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Re-evaluating the residual risk of transfusion-transmitted Ross River virus infection

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Background and objectives Ross River virus (RRV) is an enveloped, RNA alphavirus in the same antigenic group as chikungunya virus. Australia records an annual average of 5000 laboratory-confirmed RRV infections. While RRV is currently geographically restricted to the Western Pacific, the capacity of arboviruses for rapid expansion is well established. The first case of RRV transfusion-transmission was recently described prompting a comprehensive risk assessment.

Materials and methods To estimate the RRV residual risk, we applied laboratory-confirmed RRV notifications to two published models. This modelling generated point estimates for the risk of viraemia in the donor population, the risk of collecting a viraemic donation and the predicted number of infected components.

Results The EUFRAT model estimated the risk of infection in donors as one in 95 039 (one in 311 328 to one in 32 399) to one in 14 943 (one in 48 593 to one in 5094). The point estimate for collecting a RRV viraemic donation varied from one in 166 486 (one in 659 078 to one in 49 158) (annualized national risk) to one in 26 117 (one in 103 628 to one in 7729) (area of high transmission). The modelling predicted 8–11 RRV-infected labile blood components issued in Australia during a 1-year period.

Conclusion Considering the uncertainty in the modelled estimates, the unknown rate of RRV donor viraemia and the low severity of any recipient RRV infection, additional risk management for RRV in Australia will initially be restricted to strengthening the messaging to donors regarding prompt reporting of any post-donation illnesses.

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Introduction

Ross River virus is an arthropod-borne virus (arbovirus) belonging to the *Alphavirus* genus in the same antigenic group as chikungunya virus and transmitted by a number of mosquito species [1]. RRV is not transmitted from human-to-human but the potential for transfusion-transmission has raised concerns as the course of RRV infection includes an asymptomatic viraemic period and other arboviruses, such as dengue virus (DENV) and West Nile virus (WNV), are known to be transfusion-transmissible pathogens. [2, 3]. This potential threat to blood safety has recently been highlighted by a report in Australia of the first probable case of transfusion-transmitted RRV [4].

Ross River virus infection is the most common and widespread human arboviral disease in Australia with an average annual of 5000 laboratory-confirmed cases. RRV is endemic throughout coastal regions of northern and central Australia and epidemic in the rest of the country [5]. The pattern of RRV transmission shows seasonal and regional variability due to differences in environmental conditions that affect the mosquito vectors and native

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animal hosts of the virus. In most areas of Australia, the peak incidence of RRV infections occurs during summer and early autumn (January to March). RRV is also endemic to Papua New Guinea (PNG) and the Solomon Islands, and epidemics have previously been reported throughout the late 1970s to early 1980s in Fiji, Samoa, the Cook Islands and New Caledonia [6]. A recent seroprevalence study among donors in French Polynesia suggests continuing silent circulation of the virus [7].

Most people (55 to 75%) infected with RRV will remain asymptomatic [1]. In the 25 to 45% of symptomatic infections, the incubation period varies from 2 to 21 days with an average of 7 to 9 days [1]. The most common symptoms are fever, polyarthralgia (joint pain most commonly involving fingers, toes, wrists, ankles, knees and elbows) and rash; other symptoms may include polyarthritis, lymphadenopathy, lethargy, headache, myalgias, photophobia and glomerulonephritis [1, 8]. Fever, nausea and skin rash usually disappear within the first 2 weeks of illness, while joint, muscle and tendon pain may last longer. The typical period of incapacity is 1–2 weeks followed by a consistent path to recovery in 3–6 months [9]. Chronic RRV infection has not been reported and there have been no recorded fatalities resulting from infection with RRV. There is no currently available vaccine for RRV although one candidate has completed a phase 3 clinical trial with encouraging results [10].

Given other arboviruses such as DENV and WNV are known to be transfusion-transmissible pathogens, the possibility that blood components from a RRV-infected individual without symptoms could transmit RRV cannot be excluded [11]. Using a mouse model, we have previously demonstrated a period of asymptomatic viraemia following RRV infection [12]. These data were used to underpin risk modelling to assess the potential RRV transfusion-transmission risk. Modelling a 2004 RRV outbreak in Cairns (a city in north eastern Australia) estimated the risk of collecting a viraemic donation was one in 13 542 (range from one in 47 563 to one in 4765) – the same order of magnitude as that for a contiguous DENV outbreak.

