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研究報告の概要

＜背景＞
2005年から2007年の間、チクングニヤウイルス（CHIKV）が、2006年2月に症例数の最大ピークとするレユニオン島での大流行を引き起こした。レユニオン島での供血は、2006年1月に中断された。
＜研究デザインおよび方法＞
レユニオン島でウイルス血症の供血がされる平均リスクの推定を異なる流行期について計算した。計算には、定点観測の動向調査（sentinel surveillance）、ウイルス血症の期間、および無症候感染の頻度から割り出したCHIKV予想発現値を用いた。最後のこれら2つのパラメーターのデータは、最初は仮定に基づき、次いでアウトブレイクの期間に実施された検討をもとに出した。この予想リスクを、血小板ドネーションのスクリーニングのために実施したCHIKV核酸増幅検査の結果と比較した。
＜結果＞
アウトブレイクの期間中、リスクの平均値は、ドネーション100,000当たり132と予想された。このリスクは、2006年2月のアウトブレイクの最大期にピークに達し、ドネーション100,000当たり1,500であった。もし採血が中断されていなかったら、全体で47の供血がウイルス血症であったであろう。この期間、757,000人住民のうちの312,500人が蚊を媒介にして感染していたと予想される。2006年1月から5月まで、予想リスク平均値（0.7%）と血小板供血で観察されたリスク（0.4%）は同じ大きさであった。
＜結論＞
この大きなアウトブレイクの間、ウイルス血症の供血の予想リスクは高かったが、蚊媒介のCHIKV感染のリスクに比べ低かった。この予想リスクは、観察されたリスクの結果と一致したことによって裏付けられた。

報告企業の意見	今後の対応
レユニオン島におけるチクングニヤウイルス（CHIKV）の流行時のCHIKV血症献血リスクに関する報告である。血漿分画製剤からのチクングニヤウイルス伝播の事例は報告されていない。また、万一原料血漿にチクングニヤウイルスが混入したとしても、BVDをモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程において十分に不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

使用上の注意記載状況・その他参考事項等

代表として静注用ヘブスブリンーIHの記載を示す。
2. 重要な基本的注意
(1)本剤の原材料となる血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体陰性で、かつALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV及びHCVについて核酸増幅検査(NAT)を実施し、適合した血漿を本剤の製造に使用しているが、当該NATの検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した高力価の抗HBs抗体を含有する血漿を原料として、Cohnの低温エタノール分画で得た画分からポリエチレングリコール4000処理、DEAEセファデックス処理等により抗HBs人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において60℃、10時間の液状加熱処理及びろ過膜処理（ナノフィルトレーション）を施しているが、投与に際しては、次の点に十分注意すること。

TRANSFUSION COMPLICATIONS

Estimated risk of Chikungunya viremic blood donation during an epidemic on Reunion Island in the Indian Ocean, 2005 to 2007

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BACKGROUND: Between 2005 and 2007, Chikungunya virus (CHIKV) caused a massive epidemic on Reunion Island with a major peak in the number of cases in February 2006. Blood donation was interrupted on the island in January 2006.

STUDY DESIGN AND METHODS: Estimates of the mean risk of viremic blood donation on Reunion Island were computed for different phases of the epidemic. Calculations used CHIKV incidence estimates derived from sentinel surveillance, duration of viremia, and frequency of asymptomatic infection. Data on these two last parameters were initially based on hypotheses and subsequently obtained from studies carried out during the outbreak. The estimated risk was compared to the results of CHIKV nucleic acid testing (NAT) implemented for platelet (PLT) donations screening.

RESULTS: Over the course of the outbreak, the mean risk was estimated at 132 per 100,000 donations. The risk peaked at 1500 per 100,000 donations at the height of the outbreak in February 2006. In total, 47 blood donations would have been potentially viremic if blood collection had not been interrupted. During this period, an estimated 312,500 of 757,000 inhabitants had been infected by mosquito-borne transmission. From January to May 2006, the estimated mean risk (0.7%) and observed risk on PLT donations (0.4%) were of the same order of magnitude.

CONCLUSION: During this large outbreak, the estimated risk of viremic blood donation was high, but low compared to the risk of mosquito-borne CHIKV transmission. The estimated risk was corroborated by the concordant results with the observed risk.

