The risk of blood transfusion–associated Chikungunya fever during the 2009 epidemic in Songkhla Province, Thailand

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BACKGROUND: Asymptomatic Chikungunya fever (CHIKF)-viremic blood donors could be a potential threat of spreading the disease unwittingly through contaminated blood transfusions. The relatively low prevalence of Chikungunya virus antibodies in the population and the records of more than 9000 suspected CHIKF cases raised concern about the potential transfusion-associated CHIKF during the 2009 epidemic. This study assessed the potential transfusion risk for CHIKF and the implementation of blood safety measures to mitigate this risk.

STUDY DESIGN AND METHODS: A probabilistic model using key variables obtained from local information was used to estimate the weekly risk of transfusion-associated CHIKF during the 2009 epidemic. In addition, other blood safety measure–based strategies involving screening for donors at risk, donor tracing, and a 7-day quarantine of blood components at risk were implemented at the time of the epidemic.

RESULTS: The risk of viremic donations per 100,000 ranged from 38.2 (95% confidence interval [CI], 36.5-39.8) to 52.3 (95% CI, 50.4-54.2). The potential risk of transfusion-associated CHIKF per 100,000 was estimated to be 1 in 2429 (0.04%; 95% CI, 1 in 6681 [0.02%]-1 in 1572 [0.06%]) to 1 in 1781 (0.06%; 95% CI, 1 in 3817 [0.03%]-1 in 1214 (0.08%]) donations. Among 26,722 donations, 11 (95% CI, 4-17) to 15 (95% CI, 7-22) donations were predicted to associate with transfusion risk. The implementation of blood safety measure–based strategies for this epidemic period suggested to deter 11 blood donations of transfusion risk.

CONCLUSION: The interventions for blood safety measures applied in this study had mitigated the potential transfusion-associated CHIKF during the 2009 epidemic.

The presence of high viremic loads in Chikungunya virus (CHIKV)-infected individuals[1] and an abundance of *Aedes* mosquitoes[2] were important factors facilitating the widespread Chikungunya fever (CHIKF) epidemic in southern Thailand, where at least 49,089 persons were finally affected by the end of 2009.[3]

Although no cases of transfusion-associated CHIKF have yet been established,[4-6] an increasing concern is being recognized that this disease might be transferred via transfusions, particularly during an outbreak,[4-6] because CHIKV produces a high attack rate[1,7] and has a rapid replication rate,[8] high viremic levels,[1,8-10] and a significant proportion of asymptomatic infections.[1,4-6] Moreover, although CHIKV acquired via blood transfusion may constitute only a small proportion of all CHIKF cases during an outbreak, the CHIKV genome was identified in 1 of 250 donated platelet (PLT) units screened by nucleic acid amplification testing during the massive 2006 epidemic in Reunion Island.[5] Recently, we documented that viremic

ABBREVIATIONS: CHIKF = Chikungunya fever; CHIKV = Chikungunya virus; DENV = dengue virus.

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asymptomatic CHIKV-infected cases could have a high potential as disseminators of transfusion-associated CHIKF, since CHIKV levels capable of inducing CHIKF were found in the blood of these asymptomatic cases.[1] In addition, the finding of high viremic levels in the first few days of symptomatic CHIKV-infected cases led to the suggestion that high viremic levels could also be present during the presymptomatic viremic period.[1] If presymptomatic individuals donate blood, obviously there is a threat of passing on the infection through such donations. These groups of potential infected donors are unlikely to self-defer or be excluded from donation by the predonation medical screening.

Before 2009, an outbreak of CHIKF had never been reported in Songkhla Province in southern Thailand.[11-13] The seroprevalence of CHIKV antibodies in the adult population of Songkhla Province before 2009 was 1.8% to 9.8%, which was the lowest seroprevalence in Thailand.[14-16] The finding had been considered as a likely low herd immunity area to CHIKV infection.[14-16] In 2009 there was an epidemic of CHIKF involving more than 9000 cases in Songkhla Province.[12,13] These situations raised transfusion safety concerns.

