High Risk of Plasmodium vivax Malaria Following Splenectomy in Papua, Indonesia

Steven Kho,1 Benediktus Andries,2 Jeanne R. Poespoprodjo,2,3,4 Robert J. Commons,1 Putu A. I. Shanti,3 Enny Kenangalem,2,3 Nicholas M. Douglas,1 Julie A. Simpson,5 Paulus Sugianto,6 Nicholas M. Anstey,1 and Ric N. Price1,7

1Global and Tropical Health Division, Menzies School of Health Research and Charles Darwin University, Darwin, Northern Territory, Australia; 2Timika Malaria Research Program, Papua Health and Community Development Foundation, and 3Rumah Sakit Umum Daerah Kabupaten Mimika, Timika, Papua, and Pediatric Research Office, Department of Pediatrics, University of Gadjah Mada, Yogyakarta, Indonesia; 4Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Victoria, Australia; 5Rumah Sakit Mitra Masyarakat, Timika, Papua, Indonesia; and 7Center for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, United Kingdom

Background. Splenectomy increases the risk of severe and fatal infections; however, the risk of Plasmodium vivax malaria is unknown. We quantified the Plasmodium species-specific risks of malaria and other outcomes following splenectomy in patients attending a hospital in Papua, Indonesia.

Methods. Records of all patients attending Mitra-Masyarakat Hospital 2004–2013 were reviewed, identifying those who underwent splenectomy. Subsequent risks of specific clinical outcomes within 12 months for splenectomized patients were compared to nonsplenectomized patients from their first recorded hospital admission. In addition, patients splenectomized for trauma 2015–2016 were followed prospectively for 14 months.

Results. Of the 10,774 patients hospitalized during 2004–2013, 67 underwent splenectomy. Compared to nonsplenectomized inpatients, patients undergoing splenectomy had a 5-fold higher rate of malaria presentation within 12 months (adjusted hazard ratio [AHR] = 5.0 [95% confidence interval (CI): 3.4–7.3], P < .001). The AHR was 7.8 (95% CI: 5.0–12.3) for P. vivax and 3.0 (95% CI: 1.7–5.4) for P. falciparum (both P < .001). Splenectomized patients had greater risk of being hospitalized for any cause (AHR = 1.8 [95% CI: 1.0–3.0], P = .037) and diarrheal (AHR = 3.5 [95% CI: 1.3–9.6], P = .016). In the 14-month prospective cohort, 12 episodes ofP. vivax and 6 episodes of P. falciparum were observed in 11 splenectomized patients.

Conclusions. Splenectomy is associated with a high risk of malaria, greater for P. vivax than P. falciparum. Eradication of P. vivax hypnozoites using primaquine (radical cure) and subsequent malaria prophylaxis is warranted following splenectomy in malaria-endemic areas.

Keywords. malaria; vivax; falciparum; splenectomy; Indonesia.

The spleen plays a vital role in host immunity and erythrocyte regulation. Reduced splenic function increases the risk of severe and fatal infections, particularly those from encapsulated bacteria, and parasites such as Plasmodium and Babesia [1–5]. Although patients undergoing splenectomy should be vaccinated and take antimicrobial prophylaxis to minimize these risks, these are rarely delivered in resource-poor settings.

Malaria remains the most important human parasitic disease, with approximately 3.4 billion people at risk [6]. The spleen is vital for immunity to Plasmodium species [1, 7–11]. Splenectomized patients are more susceptible to severe falciparum malaria and have a greater risk of hospitalization and mortality [12–14]. Studies of splenectomized individuals in malaria-endemic regions of Malawi and Papua New Guinea suggest a risk of malaria almost double that of nonsplenectomized controls [1, 2]. No studies have quantified the risk of vivax malaria after splenectomy. This is important given the recent recognition of P. vivax as a major cause of morbidity in malaria-endemic areas, including anemia and a risk of severe and fatal disease [15–17].

The aim of this study was to quantify the clinical consequences of splenectomy, particularly the species-specific risks of malaria, in individuals living in a malaria-endemic area in Indonesia.

METHODS

Between April 2004 and December 2013, data were prospectively collected as part of routine surveillance of patients presenting to a referral hospital in Timika, Papua, Indonesia. A retrospective analysis of this data set quantified the comparative risk of malaria and other clinical outcomes in patients who had undergone splenectomy compared to non-splenectomy patients. In addition, from 2015–2016, a group of
spleenectomized individuals were followed prospectively and the risks of malaria over a 14-month period quantified.