Chikungunya virus (CHIKV) is an alphavirus that belongs to the Togoviridae family, transmitted by *Aedes* mosquitoes. It was first identified in 1952 during an outbreak in Tanzania.[1,2] Afterward, it caused many outbreaks in Africa[3-7] and in Asia.[3,8-11] In Africa, a sylvatic transmission cycle between wild primates and mosquitoes is thought to maintain the virus, whereas in Asia, it is transmitted from human to human through an urban transmission cycle.[3] CHIKV infection is mainly characterized by sudden onset of fever, arthralgia, myalgia, headache, and edemas.[1,3,8,12,13] Other symptoms like rash, epistaxis, gingivorrhagia, nausea, vomiting, flushed face, or photophobia have also been described. The most typical clinical sign is polyarthralgia that is generally very painful, as suggested by its name Chikungunya meaning in the language of the Tanzanian Makonde plateau "that which bends up" in reference to the stooping posture adopted by patients because of the severity of the joint pains. The symptoms usually resolve within a few days, but in some severe cases, arthralgia may persist for months or years.[3,13] Serosurveys implemented during prior outbreaks have demonstrated that Chikungunya infection can also be asymptomatic.[9]

In early 2005, CHIKV emerged for the first time in the southwest Indian Ocean region (Comoros, Reunion,

ABBREVIATIONS: CHIKV = Chikungunya virus; WNV = West Nile virus.

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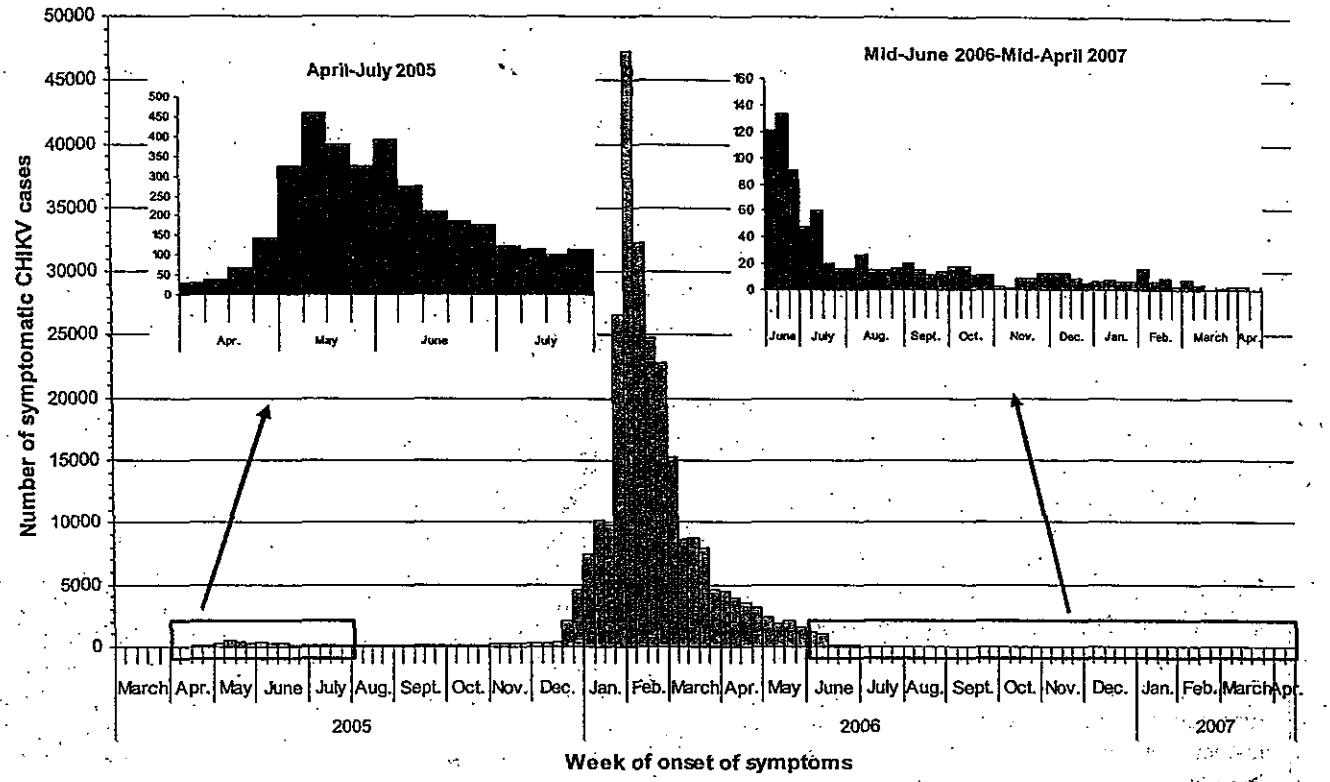