In this report, we used key variables with values specified using local information in the probabilistic model to estimate the potential transfusion risk of CHIKF, aiming to aid decisions to implement safety measures. This study also assessed the implementation of blood safety measures to mitigate this potential risk.

MATERIALS AND METHODS

A probabilistic model for transfusion risk

A probabilistic model,[17] as shown in the formula below, was used to estimate the transfusion-associated risk during the 2009 epidemic. The modeling assumptions were mainly dependent on the proportion of asymptomatic viremic donors, the duration of viremia, and the prevalence of infected donors.

$$\text{Estimated transfusion-associated risk} \approx [(Pa \times Da) + (Ps \times Ds)]/L \times Pr,$$

where Pa is the proportion of asymptomatic CHIKV-viremic donors, Da is the duration of viremia for asymptomatic donors, Ps is the proportion of presymptomatic CHIKV donors, Ds is the duration of viremia for presymptomatic CHIKV donors, Pr is the prevalence of CHIKV-viremic donations, and L is the length of the outbreak.

The modeling assumptions used in this study were, first, symptomatic CHIKF cases would either self-defer owing to their being too sick to donate or be excluded from donation by the predonation screening.[4] However, these assumptions would not exclude infected individuals who remained asymptomatic or became symptomatic after their blood donations. Second, the blood of any viremic asymptomatic CHIKF donor could potentially transmit the disease due to the presence of relatively high viremic levels in asymptomatic CHIKV-infected cases[1] and the relatively low herd immunity to CHIKV in the recipients.[14-16] Third, the incidence of viremic blood donors with respect to mosquito exposure and infection risk was assumed to be similar to the population at large.[17]

The confidence intervals (CIs) of mean and maximal risk estimates[18] as well as key variables with values specified using local information[1] (Table 1) were used to encapsulate uncertainty in the variable assumptions. The CIs were computed using the methods described by Petersen and colleagues.[18]

Risk model variables

The number of clinically suspected CHIKF patients

Clinically suspected CHIKF cases were defined as patients who developed acute fever of up to 7 days' duration, arthralgia, and/or rash.[12,13] The numbers of suspected CHIKF cases were determined from the records of the two main offices dealing with such things in this part of southern Thailand, the Office of Disease Prevention and Control 12 Songkhla (ODPC 12) and the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand (Fig. 1).[12,13]

The epidemic was first reported in August 2008 from Narathiwat Province in southern Thailand and

TABLE 1. Key variables for modeling assumptions

	Modeling assumption	
Variable	Mean risk	Maximal risk
Proportion of asymptomatic cases (Pa)	10%	10%
Proportion of presymptomatic cases (Ps)	90%	90%
Total duration of viremia (Da)	9.5 days	18.5 days
Duration of presymptomatic viremia (Ds)	1.5 days	1.5 days
Estimated number of symptomatic CHIKF cases	Number of suspected CHIKF cases × 0.938* × 8.03†	Number of suspected CHIKF cases × 0.938 × 8.03

* 0.938 = factor for adjusting exclusive CHIKF cases (see Materials and Methods).
† 8.03 = factor for adjusting active CHIKF cases (see Materials and Methods).