There is no licensed RRV blood donor screening test available. The Australian Red Cross Blood Service's (Blood Service) current risk mitigation strategy for RRV transmission by blood is predominantly based on identifying donors with known RRV infection using a specific screening question in the predonation questionnaire. The Blood Service's 'Guidelines for Selection of Blood Donors' stipulates that donors with a diagnosed RRV infection are unable to donate fresh components for 4 weeks after recovery. Moreover, fresh components donated from 4 weeks before illness onset to 4 weeks after recovery must be recalled. Donors are also advised to contact the Blood Service if they develop a cough, cold, diarrhoea or other infection within a week after donation which may interdict a proportion of asymptomatic (at donation) infections conditional on donor compliance.

In May 2014, a donor reported becoming unwell 2 days after their last donation in March 2014 with what was subsequently diagnosed as RRV infection. The Blood Service commenced an investigation that provided strong evidence supporting the conclusion that a case of RRV infection in an associated recipient was transmitted by transfusion – the first ever reported case [4]. As required in Australia for any infectious agent that is newly identified as potentially transfusion-transmissible, the Blood Service undertook a risk assessment to evaluate the risk to the blood supply and determine appropriate risk management.

In this report, we present the modelled risk estimates for RRV transfusion-transmission using two published methods and assess the modelling and its implications for transfusion safety.

Materials and methods

Residual risk modelling approach

As RRV outbreaks vary in intensity and duration, the risk to the blood supply will also vary [5]. At any given time, this risk will be proportional to the rate of RRV viraemia in the donor population. As the rate of viraemia among blood donors is unknown, modelled estimates are necessary. Our previous analysis and RRV risk modelling[12] provides one such model (Blood Service model). Briefly, the central premise of this deterministic model is that the transmission risk equates to the frequency of viraemic donations, and correlates with the incidence of asymptomatic viraemia among the population-at-large. In addition, a generic infectious disease risk model has been developed for the European Centre for Disease Prevention and Control (ECDC). This model, referred to as the European Upfront Risk Assessment Tool (EUFRAT), has been validated for chikungunya and Q Fever [13, 14]. The EUFRAT is a compartmental, simulation module that comprises five sequential steps to estimate the infection risks in the blood transfusion chain: (i) the prevalence of infection (viraemia) in the donor population, (ii) the risk of obtaining infected donations, (iii) infected components, (iv) infected blood products and (v) the risk of transmitting the infection to recipients. The model uses inputs from epidemiologic characteristics of the pathogen of interest and transfusion practice.

The previously noted probable case of transfusion-transmitted RRV occurred following a visit by the donor to south Western Australia (WA) during March 2014 – traditionally a location of high-intensity RRV transmis-

sion at that time of year [5]. Given this, the approach used in this analysis was to model the residual risk of RRV transmission (using both the Blood Service and EUFRAT models) by place of residence in WA for a 12-month period and during the period of highest RRV notifications (January to March, 2014). The latter allows for a more precise spatial risk estimate, which is important in the context of any mitigation strategy based on targeted discontinuation of blood collection in areas of high transmission. For comparison, we also estimated the 'average' national risk using annual RRV notifications from all Australian jurisdictions.

Outbreak data

Population data

Blood donors in Australia are eligible to donate between the ages of 16 and 80 years; thus, where possible, we sourced age-matched general population data for use as the denominator to estimate the incidence of RRV infection. We used national data from the Australian Bureau of Statistics (ABS) for the number of 16- to 80-year-old residents of Australia as at 30 June 2013 [15]. For WA, we used population data for the combined total of individuals 15–84 years (as at August 2014) provided by the Communicable Disease Directorate of the WA Department of Health.