Fig. 1. Distribution of symptomatic cases of CHIKV infection per week of onset of symptoms, Reunion Island, March 28, 2005, through April 15, 2007.

Mayotte, Seychelles, Mauritius, and Madagascar Islands). On Reunion Island, the first cases were identified at the end of April 2005. After a first epidemic peak in May through June 2005 with a maximum of 450 cases during the second week of May, the number of cases decreased during the southern hemisphere winter season. At mid-December, an exponential increase in cases occurred, with almost 10,000 estimated cases at mid-January 2006 (Fig. 1). Because of concerns about the possible transmission of CHIKV by blood transfusion, the French Blood Services (EFS) interrupted blood donations on the island from January 23, 2006, except donations for platelets (PLTs) for which systematic screening for CHIKV genome by nucleic acid amplification testing (NAT) was set up.

At that moment, we estimated the risk of CHIKV viremic blood donation. Afterward, we updated these estimates since more accurate data were available on the incidence of infection and on the frequency of asymptomatic infections. We compared the estimated risk of viremic blood donation to the observed proportion of viremic PLT donations determined by CHIKV NAT screening.

MATERIALS AND METHODS

The estimates were performed by the French Institute of Public Health Surveillance (InVS) in the setting of a work-group including the French Agency for the Safety of Health Products (Afssaps), the French Blood Services (EFS), and the National Institute for Blood Transfusion (INTS). In early 2005, this group initiated a project with the aim of obtaining a priori quantitative risk estimates of contamination of blood donations by infectious agents for various scenarios in terms of incidence and time-space distribution.[14]

General approach

The first estimates performed in January 2006 ("preliminary estimates") concerned the two following periods: Period A, from the detection of the first cases in April 2005 to mid-December 2005 when a large increase of cases occurred (March 28-December 18, 2005; 266 days); and Period B, from mid-December until the interruption of blood collection (December 19, 2005-January 22, 2006; 35 days; Fig. 2).

These estimates were later refined with consolidated incidence data, corrected for delayed care-seeking and delayed reporting and more precise estimates of the proportion of asymptomatic infections obtained through a seroepidemiologic survey carried out at the final phase of the outbreak ("retrospective estimates"). We also estimated the risk of viremic blood donation for five different