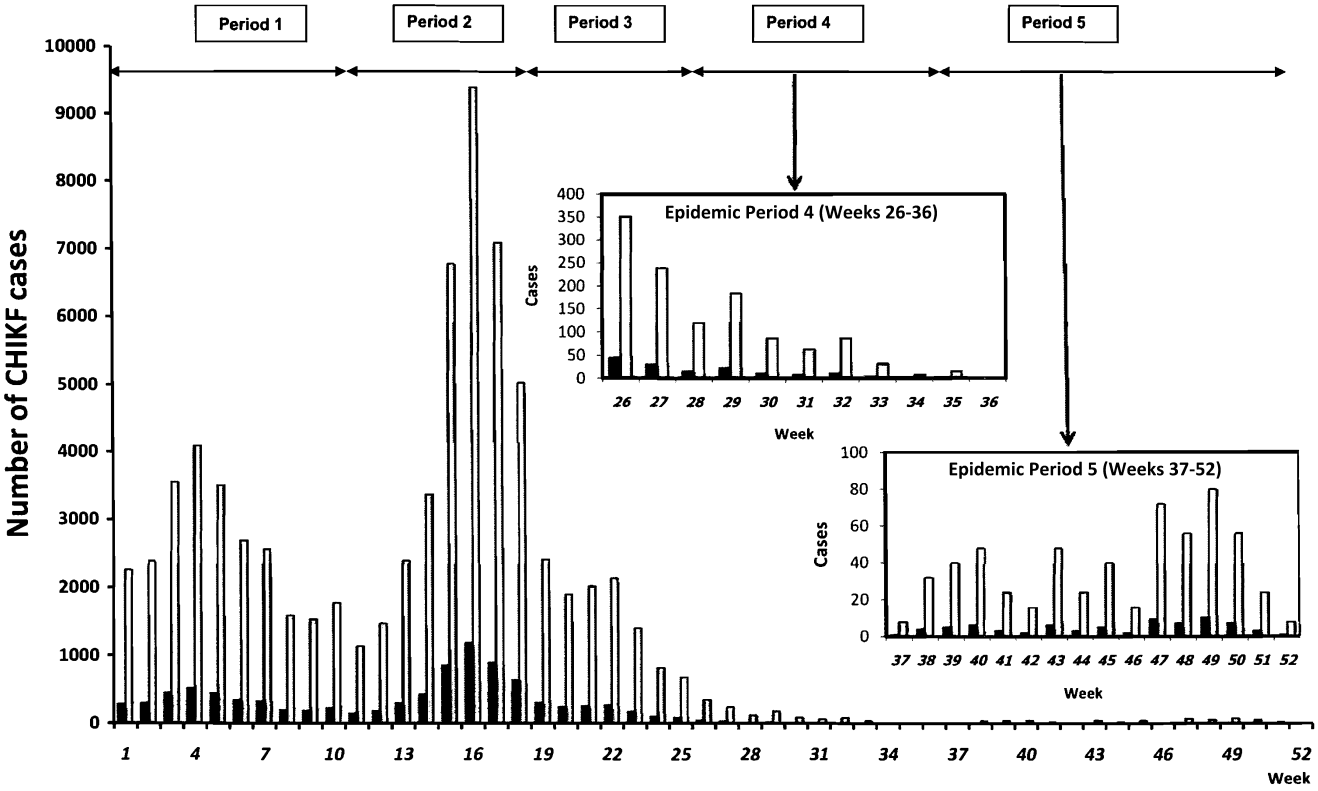

Fig. 1. Number of clinically suspected CHIKF cases (■) and estimated number of CHIKF cases (□) by week of onset reported during the 2009 epidemic periods in Songkhla Province, southern Thailand. *Epidemic periods: Period 1, Weeks 1 to 11 (January 4-March 21, 2009); Period 2, Weeks 12 to 18 (March 22-May 9, 2009); Period 3, Weeks 19 to 25 (May 10-June 27, 2009); Period 4, Weeks 26 to 36 (June 28-September 12, 2009); and Period 5, Weeks 37 to 52 (September 13, 2009-January 2, 2010).

subsequently spread to neighboring provinces including Pattani, Yala, and Songkhla. We chose to model the CHIKF epidemic period in Songkhla Province from January to December 2009. The estimated population size of Songkhla Province in 2009 was 1,343,954.[12]

Prevalence of CHIKV infection

Our previous report performed at the time of this epidemic found that 6.2% of patients with clinically suspected CHIKF were actually affected by other febrile illnesses.[1] In this study, we thus readjusted the incidence of exclusive symptomatic CHIKF patients by multiplying the number of clinically suspected CHIKF patients by a factor of 0.938.