**Study Site**
Timika is located in Mimika district, south-central Papua, Indonesia [17, 18]. Approximately 200,000 people populate the area comprising highland-Papuans, lowland-Papuans and non-Papuan migrants [18]. Malaria transmission in Timika is high but unstable in lowland areas, with parasite prevalences of 13.9% and 38% by microscopy and polymerase chain reaction, respectively [19].

**Hospital and Malaria Treatment**
The study was conducted at Mitra Masyarakat hospital (RSMM), which served 100% of malaria patients attending surrounding healthcare facilities before November 2008, and ~80% thereafter. The hospital has 110 inpatient beds, surgical theatres, and outpatient clinics. Approximately 1800 patients are reviewed each week. The hospital laboratory does not have bacteriology facilities.

Quinine and chloroquine were used as the first-line treatment of uncomplicated malaria due to any *Plasmodium* species until March 2006. Following this, treatment of uncomplicated malaria changed to dihydroartemisinin-piperaquine plus a 14-day course of primaquine for vivax malaria [20]. Post-splenectomy antimalarial and antibiotic prophylaxis was not hospital policy.

**Retrospective Data Collection**
All patients are given a unique hospital record number (HRN) at their first hospital presentation, and all subsequent presentations can be linked to this HRN. Hospital clerks electronically record basic demographic information, mortality data, and the diagnoses given by the attending doctor (classified using the International Classification of Diseases) for each patient-presentation to hospital. Laboratory and pharmacy records are collected separately, with patients also identified by their HRN. Hospital clerks electronically record basic demographic information, mortality data, and the diagnoses given by the attending doctor (classified using the International Classification of Diseases) for each patient-presentation to hospital. Laboratory and pharmacy records are collected separately, with patients also identified by their HRN.

All inpatients and febrile outpatients are required to have a Giemsa-stained blood film checked for malaria by trained microbiologists or a rapid-diagnostic-test. Previous quality-control of RSMM microscopy suggests an accuracy of malaria diagnosis of >90% [17].

**Identifying Splenectomy Patients**
To identify all splenectomy patients accurately during the study period, surgery logbooks and registers from 2004 to 2013 were analyzed by 2 independent researchers (S. K. and B. A.) to identify individuals who may have had splenic surgery. Medical records of these individuals were then checked manually to confirm the diagnosis and reasons for surgery.

**Data Preparation**
Clinical and laboratory data were merged into a single database using the HRN and date of presentation. All splenectomy patients were aged between 13 and 51 years, and none were pregnant at the time of splenectomy. The primary comparative group was therefore nonsplenectomy controls, identified from nonpregnant patients aged between 12 and 60 years on their first hospital admission for any reason other than splenic surgery. In a sensitivity analysis, clinical outcomes post-splenectomy were compared to outcomes in patients who were admitted for trauma who did not undergo splenectomy (search terms for nonsplenectomy trauma control in Supplementary File 1).

Malaria reinfection or relapse within 2 weeks of an initial infection is highly unlikely [21], and therefore multiple malaria presentations within 14 days were considered to represent a single episode. No splenectomy patients were infected or represented with *P. malariae* or *P. ovale*.

**Statistical Analyses**
All statistical analyses were performed in SPSS v23. Baseline characteristics were presented for the splenectomized and nonsplenectomized patients and compared using the χ2 test. In the primary analysis, the risks of representation with any malaria, *P. falciparum* malaria and *P. vivax* malaria by 12 months were compared in splenectomized versus nonsplenectomized patients. Patients were assumed to have been present in Timika for the full 12 months from the date of their splenectomy or first hospital admission (for controls). Study follow-up was curtailed at 31 December 2013. Other outcomes compared included risk of admission with other clinical outcomes (pneumonia, diarrheal illness, sepsis, cellulitis, tuberculosis, and urinary tract infections), any hospital representation, any admission, and death. The incidence of these outcomes was calculated from the cumulative number of episodes observed over 12 months or until the last day of follow-up and reported as a rate “per thousand patient-years.” Analyses of the time-to-first-event were calculated by survival analysis and compared using Kaplan-Meier and Cox regression models. Potential confounders included in the multivariable Cox models were age (<15 years, ≥15–60 years), sex, ethnicity (highland-Papuan, lowland-Papuan, non-Papuan), and presence and species of parasitemia at the time of initial admission. To control for changes in background malaria endemicity, multivariable Cox models were stratified by year of splenectomy or year of first hospital admission for controls. In the sensitivity analysis, comparisons were repeated between splenectomy patients and nonsplenectomy trauma controls.