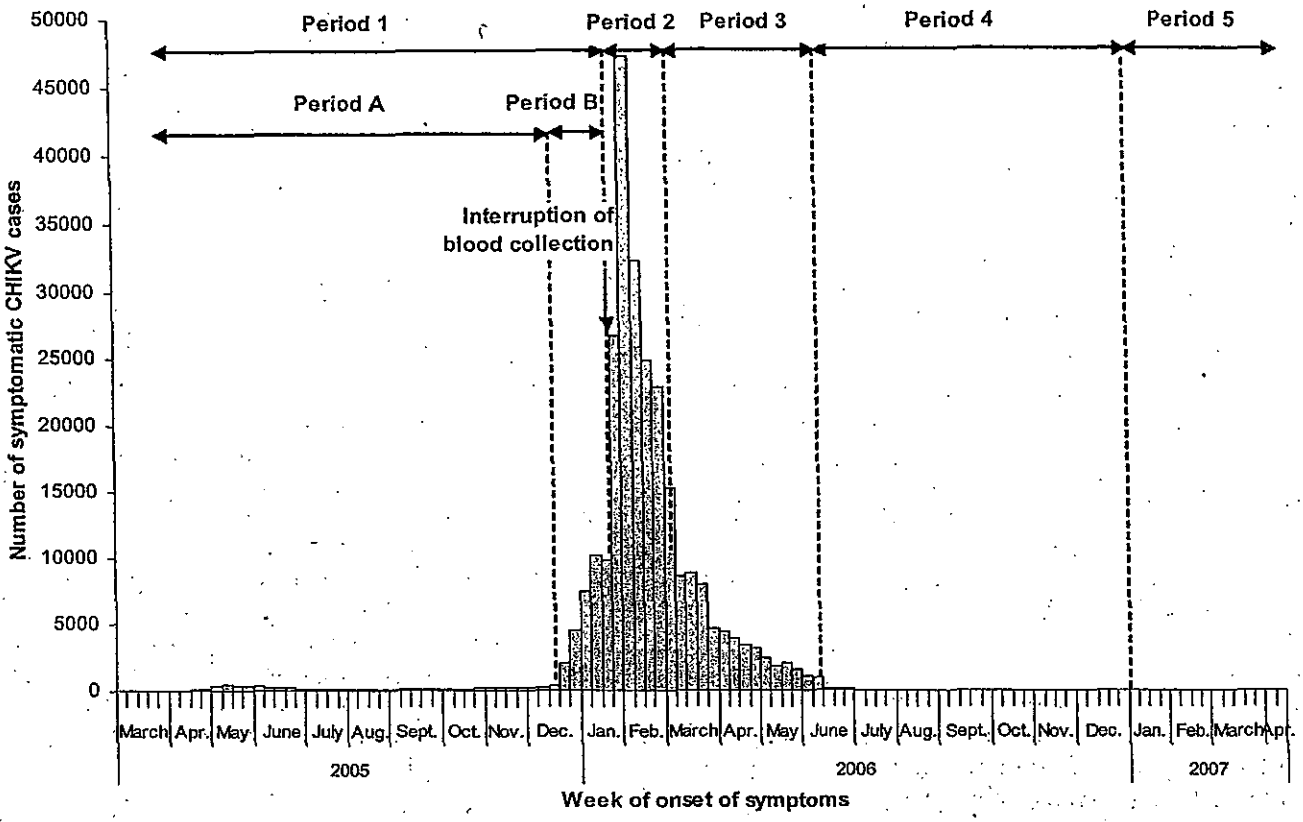

Fig. 2. Periods for risk estimates and distribution of symptomatic cases of CHIKV infection per week of onset of symptoms, Reunion Island, March 28, 2005, through April 15, 2007.

periods of the outbreak with these updated data (Fig. 2).

By use of the quarterly numbers of blood donations collected on Reunion Island in 2005 (unpublished data from EFS), we could then estimate the number of blood donations that would have been collected in 2006 if blood donations had not been interrupted.

To assess the validity of our risk estimates, we compared the estimated risk of viremic blood donation ("estimated risk") to the observed proportion of viremic PLT donations collected and screened for CHIKV genome ("observed risk") over the same period.

Statistical approach

An approximating formula developed by Biggerstaff and Petersen[15] in 2002 for West Nile virus (WNV) was used to estimate the mean risk of viremic blood donation by CHIKV. This formula combines the proportion of asymptomatic (*Pa*) and symptomatic (*Ps*) infections with the duration of viremia among asymptomatic infected individuals (*Va*) and the duration between onset of viremia and onset of symptoms in symptomatic patients (*Vs*). This provides the mean time an infected individual is viremic and asymptomatic. Dividing this mean duration of viremia by the length of the outbreak period (*L*) then provides an estimate of the probability that an individual donates blood during viremia, assuming that a person with symptoms would self-defer or be excluded from donation by the predonation medical examination. Combined with the incidence (*I*) of the infection (including both symptomatic and asymptomatic infection), it gives an estimate of the mean risk of viremic blood donation:

$$\text{Mean risk} = \frac{(Pa \times Va) + (Ps \times Vs)}{L} \times I.$$

As suggested by Biggerstaff and Petersen,[15] risk confidence bounds were obtained by multiplying the confidence bounds of *I* by $[(Pa \times Va) + (Ps \times Vs)]/L$. Confidence intervals (CIs) of *I* were calculated with Fleiss quadratic method.[16]

Data on duration of viremia

In January 2006, few data were available on the duration of CHIKV viremia. In 1964, Sarkar and coworkers[17] described, from virologic studies of hemorrhagic fever in Calcutta, that CHIKV was most frequently isolated from blood within 48 hours after the onset of symptoms, but that it had been isolated as late as 6 days after the onset of illness.