It had to be noted that, during the 2009 epidemic, the records of suspected CHIKF cases were underestimated[12,13] as evidenced by a comparative study between an active community-based surveillance and passive notification records in the late epidemic period (June 28-November 4, 2009): an actual 8.03 suspected CHIKF cases were identified by this active case finding for every suspected case identified by the passively noticed (http://www.chikungunya.org/, access date November 18, 2009). Thus, the final estimated number of symptomatic CHIKF cases used in the calculation was the number of clinically suspected CHIKF cases multiplied by 8.03.

The proportion and the duration of viremia in presymptomatic CHIKF cases

The proportion of presymptomatic CHIKV-infected cases in modeling assumptions was assumed to be similar to the symptomatic CHIKF patients at 90%.[1] The duration of the presymptomatic viremic period (Ds) was approximated based on previous published studies to be 1.5 days (range, 1-2 days).[6,19]

The proportion and the duration of viremia in asymptomatic CHIKF blood donors

The proportion of viremic asymptomatic CHIKF cases obtained from a case-control study carried out in CHIKV-affected areas between March and April 2009 in Songkhla Province was 10%.[1] There have been no published data about the kinetics of CHIKV viremia in asymptomatic cases. We, however, assumed that the total duration of viremia in asymptomatic CHIKV infection was similar to those in symptomatic cases, which was up to 8 days after the onset of symptoms as revealed by viral isolation or clinical symptoms, or up to 17 days by detection of CHIKV

RNA.[1] Therefore, we assumed that the duration of transfusion risk in asymptomatic CHIKV infection was 9.5 days (1.5 + 8) on average with a maximum of 18.5 (1.5 + 17) days, respectively (Table 1).

Numbers of blood donations

From January to December 2009, a total of 26,722 blood donations were collected at Songklanagarind University Hospital in Songkhla Province.

Accuracy of the risk model

The accuracy of the risk model[17] was assessed by CHIKV RNA assay of 2000 donated blood units collected near the final weeks of the epidemic (Week 36 to Week 41, September 12-October 18, 2009). Two-hundred pooled serum samples from every 10 donors were first screened for the presence of CHIKV RNA. If any pooled serum sample was positive, each of the 10 individual serum samples was then individually tested for CHIKV RNA.[20]

Transfusion-associated CHIKF management

Measures to ensure blood safety were applied from April to October 2009, by using specific predonation questions about CHIKF-related symptoms (acute fever, arthralgia, and/or rash)[9,10,14] and an enhanced postdonation report by donors to call back if CHIKF-related symptoms developed. Donated blood components at risk were quarantined for 7 days after donation and all donors at risk were interviewed by telephone to confirm the status of the donors on Day 7 after their donation. Blood units from donors at risk who developed CHIKF-related symptoms within 7 days of donations were discarded.

Ethical approval

This study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University.

RESULTS

The number of clinically suspected CHIKF cases

From January to December 2009, a total of 9440 clinically suspected CHIKF cases were reported. The number of suspected CHIKF cases dramatically increased from the first week of 2009 and fluctuated between 0 (Week 36) and 1170 cases (Week 16) per week with three peaks appearing at Week 4 (510 cases), Week 16 (1170 cases), and Week 22 (266 cases; Fig. 1).

The epidemic can be divided into five periods: Period 1 (Weeks 1-11), Period 2 (Weeks 12-18), Period 3 (Weeks 19-25), Period 4 (Weeks 26-36), and Period 5 (Weeks 37-52). The numbers of suspected CHIKF cases were 251.2, 329.1, 105.4, 10.7, and 5.9 per 100,000 in Periods 1, 2, 3, 4, and 5, respectively, with three peaks: Week 4 (37.9 per 100,000), Week 16 (87.0 per 100,000), and Week 22 (19.8 per 100,000; Fig. 1).

