HEV are notified, and HEV has been nationally notifiable since 1999. Cases therefore represent only those HEV infections for which health care was sought by the patient, a test conducted, diagnosis made and confirmed, followed by notification to a health authority.

Case definition

A confirmed case of HEV infection refers to one confirmed by definitive laboratory evidence. During the period of this study, the evidence was based on detection of: HEV RNA by nucleic acid testing; identification of the virus by electron microscopy; IgG seroconversion; or a 4-fold or greater rise in antibody titre to HEV[15]. A case was also considered to be confirmed if suggestive laboratory evidence (detection of HEV IgG or IgM) was

supported by clinical evidence (a clinically compatible illness) and epidemiological evidence (travel to an HEV endemic country 15-64 days prior to the onset of disease or an epidemiological link to a confirmed case)[15].

Hepatitis E virus cases

Details of all HEV cases notified to public health authorities based on diagnosis date between 2002 and 2014 inclusive were extracted from the NNDSS. These data included date of diagnosis, age, sex, state/territory of residence, and country of acquisition. The age of an individual was as reported to the health authority or calculated at onset, using the difference between date of birth and date of diagnosis. The place of acquisition was usually obtained through public health follow-up.

Overseas travel data

The number of short-term resident returns and visitor arrivals in Australia were obtained from the Australian Government Department of Immigration and Border Protection website[29]. Visitor arrivals were included in this analysis because all hepatitis E infections diagnosed in Australia are notified to the NNDSS, including international visitors. Furthermore, providing that all other donation requirements are met, international visitors are able to donate in Australia, although this group likely accounts for a small proportion of the total donor pool. These data were obtained from July 2004 to December 2014 for countries of relevance. The source of Overseas Arrival and Departure (OAD) data (arrival and departure data for Australian residents or overseas visitors, through Australian airports and seaports) was incoming and outgoing passenger cards, which were matched with data from passports and visas[30]. OAD data describe the number of movements of travellers rather than the number of travellers[29].

Data analysis

Firstly, HEV cases in Australia were separated based on place of acquisition (local, overseas, and unknown). As this study focused on HEV cases in Australia acquired overseas, only overseas-acquired infections were included in subsequent analyses. These cases were then described by age, sex, year and seasonal of acquisition, as well as country of acquisition. The estimated HEV importation rate was then determined for countries with five or more cases of overseas-acquired HEV, based on the number of people in Australia who had recently (within 1 year) travelled to such countries. Short-term movement information was used rather than long-term movement to capture recent travel and to minimise inaccuracies due to travel to multiple countries (more likely with longer travel). Short-term movements refer to movements within 1 year and include short-term resident departures, short-term resident returns, short-term visitor departures and short-term visitor arrivals[30]. Short-term resident return data were used to capture travel of Australian residents, while short-term visitor arrival data were used for travelling non-residents. The number of people (short-term resident returns and short-term visitor arrivals) arriving in Australia following travel to countries where five or more HEV cases were acquired during the study period were calculated. Importation rates over the study period were calculated per 10,000 persons. Countries that were a source of overseas-acquired HEV were then compared to those for which donations are restricted for travel due to malaria-risk in accordance with the Blood Service's *Guidelines for Selection of Blood Donors (GSBD)*. Only individuals between the ages 15-69 years, representing those who are eligible to donate blood in Australia, were included in this analysis.

Results

During the study period, there were 400 cases of HEV notified to Australian health authorities. Of these, 332 cases (83%) were acquired overseas, with 41 (10%) locally-acquired and 27 (7%) cases with an unknown country of acquisition (Table I). Only those cases confirmed to be acquired overseas were included in subsequent analyses. No individual had more than one country of acquisition listed. The highest number (13%) of overseas-acquired HEV cases occurred in 2008, however, trends by year were non uniform and no seasonality was

Table I - Place of acquisition of HEV infection in cases notified in Australia between 2002 and 2014.