The duration of viremia has been more extensively documented for dengue viruses: 1 or 2 days before the onset of symptoms and between 4 and 6 days and as late as 12 days after the first symptoms.[18-20] We thus used the following parameters for CHIKV: 1.5 days for the mean duration between onset of viremia and onset of symptoms among symptomatic patients (*Vs*) and 1.5 + 6 = 7.5 days for the mean duration of viremia among asymptomatic infected individuals (*Va*) assuming that the whole duration of viremia is similar in symptomatic and asymptomatic infections.

The same estimates of duration of viremia were used for the retrospective estimates since consistent observations were reported during the outbreak on Reunion Island. Thus, during this epidemic, CHIKV has been isolated from blood mostly within 5 days and as late as 12 days after the onset of symptoms. In some cases, CHIKV viremia might have persisted over 12 days since viral loads at 12 days were high.[21]

Data on the proportion of asymptomatic infections

For the preliminary estimates in January 2006, in the absence of data on the proportion of asymptomatic CHIKV infection, two hypotheses were formulated based on the proportion of asymptomatic infections reported during outbreaks of dengue:[22,23] a minimal proportion of asymptomatic infection of 30 percent and a maximal proportion of 70 percent.

Between August and October 2006, a seroprevalence study was conducted among the general population of Reunion Island.[24] This survey showed that 38 percent of the inhabitants of Reunion Island had been infected by CHIKV. The preliminary results indicated that 6 percent of the study population had a positive CHIKV serology without having reported CHIKV symptoms. This suggests that approximately 15 percent of infected individuals during this outbreak may have had an asymptomatic infection. Therefore, this proportion of 15 percent was used for *Pa* for the retrospective estimates.

Incidence of CHIKV infection

We used the incidence data in the general population for the risk estimations assuming that potential blood donors had the same risk of CHIKV infection as the general population. The population of interest was the inhabitants of Reunion Island estimated at 756,745 by a population census conducted in 2004 by the National Institute for Statistics and Economics Studies (INSEE). CHIKV incidence data, by week of onset of symptoms, were obtained from the Reunion-Mayotte Interregional Epidemiology Unit, which had started surveillance for CHIKV infection as soon as the first cases were reported in April 2005. A suspect case of CHIKV infection was defined as a patient with an abrupt onset of fever over 38.5°C associated with incapacitating arthralgia in the absence of any other potential cause of infection. From April to December 2005, surveillance relied on vector control teams, which conducted active and retrospective case-finding around the cases reported by a sentinel physician network, medical laboratories, private practitioners, and patients themselves. The number of cases took into account the symptomatic patients responding to the case definition whether or not they had consulted a general practitioner. During this period, approximately 67 suspect CHIKV cases were identified by active case-finding for every suspect case identified by the sentinel network physicians. From mid-December onward, the number of cases exceeded the capacity of the active surveillance system, and surveillance was then entirely based on the sentinel network. To estimate the total number of cases from the sentinel network data, the multiplier of 67, derived during the phase of active case finding, was used.[25]

For the estimations of the risk of viremic donations, we calculated the estimated incidence of symptomatic and asymptomatic CHIKV infection by multiplying the estimated incidence of suspect cases by 100/(proportion of symptomatic infections).

RESULTS

Preliminary estimates

When the preliminary estimates were performed at the end of January 2006, the number of CHIKV suspect cases was 6500 for Period A and 25,000 for Period B. For Period A, the estimated mean risk of viremic blood donation was 15.2 per 100,000 donations, under the minimal hypothesis of 30 percent asymptomatic infections, and 61.3 per 100,000 donations, under the maximal hypothesis of 70 percent asymptomatic infections (Table 1). For Period B, the mean risk reached 445 per 100,000 donations, under the minimal hypothesis and 1,793 per 100,000 donations, under the maximal hypothesis.