RRV notifications

As RRV is a nationally notifiable disease, monthly notification totals for the period from 1 June 2013 to 31 May 2014 were sourced from the National Notifiable Disease Database [16]. RRV notifications for the same period for the state of WA were provided by Communicable Disease Control Directorate of the WA Department of Health. National data did not identify RRV notifications by age so the total RRV notifications include those from all ages, whereas the WA data were provided within age categories, and therefore, we included only notifications from 15- to 84-year-olds.

Modelling

We applied both the published Blood Service model [12] and the EUFRAT model[13] to laboratory-confirmed RRV notifications for the 12-month period from 1 June 2013 to 31 May 2014 (National and WA) and for the period from 1 January 2014 to 31 March 2014 (WA only). The annual notification data provide an average or baseline risk, whereas the 3-month period was selected as it represents the period of highest WA notifications (as indicated by long-term data reporting) and included the date of the reported probable RRV transfusion-transmission case [4].

Input parameters and assumptions

Key input parameters for the Blood Service and EUFRAT models were derived (Supporting information Tables S1 and S2). For the Blood Service model, these remain unchanged from the previously reported application to the 2004 Cairns outbreak [12]. EUFRAT model input parameters were selected from the most appropriate published values or based on internal Blood Service data. Chronic infection is not a feature of RRV disease, and accordingly, the input parameter for chronic infections was set at zero. To date, there are no data on the probability of an infected blood component transmitting RRV to a recipient.

Results

Risk of RRV donor viraemia and risk of collecting a viraemic donation

Highlighting the 'focal' nature of the risk to the blood supply, the risk of a viraemic donor as calculated by the EUFRAT model was one in 95 000 nationally for the 12-month study period but increased to one in 15 000 in WA during the peak transmission period (January to March 2014). Similarly, using the Blood Service model, the estimated risk of collecting a RRV viraemic donation was one in 166 000 nationally for the 12-month study period and one in 26 000 in WA during the peak transmission period (Table 1). These estimates are similar orders of magnitude to those derived for the risk of collecting a DENV-infected donation during outbreaks that occur seasonally in northern Queensland [17].

Predicted number of infected issued blood components

The EUFRAT model predicts a national annual RRV infection prevalence in donors of one in 95 000 resulting in the issue of 11 RRV-infected labile blood components in Australia (Table 1). However, the predicted 11 infected components nationally were not evenly distributed, either across all jurisdictions or over the course of the 12-month study period, reflecting concomitant variation in the number of RRV notifications. For example, while WA represented only 12·4% of the national population, it accounted for 32·4% of the nationally reported cases of RRV infection and, according to the EUFRAT model, 17·3% of predicted infected components released nationally. Further, donations from WA in the 3-month period between January and March 2014 accounted for 51·2% of the total RRV notifications for the 12-month study period, and one of the two predicted infected components.

Table 1 Estimated risk of RRV viraemic donation, infected donor/blood component

Region	Period	RRV notifications	Risk of collecting viraemic donation (Blood Service model)[12]	Risk of infection in donors (EUFRAT)[13]	Predicted number of infected released components (EUFRAT)
Australia	1 June 2013 to 31 May 2014	4530	1 in 166, 486[a] (659 078 to 49 158)[b]	1 in 95, 039[c] (311 328 to 32 399)[d]	11[c] (4·1 to 39)[d]
Western Australia	1 June 2013 to 31 May 2014	1466	1 in 58 657 (232 208 to 17 320)	1 in 33 481 (109 695 to 11 415)	1·9 (0·6 to 5·5)
	1 January 2014 to 31 March 2014	756	1 in 26 177 (103 628 to 7729)	1 in 14 943 (48 593 to 5094)	1·0 (0·3 to 2·9)

[a]Most plausible estimate.
[b]Uncertainty range representing minimal and maximal risk, respectively.
[c]Mean.
[d]95% confidence interval.

Discussion

Ross River virus is the most common and widespread human arboviral infection in Australia, a probable transfusion-transmitted case has been reported and there is no licensed assay for blood donor screening. Therefore, the Blood Service must be able to accurately assess the potential risk of RRV to blood safety and consider risk mitigation strategies. However, the EUFRAT modelled risk of 8–11 infected components per year modelled on the notification of RRV infections in Australia (averaging 5000 notified cases a year) is in contrast to the single case report of probable transfusion-transmission [4].