Estimated prevalence of CHIKV infection

The mean weekly prevalence of CHIKV infections (symptomatic and asymptomatic cases) among the population at large during the entire epidemic period was estimated to be 111.9 (95% CI, 109.1-114.7), varying from 0 to 721.2 (95% CI, 668.8-773.7) per 100,000 (Fig. 2).

Estimated risk of viremic donations

A probabilistic model was used to estimate the weekly risk of viremic donations during the 2009 epidemic under the indicated assumptions of a potential estimated mean and maximal risk (Table 1). The mean weekly risk of viremic donations during the entire epidemic period was estimated to be 38.2 (95% CI, 36.5-39.8), varying from 0 to 237.0 (95% CI; 206.9-267.1) per 100,000 (Fig. 2). Similarly, the maximum weekly risk of viremic donations during the entire epidemic period was estimated to be 52.3 (95% CI, 50.4-54.2), varying from 0 to 329.6 (95% CI; 294.1-365.1) per 100,000 (Fig. 2). Overall, the maximal risk estimates were 1.4-fold greater than the mean risk estimates.

The potential risk of blood transfusion–associated CHIKF

Among the 26,722 blood donations collected from January to December 2009, on mean potential risk of transfusion-associated CHIKF, 11 (95% CI, 4-17) CHIKF-contaminated blood donations would be expected to be received, with a risk of transfusion-associated CHIKF being 1 in 2429 (0.04%; 95% CI, 1 in 6681 [0.02%]-1 in 1572 [0.06%]). The highest peak of the epidemic (Week 16) was 1 in 422 (0.24%; 95% CI, 1 in 382 [0.26%]-1 in 462 [0.22%]).

Similarly, on maximal potential risk of transfusion-associated CHIKF during the entire epidemic period, 15 (95% CI, 7-22) CHIKF-contaminated blood donations would be received, with a risk of transfusion-associated CHIKF being 1 in 1781 (0.06%; 95% CI, 1 in 3817 [0.03%]-1 in 1214 [0.08%]). The highest peak of the epidemic was 1 in 303 (0.33%; 95% CI, 1 in 273 [0.37%]-1 in 330 [0.30%]).

To assess the accuracy of the risk model, the following facts were noted: 0.10% of the 2000 blood units collected during Weeks 36 to 41 (September 12 to October 18, 2009) were found to be positive for CHIKV RNA whereas 0.20% (95% CI, 0.19-0.20) to 0.33% (95% CI, 0.32-0.33) were predicted by this model. Overall, 11 (95% CI, 4-7) to 15 (95% CI, 7-22), or 0.04% (95% CI, 0.02%-0.06%) to 0.06% (95%