Retrospective estimates

The retrospective estimates used the results of the seroprevalence survey that estimated the proportion of asymptomatic CHIKV infections during this outbreak at 15 percent. The updated estimate of the number of symptomatic cases was 6,864 for Period A and 34,002 for Period B (Table 2). Risk of viremic blood donation was then estimated at 9.6 and 362.5 per 100,000 donations for Periods A and B, respectively. The risk estimates for the five periods of the outbreak are shown in Table 3. Between the identification of the first CHIKV cases and the interruption of blood donations (Period 1), 7 of 14,450 blood donations collected could have been viremic. During

TABLE 1. Preliminary risk estimates of viremic blood donation, Reunion Island, March 28, 2005, through January 22, 2006

	Period A, Mar 28-Dec 18, 2005		Period B, Dec 19, 2005-Jan 22, 2006	
	Minimal hypothesis	Maximal hypothesis	Minimal hypothesis	Maximal hypothesis
Estimated number of symptomatic cases	6,500	6,500	25,000	25,000
Proportion of asymptomatic infections (%)	30	70	30	70
Estimated number of infected cases	9,286	21,667	35,714	83,333
Period length (days)	266	266	35	35
Estimated incidence of CHIKV infection per 100,000	1,227	2,863	4,720	11,012
Estimated risk of viremic blood donation				
Per 100,000 blood donations (95% CI)	15.2 (14.9-15.5)	61.3 (60.6-62.2)	445.0 (440.5-449.5)	1,793.4 (1,781.9-1,804.9)
Per estimated number of blood donations (95% CI)	2.0/12,800 (1.9-2.0)	7.9/12,800 (7.8-8.0)	7.1/1,600 (7.0-7.2)	28.7/1,600 (28.5-28.9)

TABLE 2. Retrospective risk estimates of viremic blood donation, Reunion Island, March 28, 2005, through January 22, 2006

	Period A, Mar 28-Dec 18, 2005	Period B, Dec 19, 2005-Jan 22, 2006
Estimated number of symptomatic cases	6,864	34,002
Proportion of asymptomatic infections (%)	15	15
Estimated number of infected cases	8,075	40,002
Period length (days)	266	35
Estimated incidence of CHIKV infection per 100,000	1,067	5,286
Estimated risk of viremic blood donation		
Per 100,000 blood donations (95% CI)	9.6 (9.4-9.8)	362.5 (359.0-366.0)
Per estimated number of blood donations (95% CI)	1.2/12,800 (1.2-1.3)	5.8/1,600 (5.7-5.9)

Period 2, at the height of the epidemic, the estimated risk of viremic blood donation was 1,500 per 100,000, that is, 29 potentially viremic donations if blood collection had continued. The estimated risk then decreased due to diminishing CHIKV transmission: 210 per 100,000 between March and June 2006 (Period 3), 1.4 per 100,000 for the second semester of 2006 (Period 4), and 0.27 per 100,000 for the first months of 2007 (Period 5), that is, 1 potentially viremic blood donation every 21 years on the basis of 17,500 blood donations collected each year. Finally, over the course of the outbreak, a total of 47 of 35,750 blood donations might have been viremic if blood collection had continued. Simultaneously, an estimated 312,500 of 757,000 inhabitants have been infected by mosquito-borne transmission.

Comparison between estimated risk and observed risk

Between January 23 and May 7, 2006, 2 of the 500 PLT donations screened for CHIKV RNA were positive (0.4%). One donor developed CHIKV symptoms on the day after the blood donation, the other remained asymptomatic. The risk of viremic blood donation over this period was estimated at 720 per 100,000 blood donations, that is, 0.72 percent.

Although an estimated 7 viremic donors had donated blood before the collection was interrupted, no case of transfusion-transmitted CHIKV infection has been identified during this period.

DISCUSSION

During this first and massive epidemic of CHIKV infection on Reunion Island, we computed estimates of the risk of CHIKV viremic blood donation, in real time during the ascending phase of the major epidemic peak, and afterward, we refined these estimates with newly available data. Although we underestimated the incidence of CHIKV infection in our preliminary calculations, we overestimated the proportion of asymptomatic infections. Consequently, the preliminary estimates were 1.2- to 6.4-fold greater than the retrospective calculations. The preliminary estimates, however, provided a right order of magnitude of the risk in real time in an emergency context. The retrospective calculations indicate a mean risk over the course of the outbreak, between April 2005 and April 2007, of 132 per 100,000 donations. The mean risk peaked at approximately 1,500 per 100,000 donations at the height of the outbreak in February 2006. In total, potentially 47 of 35,750 blood donations might have been viremic between April 2005 and April 2007 if blood collection had not been interrupted. We also estimated that 7 blood donations were viremic before the interruption of blood donations on the island. Therefore, this measure enabled the avoidance of 40 potentially viremic donations. By way of comparison, during the outbreak, the total number of individuals infected through mosquito-borne CHIKV transmission is estimated at 312,538 individuals.