**Prospective Cohort**
In a complementary prospective study, 11 patients undergoing splenectomy at an adjacent hospital (Rumah Sakit Umum Daerah [RSUD]) between July 2015 and November 2016 were followed from their day of splenectomy for 14 months. Malaria encounters were recorded by monitoring visits to healthcare facilities and conducting monthly interviews. Patients were checked for peripheral parasitemia on the day of surgery and
were treated according to local treatment guidelines. Data from these patients are presented using descriptive statistics only.

Ethical Approval
This study was approved by the Ethics Committees of the University of Gadjah Mada (KE/FK/544/EC, January 2015), Indonesia, and Menzies School of Health Research, Australia (10.1397, September 2014). In the retrospective cohort, hospital records were anonymized with informed consent not requested because data were collected as part of routine hospital surveillance. Informed consent was obtained in the prospective cohort.

RESULTS
Between April 2004 and December 2013, 162,966 patients attended RSMM hospital of whom 56,458 (34.6%) were admitted at least once and 67 patients underwent splenectomy (Figure 1). A total of 10,707 non-pregnant patients aged 12–60 years admitted on their first encounter to hospital did not have a splenectomy, of whom 1,631 (15.2%) presented with a trauma-related diagnosis (Figure 1).

Baseline Characteristics
Of the 67 splenectomized patients, 43 (64.2%) were male, 44 (65.7%) were highland-Papuans, and 4 (6.0%) were lowland-Papuans; Table 1. The median age at the time of splenectomy was 25.4 years (range 13.7–51). The number of splenectomy patients per year varied with the highest number recorded in 2012. Fifty patients (74.6%) were splenectomized due to traumatic injury; Supplementary Table 1.

The nonsplenectomized patients had similar demographics to that of the cases, with a median age at first admission of 26.8 (range 12–60; Table 1). The number of nonsplenectomy controls per year peaked in 2005 and declined thereafter. Thirteen splenectomy patients (19.4%) had peripheral parasitemia at the

![Flow diagram of data merging process and exclusion criteria.](https://academic.oup.com/cid/article-abstract/68/1/51/4996544)
time of surgery compared to 4713 patients (44.3%) at the time of admission in the nonsplenectomy control group (Table 1).

Risk of Representation With Malaria

In total, 56.1% (6041/10 774) of patients represented to hospital within 4 years following initial presentation, of whom 86.2% (5298/6 084) did so within 12 months. The overall risk of representing with any malaria within 12 months was 13.5% (95% confidence interval [CI]: 12.9–14.2) and was greater in females compared to males (hazard ratio [HR] = 1.3 [95% CI: 1.2–1.5], \( P < .001 \)) and in children compared to adults (HR = 1.4 [95% CI: 1.1–1.7], \( P = .001 \)), and highlanders compared to non-Papuans (HR = 3.4 [95% CI: 2.9–4.0], \( P < .001 \)). The risk of representing with malaria was also elevated in those presenting initially with malaria and this was apparent for all species; Table 2.

Overall 43.3% (29/67) of splenectomized patients represented with malaria within 12 months of surgery compared to 13.3% (1426/10 707) of those in the control group (HR = 4.3 [95% CI: 3.0–6.2], \( P < .001 \); Table 2 and Figure 2a). After categorizing malaria by species, 17.9% (12/67) represented with \( P. \) falciparum and 31.3% (21/67) with \( P. \) vivax within 12 months of splenectomy compared to 8.4% (901/10 707) and 4.9% (523/10 707) in the control group, respectively (Figure 2b and 2c).

Table 1. Baseline Characteristics of Splenectomy Patients and Nonsplenectomy Controls