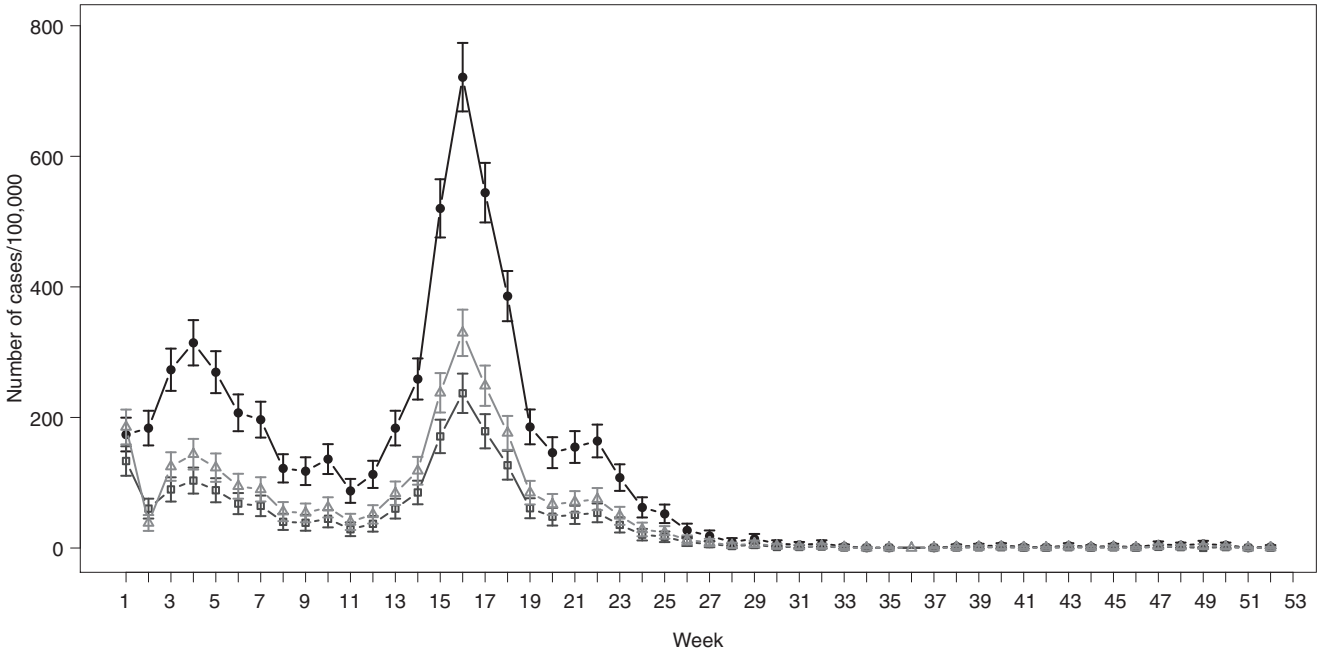

Fig. 2. Estimated weekly prevalence of CHIKV infection (●) and estimated weekly risk of viremic donations (□, mean; △, maximal) during the 2009 epidemic in Songkhla Province, Thailand. Simultaneous 95th percentile-t CIs are shown as vertical bars.

CI, 0.03%-0.08%), viremic asymptomatic CHIKF blood donors were predicted to associate with transfusion-induced CHIKF.

Transfusion-associated CHIKF management

Blood safety measure–based strategies involving screening of donors at risk using specific predonation questions and a 7-day quarantine of blood components as well as donor tracing were implemented from Week 13 to Week 43 (April to October 2009). Among the 15,513 donations collected from April to October 2009, seven (95% CI, 4-12) to nine (95% CI, 6-22) donations were predicted to associate with a transfusion risk. The implementation of blood safety measured–based strategies for this period suggested that 299 of the 13,202 (2.3%) were donations at risk. Of those 299 donations at risk, 271 (90.6%) were normal individual donations, 17 (5.7%) could not be contacted on Day 7 after their donations, and 11 (3.7%) were suggestive CHIKF-contaminated blood donations. Only one available serum sample of those 11 suggestive CHIKF-contaminated blood donations was confirmed for positive CHIKV viremia at the levels of 8.7×10^6 plaque-forming units per milliliter. However, these 11 blood units were deterred transfusion-associated risk by removing from the blood bank.

DISCUSSION

This study applied a probabilistic model using key variables obtained from local information to estimate the weekly CHIKV-viremic donations during the 2009 CHIKV epidemic in Songkhla Province, Thailand. This type of prediction is useful in helping policy makers to implement safety measures.[4-6,17] The interventions for blood safety measures applied at the time of the epidemic had mitigated this potential risk.