Modelled risks are directly dependent on the accuracy of a number of key assumptions and estimates of input parameters. [18] [14] Our modelling of the transfusion-transfusion risk of RRV includes the following key assumptions: (i) the validity of extending the two models to RRV given that neither methodology was specifically developed for this virus. [17, 19] [13] (ii) The RRV population incidence, which has been estimated from confirmed RRV notifications, accurately reflects the symptomatic RRV incidence among donors. This may be problematic given that initial mapping of high RRV notification areas versus current blood collections suggests an underrepresentation of collections from areas at 'high risk' of RRV transmission (Blood Service, unpublished). (iii) The period of RRV viraemia in the mouse model can be directly extrapolated to humans and that any level of viraemia in a blood component is infectious. (iv) The RRV notification data report all symptomatic infections and this represents only 25–45% of all infections as 55–75% will be asymptomatic. Our modelling therefore incorporates a correction factor to take into account the proportion of asymptomatic infections. Additionally, there is evidence that Australian notification data may include a significant proportion of false-positive cases, [20] which would overestimate the risk. (v) All recipients of a viraemic blood component are susceptible to RRV infection. However, a recent RRV seroprevalence study has shown that there is a community background immunity level which is highly variable on a regional basis, ranging from 0·8% (Melbourne) to 21·8% (Townsville) [21].

While acknowledging the uncertainties of the model assumptions, it is unclear why more transfusion-transmitted RRV cases have not been reported. This is not unique to RRV as application of the EUFRAT model to Q fever [14], and chikungunya [13] has resulted in estimates of infected recipients that are in contrast to the number of reported cases (1 and 0, respectively)[14][13]. A similar phenomenon has been observed for DENV where only a small number of transfusion-transmitted cases have been reported worldwide, despite a global epidemic affecting over 100 countries with over a million dengue fever cases annually [22]. There are a number of other possible explanations for the lack of reported cases of transfusion-transmitted RRV infections including (i) the level of RRV viraemia in components may be below the (unknown) infectious threshold, (ii) RRV may not survive the storage conditions of blood components, (iii) transmission may require mosquito saliva to enhance viral replication and virulence, (iv) recipients may be immune or passively immunized due to transfusion with another unit from an immune donor, (v) on average, 60% of recipients of RRV-infected components would be expected to develop asymptomatic infection and therefore not be recognized, (vi) in the context of the predominance of mosquito-borne transmission, clinicians may not consider transfusion as a possible risk and therefore misclassify a transfusion-transmitted case as mosquito-borne, and (vii) while

there are state-based adverse event reporting systems, currently there is no national haemovigilance system in Australia, and therefore, transfusion-transmitted cases may not be captured.

An important consideration when assessing the risk to blood safety from a transfusion-transmissible pathogen is the disease implications for recipients. RRV infection lacks the potential for life-threatening disease, a feature of other transfusion-transmissible arboviral infections such as DENV and WNV [11]. The majority of RRV infections are asymptomatic, and symptomatic infections are characterized by a generally mild clinical course without the requirement for specific therapy. There is currently no reason to suspect a more severe outcome from transfusion-transmission and, to date, the only known case has not developed severe disease [4].

Characteristically for outbreak driven vector-borne agents like RRV, the predicted residual risk varies significantly both temporally and geographically, correlating primarily with the number of notified cases. The average risk of collecting a RRV-infected (viraemic) donation Australia-wide is low at one in 166 000. The focal and seasonal nature of the risk is evident from the markedly higher estimate of one in 26 000 for the 'high-transmission' period in WA during the summer/autumn period when notifications generally peak. Notably the implicated donor in the probable transfusion-transmission case acquired their infection during the peak notification period.