Year	Place of acquisition		
	Overseas	*Local*	*Unknown*
2002	6	0	5
2003	7	2	3
2004	25	1	2
2005	29	1	0
2006	22	1	1
2007	16	1	1
2008	42	2	0
2009	30	2	1
2010	33	2	2
2011	35	3	3
2012	31	0	1
2013	27	5	2
2014	29	21	6
Total	332	41	27

HEV: hepatitis E virus.

observed (Figure 1a). Sixty-five percent of overseas-acquired HEV infections were in males, and 22% of cases were in individuals aged 25-29 years (Figure 1b). Forty percent of the individuals with overseas-acquired HEV resided in the state of New South Wales, 32% came from Victoria, 13% from Queensland and 13% from the remaining states/territories (Table II).

Travel to India accounted for 48% of overseas-acquired HEV infections, followed by travel to Bangladesh (12%), Nepal (7%) and Pakistan (4%) (Table II). Based on the number of travellers arriving in Australia, the risk of HEV acquisition was highest for travel to Nepal (18 per 10,000 arriving travellers), and Bangladesh (17 cases per 10,000 travellers) followed by Sudan (14 cases per 10,000 travellers) and Pakistan (5 per 10,000 travellers) (Table III).

All these "higher-risk" countries are also endemic for malaria; blood donors returning from these countries are unable to donate fresh components for 4 months following their return. Moreover, countries for which