| Variable                  | Splenectomy Patients | Nonsplenectomy Controls | Total | Nonsplenectomy Trauma Controls* |
|---------------------------|----------------------|-------------------------|-------|---------------------------------|
|                           | No. (%)              | No. (%)                 | P     | No. (%)                         | P     |
| **Sex**                   |                      |                         |       |                                 |       |
| Male                      | 43 (64.2)            | 6558 (61.2)             | .624  | 6601 (61.3)                     | 1254 (76.9) | .016 |
| Female                    | 24 (35.8)            | 4149 (38.8)             |       | 4173 (38.7)                     | 377 (23.1)   |
| **Ethnicity**             |                      |                         |       |                                 |       |
| Non-Papuan                | 19 (28.3)            | 2745 (25.7)             | .091  | 2764 (25.7)                     | 482 (29.6) | .002 |
| Highland-Papuan           | 44 (65.7)            | 6262 (58.6)             |       | 6306 (58.7)                     | 780 (47.9)   |
| Lowland-Papuan            | 4 (6.0)              | 1678 (15.7)             |       | 1682 (15.6)                     | 366 (22.5)   |
| **Age, years**            |                      |                         |       |                                 |       |
| Median [Range]            | 25.4 [13.7–51.0]     | 26.8 [12.0–60.0]        |       | 26.8 [12.0–60.0]                | 25.8 [12.0–60.0] | .235 |
| ≥15 to 60                 | 66 (98.5)            | 10 164 (94.9)           | .182  | 10 230 (95.0)                   | 1557 (95.5) |
| **Parasitemia**           |                      |                         |       |                                 |       |
| Negative                  | 54 (80.6)            | 5936 (55.8)             | <.001 | 5990 (55.9)                     | 1484 (91.3) | .001 |
| \( P. \) falciparum       | 10 (14.9)            | 3291 (30.9)             |       | 3301 (30.8)                     | 75 (4.6)   |
| \( P. \) vivax            | 2 (3.0)              | 812 (7.6)               |       | 814 (7.6)                       | 60 (3.7)   |
| Mixed infections          | 1 (1.5)              | 610 (5.7)               |       | 611 (5.7)                       | 7 (0.4)   |
| **Year**                  |                      |                         |       |                                 |       |
| 2004                      | 6 (9.0)              | 1462 (13.7)             |       | 1468 (13.6)                     | 155 (9.5)   |
| 2005                      | 7 (10.4)             | 1540 (14.4)             |       | 1547 (14.4)                     | 203 (12.5)   |
| 2006                      | 6 (9.0)              | 1484 (13.9)             |       | 1490 (13.8)                     | 242 (14.8)   |
| 2007                      | 8 (11.9)             | 1481 (13.8)             |       | 1489 (13.8)                     | 190 (11.6)   |
| 2008                      | 8 (11.9)             | 1075 (10.0)             |       | 1083 (10.1)                     | 184 (11.3)   |
| 2009                      | 3 (4.5)              | 888 (8.3)               |       | 888 (8.3)                       | 137 (8.4)   |
| 2010                      | 4 (6.0)              | 688 (6.2)               |       | 672 (6.2)                       | 102 (6.3)   |
| 2011                      | 5 (7.5)              | 556 (5.2)               |       | 561 (5.2)                       | 114 (7.0)   |
| 2012                      | 15 (22.3)            | 534 (5.0)               |       | 549 (5.1)                       | 111 (6.8)   |
| 2013                      | 5 (7.5)              | 1022 (9.5)              |       | 1027 (9.5)                      | 193 (11.8)   |
| Total                     | 67 (100)             | 10 707 (100)            |       | 10 774 (100)                    | 1631 (100)   |

\( P \) values from \( \chi^2 \) test of control group versus splenectomy patients.

*Subgroup of patients from non-splenectomy controls.

Data missing in 22 nonsplenectomy controls (3 trauma).

58 nonsplenectomy controls with \( P. \) malariae or \( P. \) ovale infection omitted from analysis (5 trauma).

Downloaded from https://academic.oup.com/cid/article-abstract/68/1/51/4996544 by Said Business School user on 02 January 2019
Table 2. Baseline Risk Factors for Representing With Any Malaria, *P. falciparum*, or *P. vivax* Within 12 months