It was found that the mean and maximal risks of viremic donations were 38 to 52 per 100,000 donations or 1 in 2429 (0.04%) to 1 in 1781 (0.06%) donations, respectively. In a risk modeling performed by Brouard and colleagues[5] during the 2005 to 2007 epidemic on Reunion Island, where 38% of the 766,000 subjects of the study were infected, the mean risk was estimated to be 32 per 100,000 donations or 1 in 758 (0.13%) donations, whereas the highest peak of the outbreak was 1500 per 100,000 donations or 1 in 67 (1.49%) donations. Similarly, at Cervia where the largest outbreak in Italy occurred, the highest weekly risk was estimated at 1 in 3801 (0.03%) donations.[6] [Correction statement added after online publication 17-Feb-2014: mean risk changed to highest weekly risk.] The estimated CHIKV transfusion risk found in this study and in the previous publications were of the same magnitude. In addition, the estimates of CHIKV-viremic donations were also comparable to that of dengue virus (DENV).[18,21]

The model variables used in this study (Table 1) were compared to other reports. There were fewer variables and more certainty in the duration of presymptomatic viremia (1.5 days[6,19] vs. 1.5-2 days[5,6]) and the duration of viremia in asymptomatic CHIKF by means of viral isolation or

clinical symptoms (8.0 days[1] vs. 6.0 days of illness[4-6]) while the prevalence of asymptomatic CHIKF (10%[1] vs. 15%[4-6]) was more variable. Theoretically, the ratio of asymptomatic CHIKF to symptomatic CHIKF may not be constant over time. Since Songkhla Province had been considered as a likely low herd immunity area to CHIKV infection,[11,14-16] both of the current circulating CHIKV strains (A226 and 226V strains) displayed not prominent distinct antigenic structure,[15,22,23] CHIKV infection has low infective dose,[24,25] and CHIKV produces a high rate of prominent symptomatic CHIKF;[1,7,9,11] therefore, the authors hypothesized that the uncertainty of low asymptomatic rate would have narrow range and hence the variation of viremic asymptomatic rate could be neglected.[1,4-7,9,10] This is in contrast to a DENV transfusion risk model because the DENV viremic donations varied considerably by season and year.[18] Several factors may be responsible for this involving population including herd immunity to DENV,[11,14-16,26] geography,[18,26] age of cases,[14,15] virus circulating strains,[14,26] prevalence of infection,[18,26] and human genetic-associated factors.[27] Previously, the authors have suggested that the duration of detectable viable CHIKV (up to 8 days of illness) is less than the duration of CHIKV RNA positivity (up to 17 days of illness).[1] Nevertheless, from the viewpoint of recipient safety and to get more information on decision-making policies, all CHIKV RNA–positive units should conservatively be considered potentially infectious donations. In this study, the authors used the total duration of viremia in asymptomatic CHIKF by means of RNA detection (up to 18.5 days instead of 9.5 days of illness) as the maximum estimated transfusion risk. Generally, the maximal risk estimate was 1.4-fold greater than the mean risk estimates. Another difference was the use of the prevalence of exclusive CHIKV-infected individuals as mentioned earlier under Materials and Methods.

A limitation of this study on accuracy of the risk model is the absence of blood testing at the appropriate times (e.g., March to July 2009). However, the estimated potential risk (0.20%-0.33%) and the observed potential risk (0.10%) of blood transfusion–associated CHIKF that were evaluated near the end of the epidemic period (September 12 to October 18, 2009) were in the same magnitude. In addition, this risk model was previously validated to be reliable for the prediction of transfusion-associated CHIKV,[5] DENV,[18,20] and West Nile virus modeling.[17] For example, Brouard and colleagues[5] estimated the mean risk of having viremic donations at 0.7%, which agreed closely with the observed rate of 0.4% CHIKV RNA–positive testing of PLT donations. Another limitation of this study was the inference of actual CHIKV infection prevalence from the underestimated sentinel records as mentioned earlier.