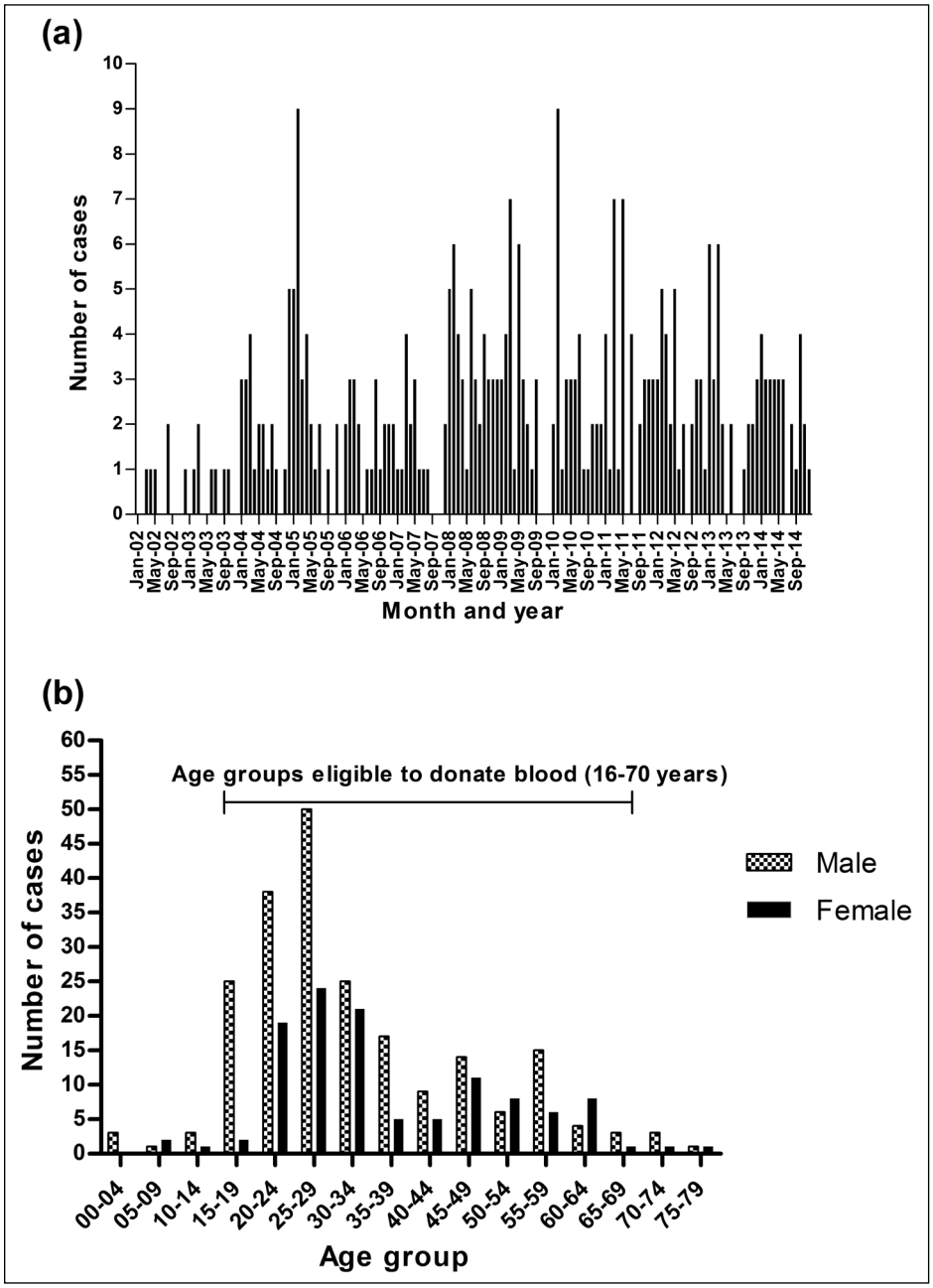

Figure 1 - Overseas-acquired HEV cases notified in Australia between 2002 and 2014, by month and year (a) and by age group and sex (b).
HEV: hepatitis E virus.

donations are restricted following travel due to malaria-risk accounted for 94% (298/316) of overseas-acquired HEV cases, within the age range of people eligible to donate blood in Australia.

Discussion

Due to accumulating reports of TT-HEV, this agent has gained the attention of the transfusion medicine community globally. In Australia, diagnosed autochthonous HEV is rare, with the majority of infections occurring in overseas travellers. Indeed, we previously showed that 6.4% of Australian blood donors who had travelled overseas had been previously exposed to HEV[16]. The present study demonstrates that the majority of notified overseas-acquired HEV infections in Australia were in travellers returning from South Asia, namely India, Bangladesh and Nepal. These countries are endemic for HEV, where large water-borne outbreaks occur seasonally[9,31-33]. Thus, there is a potential risk to blood safety in Australia from donors after their return from such countries. However, we also show that the majority of cases of imported HEV were acquired in countries for which donation-related travel restrictions for malaria exist, demonstrating that existing Blood Service travel deferral policies assist with minimising the risk to fresh components from imported HEV infections.

Table II - Country of acquisiton of overseas-acquired HEV cases notified in Australia between 2002 and 2014.

Country	State of residence									Total
	ACT	*NSW*	*NT*	*QLD*	*SA*	*TAS*	*VIC*	*WA*	*Unknown*	
India	6	58	0	17	0	1	66	11	1	160 (48.19%)
Bangladesh	2	24	0	2	0	0	10	2	0	40 (12.05%)
Nepal	1	12	0	1	0	0	6	0	2	22 (6.63%)
Pakistan	2	7	0	0	0	0	5	0	0	14 (4.22%)
China[a]	0	7	0	4	0	0	3	0	0	14 (4.22%)
Thailand	0	4	0	1	0	0	3	4	0	12 (3.61%)
Vietnam	0	2	0	3	0	0	4	0	0	9 (2.71%)
Indonesia	0	4	0	0	0	0	0	2	1	7 (2.10%)
Sudan	0	2	0	1	0	0	2	0	0	5 (1.51%)
Hong Kong	0	3	0	1	0	0	0	1	0	5 (1.51%)
Papua New Guinea	0	1	0	1	0	0	1	0	0	3 (1%)
Timor-Leste	0	0	3	0	0	0	0	0	0	3 (1%)
Other countries[b]	2	9	0	12	0	2	7	4	2	38 (11.45%)
Total	13 (3.92%)	133 (40.06%)	3 (1%)	43 (12.95%)	0	3 (1%)	107 32.23%)	24 (7.23%)	6 (1.81%)	332