| Outcome | Baseline Risk Factor | Prevalence of Outcome (n/N) | Univariable Analysis | Multivariable Analysisa |
|---------|----------------------|-----------------------------|----------------------|------------------------|
|         |                      |                             | HR [95% CI]          | AHR [95% CI]          |
| Any malaria | Splenectomy | No | 13.3% (1426/10707) | Reference | Reference |
|          |                      | Yes | 43.3% (239/67) | 4.3 [3.0–6.2] | <.001 | 5.0 [3.4–7.3] | <.001 |
| Sex     |                      | Male | 12.2% (803/6601) | Reference | Reference |
|         |                      | Female | 15.6% (652/4173) | 1.3 [1.2–1.5] | <.001 | 1.3 [1.1–1.4] | <.001 |
| Age, years |            | ≥15 to 60 | 13.2% (1353/10230) | Reference | Reference |
|         |                      | 12 to 14 | 18.8% (102/544) | 1.4 [1.1–1.7] | .001 | 1.2 [1.0–1.5] | 0.98 |
| Ethnicity |          | Non-Papuan | 5.8% (160/2764) | Reference | Reference |
|         |                      | Highland-Papuan | 19.2% (1213/6306) | 3.4 [2.9–4.0] | <.001 | 3.4 [2.8–4.0] | <.001 |
|         |                      | Lowland-Papuan | 11.9% (81/1682) | 0.8 [0.6–1.1] | .122 | 1.0 [0.8–1.3] | 0.979 |
| Parasitemia |          | Negative | 8.8% (530/5990) | Reference | Reference |
|         | P. falciparum | 18.4% (607/3301) | 2.1 [1.8–2.3] | <.001 | 1.8 [1.6–2.0] | <.001 |
|         | P. vivax | 20.8% (169/814) | 2.4 [2.0–2.8] | <.001 | 2.4 [2.1–2.9] | <.001 |
|         | Mixed infections | 22.6% (138/611) | 2.6 [2.2–3.2] | <.001 | 2.2 [1.8–2.6] | <.001 |
| P. falciparum | Splenectomy | No | 8.4% (901/10707) | Reference | Reference |
|          |                      | Yes | 17.9% (12/67) | 2.3 [1.3–4.0] | .005 | 3.0 [1.7–5.4] | <.001 |
| Sex     |                      | Male | 7.8% (518/6601) | Reference | Reference |
|         |                      | Female | 9.5% (395/4173) | 1.2 [1.1–1.4] | .002 | 1.2 [1.0–1.3] | .016 |
| Age, years |            | ≥15 to 60 | 8.3% (847/10230) | Reference | Reference |
|         |                      | 12 to 14 | 12.1% (66/544) | 1.4 [1.1–1.8] | .006 | 1.2 [0.9–1.5] | .211 |
| Ethnicity |          | Non-Papuan | 3.0% (84/2764) | Reference | Reference |
|         |                      | Highland-Papuan | 12.2% (770/6306) | 4.0 [3.2–4.0] | <.001 | 3.7 [2.9–4.7] | <.001 |
|         |                      | Lowland-Papuan | 3.4% (58/1682) | 1.1 [0.8–1.6] | .543 | 1.3 [0.9–1.8] | .119 |
| Parasitemia |          | Negative | 5.5% (331/5990) | Reference | Reference |
|         | P. falciparum | 12.4% (408/3301) | 2.2 [1.9–2.5] | <.001 | 1.8 [1.6–2.1] | <.001 |
|         | P. vivax | 11.2% (91/814) | 2.0 [1.6–2.5] | <.001 | 2.0 [1.6–2.5] | <.001 |
|         | Mixed infections | 12.3% (75/611) | 2.2 [1.7–2.8] | <.001 | 1.8 [1.4–2.3] | <.001 |
| P. vivax | Splenectomy | No | 4.9% (523/10707) | Reference | Reference |
|          |                      | Yes | 31.3% (21/67) | 7.7 [5.0–11.9] | <.001 | 7.8 [5.0–12.3] | <.001 |
| Sex     |                      | Male | 4.1% (269/6601) | Reference | Reference |
|         |                      | Female | 6.6% (275/4173) | 1.6 [1.4–1.9] | <.001 | 1.5 [1.3–1.8] | <.001 |
| Age, years |            | ≥15 to 60 | 4.9% (505/10230) | Reference | Reference |
|         |                      | 12 to 14 | 7.2% (39/544) | 1.4 [1.0–1.9] | .044 | 1.2 [0.9–1.7] | .224 |
| Ethnicity |          | Non-Papuan | 2.6% (72/2764) | Reference | Reference |
|         |                      | Highland-Papuan | 7.2% (452/6306) | 2.7 [2.1–3.4] | <.001 | 2.8 [2.2–3.6] | <.001 |
|         |                      | Lowland-Papuan | 1.2% (20/1682) | 0.4 [0.3–0.7] | .001 | 0.6 [0.4–1.0] | .041 |
| Parasitemia |          | Negative | 2.9% (173/5990) | Reference | Reference |
|         | P. falciparum | 6.5% (214/3301) | 2.1 [1.7–2.6] | <.001 | 2.0 [1.6–2.5] | <.001 |
|         | P. vivax | 11.9% (97/814) | 4.1 [3.2–5.2] | <.001 | 4.0 [3.1–5.1] | <.001 |
|         | Mixed infections | 9.3% (57/611) | 3.2 [2.4–4.3] | <.001 | 2.6 [1.9–3.5] | <.001 |

Abbreviations: AHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio.