This approach has several limitations. The estimates provided relate to a mean risk, which supposes that the risk is constant over the studied period and for the

TABLE 3. Retrospective risk estimates of viremic blood donation, Reunion Island, March 28, 2005, through April 15, 2007

	Period 1, Mar 28, 2005-Jan 22, 2006	Period 2, Jan 23, 2006-Mar 5, 2006	Period 3, Mar 6, 2006-Jun 11, 2006	Period 4, Jun 12, 2006-Dec 31, 2006	Period 5, Jan 1, 2007-Apr 15, 2007	Periods 1-5, Mar 28, 2005-Apr 15, 2007
Estimated number of symptomatic cases	40,866	169,008	54,936	772	75	265,657
Period length (days)	301	42	98	203	105	749
Proportion of asymptomatic infections (%)	15	15	15	15	15	15
Estimated number of infected cases	48,078	198,833	64,631	908	88	312,538
Estimated incidence of CHIKV infection per 100,000	6,353	26,275	8,541	120	12	41,300
Estimated risk of viremic blood donation						
Per 100,000 blood donations (95% CI)	50.7 (50.2-51.1)	1,501.4 (1,495.8-1,507.1)	209.2 (207.6-210.7)	1.4 (1.3-1.5)	0.27 (0.2-0.3)	132.3 (132.0-132.7)
Per estimated number of blood donations (95% CI)	7.3/14,450 (7.3-7.4)	29.1/1,940 (29.0-29.2)	9.9/4,710 (9.8-9.9)	0.14/9,760 (0.13-0.15)	0.01/4,890 (0.01-0.02)	47.3/35,750 (47.2-47.4)

geographic area. Although estimates were performed for several periods selected according to the level of incidence, the number of cases and consequently the risk might have been highly variable during the studied period. In addition, the risk of infection varied by geographic area as later demonstrated by the seroprevalence survey that showed that 29.6 percent of the inhabitants of the North have been infected whereas in the East, this proportion reached 48 percent.[24] Consequently, the mean risk underestimates the maximal risk, corresponding to the peak of the outbreak and to the area where CHIKV transmission was maximal. This maximum risk, however, is highly time and space limited.

To obtain a more dynamic sight of the risk over the course of the epidemic and estimates of the maximal risk, it would have been necessary to develop an approach similar to the one proposed by Biggerstaff and Petersen[15,26] for the WNV epidemic in 2002 in the United States. The latter is a statistical approach based on imputation and resampling techniques providing daily estimates of the risk of blood contamination in an epidemic setting. Conducting such an analysis in the context of this large and long-standing outbreak would have been computationally cumbersome. In our opinion, such a refinement was not essential in regard to the main objectives of the study, that is, providing a right order of magnitude of the risk as an aid for risk management. We considered that providing an approximation of the mean risk over five periods was a suitable alternative. To compute these mean risks, we therefore used the approximating formula proposed by Biggerstaff and Petersen.[15] In 2003, Biggerstaff and Petersen demonstrated for the WNV epidemic in 2002 in the United States that the approximating formula provides a reasonable approximation to the mean risk of transfusion.[15] The same work of comparison of the mean risks estimated by this method and by statistical resampling was carried out, in the setting of our workgroup, for an outbreak of acute hepatitis A in France that occurred in 1996 through 1997.[14,27] It also concluded to a good concordance of the results of both methods. Note that the CIs presented with our mean risk estimates do not take into account the uncertainty on the duration of viremia, the proportion of asymptomatic infections, nor the coefficient of 67, used to estimate incidence of symptomatic infections from the sentinel network data. Even though this limitation led to artificially narrow CIs, point estimates of mean risk should not be affected.

Our incidence data were derived from a sentinel surveillance system. Because a clinical case definition was used, it is possible that other febrile illnesses, not due to CHIKV, were included in the case count. The positive predictive value of a clinical case definition, however, greatly improves if incidence is high. Therefore, the inclusion of noncases in the case count, leading to