[a]Excludes SARs (Special Administrative Regions) and Taiwan; [b]other Countries: Afghanistan (n=1), The Americas (n=1), Cambodia (n=2), Chinese Asia (includes Mongolia; n=1), Egypt (n=1), Greece (n=2), Iran (n=2), Italy (n=1), Mainland South East-Asia (n=1), Malaysia (n=2), Mozambique (n=1), Namibia (n=1), North Africa (n=1), North-East Asia (n=1), Peru (n=1), The Philippines (n=2), Singapore (n=3), South-East Asia (n=2), Southern Asia (n=1), Sri-Lanka (n=2), Turkey (n=1), United Arab Emirates (n=1), United Kingdom Channel Islands and Isle of Man (n=1), other unknown countries (n=6). HEV: hepatitis E virus; ACT: Australian Capital Territory, NSW: New South Wales, NT: Northern Territory, QLD: Queensland, SA: South Australian, TAS: Tasmania, VIC: Victoria, WA: Western Australia

Table III - HEV importation rate per 10,000 travellers, July 2004 - December 2014, by country of acquisition.

Country	Number of imported cases	Total travellers	HEV importation rate
Bangladesh	40	23,227	17.22
China*	14	5,742,036	0.02
India	160	527,244	3.03
Indonesia	6	7,295,352	0.01
Nepal	22	12,404	17.74
Pakistan	14	28,226	4.96
Sudan	5	3,652	13.69
Thailand	12	6,320,903	0.02
Vietnam	9	1,264,056	0.07

*Excludes SARs (Special Administrative Regions) and Taiwan. HEV: hepatitis E virus.

Despite seasonal HEV outbreaks occurring in developing countries[5], no seasonality was observed in HEV cases in Australian travellers during the study period. Possible reasons for this could be due to ill travellers being diagnosed overseas, a lag between infection and notification in Australia, or the effect being masked by under-reporting given the high rate of asymptomatic infections. In many developed countries, where HEV genotype 3 and 4 infections occur, elderly males are predominantly affected[4]. Here we show higher numbers of cases among males and in younger-aged individuals. This could be due to the different genotypes present in South Asian countries[9], which account for the majority of notified overseas-acquired HEV cases in Australia. The demographics of Australian travellers and/or food habits of younger travellers could also explain this.

Where known, the countries of acquisition of all cases in this study are endemic for HEV. Specifically, 83% of overseas-acquired cases notified were acquired in India, Bangladesh, Nepal, Pakistan, Sudan, China (excluding the Special Administrative Regions and Taiwan), Vietnam or Thailand. The year with the highest number of imported HEV cases was 2008; this may be linked to outbreaks of HEV in these countries. Indeed, in 2008 there were notable outbreaks of HEV in Bangladesh and India[33,34]. Despite the highest number of cases being from India, the rate of HEV importation was higher from Nepal, Bangladesh, Sudan and Pakistan, due to the large numbers of travellers to India and smaller numbers to Nepal, Bangladesh, Sudan and Pakistan. Thus, both the number of cases and number of travellers returning from respective countries should be considered when determining which countries are "at-risk". One of the limitations of this study is that OAD data represent number of movements rather than number of travellers; however, in the absence of data in relation to the latter, we have used these OAD estimates to approximate the rate of HEV importation.

HEV is transfusion-transmissible and hence importation of HEV into Australia has the potential to compromise the safety of the Australian blood supply. Current strategies to mitigate the risk of TT-HEV include a medical and travel history examination and donor questionnaire. Symptomatic cases of HEV are managed by deferring potential donors from donating for 12 months from the date of recovery; however infected donors may escape detection if their infection is in the incubation period[27]. Indeed, given that cases are viraemic before the onset of symptoms and the majority of cases are asymptomatic, this strategy has only limited effectiveness in mitigating the risk of TT-HEV.

The Blood Service GSBD lists countries "at-risk" for various infectious diseases to ensure transfusion safety. Travel risk is assessed via a questionnaire that asks whether a donor has travelled overseas in the past 3 years. Here we show that 94% of notified overseas-acquired HEV cases were acquired from countries for which donors are currently restricted from donating fresh components for 4 months after leaving such countries, due to the risk of malaria[27]. Countries that were sources of HEV infection in Australia but are not covered by malaria restrictions include the Americas (n=1), Greece (n=2), Hong Kong (n=5), Singapore (n=3), United Arab Emirates (n=1), and the United Kingdom, Channel Islands and Isle of Man (n=1), however, based on these very small numbers of cases, travel to such countries is unlikely to pose a significant risk to transfusion safety in Australia. The typical duration of HEV viremia of 4 to 6 weeks in most individuals[2] has recently been challenged by the findings of a study of asymptomatic viraemic Dutch blood donors[35], in whom the authors estimated the mean duration of viremia to be 68 days. However, this calculation excluded donors with a shorter period of viremia in whom the duration could not be calculated, and repeat testing documented very low viral loads at levels where infectivity has not been determined. Thus, the existing 4-month travel deferral policies assist with minimising the risk to fresh components from imported HEV infections.