* Cox model stratified by year of splenectomy or 1st hospital admission (2004–2013).
After controlling for confounding factors, splenectomy was a significant risk factor for hospital representation with any malaria (adjusted hazard ratio [AHR] = 5.0 [95% CI: 3.4–7.3], P < .001), and this was more apparent with P. vivax (AHR = 7.8 [95% CI: 5.0–12.3], P < .001) compared to P. falciparum (AHR = 3.0 [95% CI: 1.7–5.4], P < .001; Table 2). Of the 29
spleenectomy patients representing with malaria within 1 year, 34.5% (10/29) had more than 1 episode of malaria, including 50% (4/8) of those with *P. falciparum*, 30% (6/19) of those with *P. vivax* and 0% (0/2) of those with mixed species infections.

The incidence of malaria was 699 (95% CI: 506–942) per thousand patient-years in spleenectomy patients compared to 222 (95% CI: 213–232) per thousand patient-years in the non-spleenectomy controls (rate ratio [RR] = 3.1 [95% CI: 2.3–4.3], P < .001; Table 3). The rate of malaria associated with spleenectomy was significantly higher for *P. vivax* (RR = 4.5 [95% CI: 3.1–6.7], P < .001) compared to that for *P. falciparum* (RR = 2.2 [95% CI: 1.4–3.5], P = .001; Table 3). In spleenectomy patients, the incidence of malaria was 236 (95% CI: 132–389) per thousand patient-years in the 12 months prespleenectomy compared to 699 (95% CI: 506–942) per thousand patient-years post-splenectomy (RR = 3.0 [95% CI: 1.6–5.7], P < .001; Table 3).

**Risk of Other Morbidity and Mortality**

The overall risk of representing at least once within 12 months was 82.1% (55/67) in spleenectomy patients compared to 48.1% (5153/10707) in controls (AHR = 2.3 [95% CI: 1.8–3.0], P < .001; Table 4). During this period, spleenectomy patients were at greater risk of being admitted to hospital for any cause (AHR = 1.8 [95% CI: 1.0–3.0], P = .037; Figure 2d), being admitted with pneumonia (AHR = 2.8 [95% CI: 0.9–8.8], P = .085; Figure 2e) or being admitted with diarrhea (AHR = 3.5 [95% CI: 1.3–9.6], P = .016; Figure 2f) but not being admitted for sepsis, cellulitis, tuberculosis, or urinary tract infection (Table 4 and Supplementary Tables 6–13). Twelve months after spleenectomy, 6.0% (4/67) of spleenectomy patients had died compared to 5.7% (613/10707) in controls (AHR = 0.8 [95% CI: 0.3–2.2], P = .671; Supplementary Table 5).

**Risk of Malaria in Patients With Trauma**

Of the 10707 nonsplenectomy controls, 1631 (15.2%) patients were admitted due to trauma and were considered nonsplenectomy trauma controls (Figure 1). Baseline characteristics were similar between spleenectomy and trauma patients (Table 1). When compared to nonsplenectomy trauma controls, the risk of malaria after spleenectomy was even greater (AHR = 6.1 [95% CI: 3.9–9.3], P < .001; Supplementary Table 2).

**Malaria in a Cohort of 11 Patients Followed Prospectively From Splenectomy**

Eleven patients underwent spleenectomy at RSUD Hospital, all due to trauma, of which 9 (81.8%) were male, 6 (54.5%) were highland-Papuans, and 2 (18.2%) were lowland-Papuans (Supplementary Table 3). The median age at the time of spleenectomy was 30 years (range 15–46). At the time of surgery, 4 had asymptomatic peripheral parasitemia by microscopy (1 *P. vivax* and 3 *P. falciparum*) and were given antimalarial treatment. In the 14 months following spleenectomy, 8 of 11 (72.7%) patients returned with 18 episodes of symptomatic microscopically confirmed malaria: 8 (72.7%) patients with 12 episodes of *P. vivax* and 6 (54.5%) with 6 episodes of *P. falciparum* infection, none severe. Four of these 8 patients (50%) returned within 3 months of surgery, on day 8 (*P. vivax*), day 18 (*P. vivax*; having had asymptomatic falciparum parasitemia on day 0), day 32 (*P. falciparum*; having had asymptomatic falciparum parasitemia on day 0) and month 3 (*P. vivax*), respectively. At 14 months of follow-up no patient had died.

**DISCUSSION**

Our large observational study quantifies the risk of morbidity and mortality in splenectomized individuals living in a malaria-endemic region. Splenectomized patients were at 5-fold higher risk of malaria within 12 months of surgery, with the risk being far greater for *P. vivax* compared to *P. falciparum*. These retrospective findings were supported by data from a prospective cohort of 11 patients followed after spleenectomy. Splenectomy patients were at increased risk of representation due to any cause, admission with diarrheal illness or pneumonia, but not mortality or other causes of infection.