There is no 'gold standard' for determining whether an infectious risk to blood safety is high enough to warrant action to mitigate the risk. However, there are some guiding principles that can be applied to assist blood safety policymakers [23]. The Blood Service framework is based on three defining criteria: the imputability of transfusion–transmission (proven, likely or theoretical), the prevalence of the infectious disease among donors (where known) and the presence/severity of disease in transfusion recipients. While the modelled risk estimates are useful in the absence of empirical data, interpreting the significance of the estimates requires careful consideration of the inherent uncertainty [18]. Based on the original modelling for a dengue outbreak in Cairns during 2004[17], a somewhat arbitrary risk threshold of one in 20 000 was initially considered as the trigger for additional risk mitigation for arboviruses (i.e. supplementary donor selection measures to restrict at-risk donors to donating only plasma for fractionation). Given the risk estimates from both models used in our analysis appear overly pessimistic the challenge is to contextualize and assess these quantitative risk estimates. RRV has a self-limiting infection course and vector-borne diseases appear to be relatively inefficiently transmitted by transfusion. For example, a recent lookback study from Brazil indicated a transmission efficiency of approximately 38% for DENV[24] compared to >90% for both HIV and HCV [25]. In the light of all these factors, a modelled threshold risk of one in 20 000 may not be appropriate for RRV. Australia has recently recorded its largest ever outbreak of RRV in 2015 with 10 079 cases reported in the last year as opposed to a rolling 5-year mean of 4777 [26]. No cases of transfusion-transmission were reported, which supports contextualizing the modelled data.

However, RRV viraemia has been confirmed in a donor and the associated probable case of transfusion-transmission establishes a real rather than potential blood safety risk. Thus, in the absence of a licensed donor screening test for RRV, we considered three potential options for additional risk mitigation:

1 Geographically-based fresh component restrictions during high-transmission periods similar to the management of local DENV outbreaks [19]. Given the scope and duration of RRV outbreaks, it was considered that this strategy would not be practically feasible, would result in a significant cost and potentially impact sufficiency. Therefore, this option was not considered to be warranted given residual risk estimates and the clinical course of RRV illness.
2 Pathogen inactivation [27]. This might be a potential future strategy pending licensing of methods in Australia, but further research is needed before this technology could be implemented.
3 Enhanced donor education/postdonation illness reporting including strengthening existing messages and advising donors to notify the Blood Service for up to 1 month (currently 1 week) postdonation if they have been diagnosed with a specific infectious disease. The transfusion-transmission of RRV was associated with a late postdonation notification. Neglecting to notify has also been documented in the literature associated with transfusion-transmission of symptomatic dengue[28], this option would not be predicted to significantly impact sufficiency while enabling identification and recall of products associated with the proportion donors who develop postdonation symptomatic RRV infections.

In consideration of the substantial uncertainty in the modelled estimates, the unknown rate of RRV donor viraemia (likely low) and the low severity of disease in recipients of RRV-infected blood products, proposed additional risk management was restricted to option 3, that is strengthening the messaging to donors regarding development of postdonation illnesses. This includes reminders postdonation to prompt donors about postdonation symptom reporting. In terms of better defining the current

residual risk for RRV transmission, it was identified that the absence of empirical data on the rate of RRV viraemia among donors was a critical unknown. To more accurately define the RRV residual risk, the Blood Service has commenced targeted testing to determine the rate of RRV RNA among donors from a variety of 'high' RRV transmission localities.

While RRV is currently geographically restricted to the Western Pacific, the capacity of arboviruses for rapid expansion and explosive outbreaks is well established [11]. Past examples include WNV, DENV, chikungunya virus (CHIKV) and most recently Zika virus [29]. Should RRV expand geographically the factors considered here will enable others to locally assess the threat RRV poses to blood safety in their jurisdictions. Our risk assessment highlights the issues international blood services face making decisions with modelled estimates and the importance of considering the risk in the context.

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Author contributions

Clive Seed and Philip Kiely conceived the Blood Service risk model. Clive Seed and Veronica Hoad performed and verified the risk modelling. All authors contributed to the data interpretation, data analysis/consolidation and drafting/approval of the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:
Table S1 List of parameter values used in estimating the transfusion-transmission risk for Ross River virus during 2014 in Australia using the European Up-Front Risk Assessment Tool (*EUFRAT*).
Table S2 List of parameter values used in estimating the transfusion-transmission risk for Ross River fever during 2014 in Australia using the Australian Red Cross Blood Service model.