Under-reporting of HEV is likely as most cases are asymptomatic[9]. There is also a likelihood of misdiagnosis, as infection with HEV shares common clinical features with other infections by other hepatitis viruses and drug-induced liver injury[36], or the possibility of under-diagnosis, perhaps due to limited knowledge among general practitioners concerning this disease. Since the majority of HEV infections with genotype 3 are asymptomatic (67-98%)[5], such cases are unlikely to be identified and notified. This is of particular significance for transfusion safety, given that genotype 3 can cause chronic infection in patients with immunosuppressive disorders, who are disproportionately represented as fresh blood component recipients. Overseas-acquired notification data may, therefore, more likely represent genotype 1 and 2 infections and these data may not reflect the transfusion risk. Under-diagnosis is also possible as laboratory diagnosis for HEV is often considered only for overseas travellers in Australia[37], however, this message is actively being challenged by public health authorities. Moreover the case data used in this study were generated after health care had been sought, laboratory testing conducted and a confirmed diagnosis made by a clinician, followed by notification to health authorities. Data analysed in this study are, therefore, only for symptomatic cases of HEV in Australia; to understand the real rate of HEV importation into Australia a study examining HEV prevalence in returned travellers is needed. In this study,

no information was available on whether a notified case was HEV antibody and/or RNA positive, and if the latter, the infecting genotype. This therefore prevented us hypothesising the mode of transmission.

Self-limiting acute cases of HEV do not require treatment. Chronic HEV infections are treated with ribavirin and pegylated interferon-α[5]. A vaccine, HEV 239 (Hecolin; Xiamen Innovax Biotech, Xiamen, China), has been licensed in China[37], and may be used for high-risk groups in countries endemic for HEV, such as women of child-bearing age. In developed countries such as Australia, HEV safety precautions should be advised to travellers, and should include general awareness of pathogens transmitted via the faecal-oral route, as well as a recommendation for proper handling and cooking of pork, deer and wild boar. Transfusion from HEV-infected donors can have potentially severe consequences in immunocompromised recipients, and hence the threat to the blood supply from such donors also needs to be assessed.

In Australia notified HEV infections predominantly occur in overseas travellers. This situation differs from that in other developed nations such as the United Kingdom where the incidence of diagnosed HEV infection based on notification data is considerably higher than in Australia (approximately 6.5 times). In addition, the proportion of indigenously acquired infections in the United Kingdom is considerably greater than in Australia, with data from 2003-2012 indicating that half of United Kingdom HEV infections are locally acquired, with 71% in 2012[38]. We observed an increase in locally acquired HEV in the later years of this study, mainly during 2014, corresponding to an autochthonous HEV outbreak[18]. Locally acquired HEV may therefore contribute to disease burden in the future.

Conclusions

To determine the threat that HEV poses specifically to the Australian blood supply the rates of HEV viraemia in the Australian and blood donation populations need to be established. However, notification data suggest that locally acquired HEV infection is a rare disease and that the majority of HEV cases were acquired from countries for which there are travel-related restrictions to donation because of malaria risk. Given the incubation period of up to 8 weeks and expected duration of infectious HEV viraemia (4-6 weeks) in most individuals, notification data indicate that existing Blood Service travel deferral policies are effective in minimising the risk from imported HEV infections.

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Authorship contributions

ACS analysed the data and prepared the first draft of this manuscript. All Authors contributed to the study design, data interpretation, data analysis/consolidation and drafting/approval of the manuscript.

The Authors declare no conflict of interest.

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