### Table 3. Incidence Rate and Rate Ratio of Malaria Episodes and Hospital Representations and Admissions Over 12-Months Follow-up, Comparing Spleenectomy Patients to Controls, and Comparing 12-Month Rate Pre- and Post-splenectomy

| Outcomes                    | Incidence Rate per 1000 Patient-Years [95% CI] | 12 Months Before vs 12 Months After Spleenectomy | Rate Ratio [95% CI] P | Rate Ratio [95% CI] P |
|-----------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------|-----------------------|
| Any malaria                 | Splenectomy Patients 12 Months Before 236 [132–389] Splenectomy Patients 12 Months After 699 [506–942] Spleenectomy Controls 12 Months After 222 [213–232] | 3.0 [1.6–5.7] <.001 | 3.1 [2.3–4.3] <.001 |
| *P. falciparum*             | 220 [120–369]                              | 325 [199–502]                              | 1.5 [0.7–3.2] 0.133   | 2.2 [1.4–3.5] .001    |
| *P. vivax*                  | 79 [26–183]                               | 439 [289–639]                              | 5.6 [2.1–8.6] <.001   | 4.5 [3.1–6.7] <.001   |
| Any hospital representation | 1556 [1265–1894]                         | 4940 [4400–5528]                         | 3.2 [2.5–4.0] <.001   | 2.3 [2.1–2.6] <.001   |
| Any hospital admission      | 189 [97–329]                              | 309 [186–482]                              | 1.6 [0.8–3.7] .092    | 1.8 [1.1–2.8] .02     |

Abbreviation: CI, confidence interval.
Several case reports and small series highlight an increased risk of malaria after splenectomy; however, these reports are limited to no more than 33 splenectomized individuals [1, 2, 12–14, 22–26]. The current analysis was able to expand the risk analysis from an endemic area where a high number of individuals undergo splenectomy, mostly following trauma or road traffic injuries. Our study was also able to quantify, for the first time to our knowledge, the risk of vivax malaria after splenectomy and surprisingly noted that the risk was even greater than for falciparum malaria. Although our primary retrospective analysis was censored at 12 months, extending the period of follow-up to 4 years did not change the results meaningfully (Supplementary Table 4).

The greatest risk of malaria occurred in the first 3 months following splenectomy. In 2005 the incidence of malaria in Papua was approximately 876 per 1000 patient-years [18]. This comparatively low baseline incidence suggests that the rate of reinfection would have been relatively low and that episodes of malaria post-splenectomy were likely to be originating from low-level preexisting bloodstream infections. This is supported by 2 of the 4 patients with asymptomatic parasitemia in the prospective study developing clinical malaria within 32 days. Removal of the spleen impairs acquired immunity [1, 7, 9–11], and this may induce splenectomized patients with chronic, asymptomatic parasitemia to develop higher levels of parasitemia and become symptomatic [24, 25]. Alternatively, the splenectomy may result in displacement into, and/or multiplication within peripheral blood, of viable parasites that would otherwise preferentially accumulate as a hidden viable biomass in the spleen [27]. If P. vivax has a greater propensity for splenic pooling [27–29], this could then explain the higher risk of very early P. vivax recurrence compared to P. falciparum. Interestingly, after splenectomy a higher proportion of patients in the retrospective study had more than one episode of P. falciparum compared to P. vivax, suggesting that P. vivax attacks may have originated from preexisting infections or relapses that were then cleared, whereas P. falciparum recurrences were attributable to an increased susceptibility to new infections.

A third explanation for the increased risk of malaria is that attributable to trauma itself. The process of splenectomy is known to be followed by malaria in previously asymptomatic individuals [23–26]. Furthermore, there is an increased risk of falciparum malaria in trauma patients, a phenomenon known as postinjury malaria [30–32]. To address the confounding effect of trauma itself, a sensitivity analysis comparing splenectomized patients with control patients admitted due to trauma was performed. The risk of malaria was even higher in splenectomized patients, suggesting that trauma itself, at least in this population, is not a risk factor. We were unable to explore the effect of general surgery; however, earlier studies have shown that frequency of falciparum attacks or P. vivax relapses after surgery do not differ from the overall population or from pre-surgery [33–35]. Only one study reported a higher risk of P. falciparum in trauma patients undergoing primary surgery [31]. Only 11% of trauma patients are predicted to undergo surgery [36]; thus, surgery as a risk factor for malaria remains to be determined.