As an estimated transfusion risk model provides only an estimated risk of viremic donations, the actual risk of disease after transfusion may differ from the risk modeling estimates. In the scenario of Songkhla Province modeled in this study, although not proven, the transfused CHIKV from the potentially viremic donors was supposed to be a high-risk transfusion transmission because of the plausible relatively high viremic levels in asymptomatic CHIKV-infected cases[1] and the existence of relatively low herd immunity to CHIKV.[15,16] In a contrary situation, transfused DENV from potentially viremic donors was considered as likely to be unpredictable, in part, due to the existence of high herd immunity to DENV[15,16,18] and the existence of various circulating DENV serotypes.[14-16,26] However, to date, the actual rates of each transfusion-transmitted disease are not known. Future studies are needed to determine the rates of transfusion-associated diseases and their clinical consequences in recipients.

The risk model is a pragmatic and cost-effective tool for risk assessment compared with a screening test. However, the threshold numbers of the viremic donors targeted for blood safety measures and CHIKF management should err on the side of caution. According to the published reports, managing the risk of transfusion-associated CHIKF varies among countries. Liumbruno and colleagues[6] described the use of blood safety measure–based strategies implemented during the entire period of the outbreak in Italy where blood collection in the affected areas was interrupted in the early period of the outbreak. Later on, new precautionary measures were applied that included predicted viremic donation modeling, 21-day deferral for blood donors who had visited the affected areas, quarantine of blood components for 5 days (subsequently reduced to 2 days), and pathogen inactivation of PLT concentrates, ultimately resulting in the loss of 5130 units of red blood cells and 2871 L of fresh-frozen plasma and an economic loss exceeding £1.3 million. In another experience from Reunion Island, Brouard and colleagues[5] also used the policy of stopping local blood donations before the peak of the outbreak to minimize transfusion-associated CHIKF and a return to regular blood donation services 18 months after the epidemic had subsided. That study reported that blood donations were interrupted from January 2006 to April 2007 and concluded that at least 40 potentially viremic donations were avoided.[5] Although the economic loss was not reported, it was thought to be high. During the 2009 epidemic in southern Thailand, including Songkhla Province the focus of this study, the implementation of blood donor testing for CHIKV RNA was conducted on a cost–benefit analysis of the effectiveness of screening and further limited due to a paucity of resources. Since CHIKV features prominent clinical symptoms along with a relatively low rate of asymptomatic-infected individuals and a relatively short viremic period,[1] the authors suggest that the affordable intervention of blood safety measures to mitigate the risk of transfusion-spread disease, involving the use of

predictive risk modeling, screening for donors at risk, donor tracing, and quarantine of blood components at risk, was suitably applied. Only 17 (5.7%) of 299 donors at risk were lost to contact 7 days after blood collection and of these 11 (3.7%) were suggestive CHIKF-contaminated blood donation donors. At least one of those suggestive CHIKF blood donations was confirmed for CHIKV-viremic donor. This approach was apparently effective as 11 suggestive viremic donations avoided transfusion-associated CHIKF.

A screening blood test and/or a deferral-based strategy should be considered for donors at risk (e.g., residents living in affected areas or having visited affected areas, tourists at risk returning to their home country and/or to nonendemic areas). Alternatively, specific CHIKF-related questions in predonation examinations coupled with deferral of at least 4 weeks (CHIKV RNA is detectable up to 17 days of illness) after each stay or visit to an affected area would cover various mosquito-borne viruses including CHIKV.[1,20]

Based on this study and previous reports, it is suggested that interventions of blood safety measures during an outbreak need to be applied. Nevertheless, it appears that currently no guideline is available.

In conclusion, the CHIKV transfusion risk in Songkhla Province donors during the 2009 epidemic was predicted by a probabilistic model using local risk model variables. [Correction added after online publication 17-Feb-2014: sentence updated for clarity.] The estimated number of viremic donors was in the same magnitude as previous reports. To mitigate the transfusion risk of CHIKF, appropriate interventions for blood safety measures need to be applied during an outbreak.

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CONFLICT OF INTEREST

The authors report no conflicts of interest or funding sources.

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