Previous studies have identified higher risk of sepsis including pneumonia following splenectomy [3, 4, 37, 38]. Although pneumonia was diagnosed in 141 patients, sepsis was recorded infrequently, a likely reflection of the lack of hospital microbiological facilities. Although splenectomized patients were at more than 2.5-fold greater risk of these outcomes, this did not reach statistical significance (P = .085 and .350, respectively). Our study was also underpowered to determine an increased risk of mortality following splenectomy, with only 4 (6.0%) patients known to have died within 12 months of splenectomy. The only outcome that reached statistical significance was a...
High Risk of Malaria After Splenectomy • CID 2019:68 (1 January) • 59

3.5-fold increased risk of diarrheal admission. Salmonellosis is caused by encapsulated bacteria, and splenectomy patients are known to be at a high risk of disease [4, 39, 40]; however, without an underlying microbiological diagnosis we were unable to explore this further.

Our study has several limitations. Although our analysis was observational and free from coercive biases associated with many clinical study designs, our data are subject to the effects of residual confounding. Retrospective analyses were confined to RSMM presentations and did not consider presentations at other health facilities or emigration from the catchment area during the follow-up period. However, it is likely that this attrition bias would apply equally to the cases and controls. Furthermore, our findings were confirmed in the 11 patients followed prospectively. In the retrospective analysis, malaria occurring within 14 days of splenectomy was not captured and diagnosis by the attending physician was determined without microbiological testing.

In conclusion, splenectomized individuals in a malaria-endemic area are at 5-fold greater risk of malaria within 12 months of surgery, with 70% of events occurring in the first 3 months. The risk is greater for P. vivax than for P. falciparum. Current guidelines recommend that patients undergoing splenectomy should be offered vaccinations and lifelong prophylactic and standby antibiotics. Our study suggests that in malaria-endemic regions these individuals should also be offered early radical cure of malaria with an artemisinin combination therapy plus, in vivax-endemic regions, 14 days prior to prevent reinfection.

Supplementary Data
Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes
Acknowledgments. We thank Yati Soenarto for support, Daniel Lampah, Leo Leonardo, Ruland Wandosa, and Hidar for assistance with patient record searches, staff and patients of Mitra Masyarakat Hospital, and participants in the prospective cohort.

Funding. This work was supported by the Wellcome Trust (Senior Fellowship in Clinical Science to RNP, grant 200909) and the Australian National Health and Medical Research Council (NHMRC) (program grant 1037304 awarded to R. N. P. and N. M. A., and Practitioner and Research Fellowships [1042072 and 1135820] to N. M. A.). S. K. was supported by an Australian Government Postgraduate Award scholarship. J. R. P. was funded by a Wellcome Trust Training fellowship in Tropical Medicine (grant 099875). J. A. S. is supported by a NHMRC Research Fellowship. R. J. C. was supported by a postgraduate NHMRC scholarship and a RACP NHMRC Kincade-Smith scholarship. The Timika Research Facility and Papuan Community Health Foundation are supported by the Australian Department of Foreign Affairs and Trade.

Potential conflicts of interest. The authors declare no conflict of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References
1. Bach O, Baier M, Pulwitt A, et al. Falciparum malaria after splenectomy: a prospective controlled study of 33 previously splenectomized Malawian adults. Trans R Soc Trop Med Hyg 2005; 99:861–7.
2. Boone KE, Watters DA. The incidence of malaria after splenectomy in Papua New Guinea. BMJ 1995; 311:1273.
3. Deodhar HA, Marshall RJ, Barnes JS. Increased risk of sepsis after splenectomy. BMJ 1993; 307:1408–9.
4. Cullingford GL, Watkins DN, Watts AD, Mallon D. Severe late postsplenectomy infection. Br J Surg 1991; 78:716–21.
5. Rosser F, Zarrabi MH, Benach JL, Habicht GS. Babesiosis in splenectomized adults: review of 22 reported cases. Am J Med 1984; 76:696–701.
6. WHO. World Malaria Report 2017. Geneva, Switzerland: World Health Organization, 2017.
7. Buffet PA, Safeukui I, Deplaine G, et al. The pathogenesis of Plasmodium falciparum malaria in humans: insights from splenic physiology. Blood 2011; 117:381–92.
8. Engwerda CR, Beattie L, Amante FH. The importance of the spleen in malaria. Trends Parasitol 2005 Feb; 21(2):75–80.
9. Kumar S, Good MF, Donfried F, Vinetz JM, Miller LH. Interdependence of CD4+ T cells and malarial spleen in immunity to Plasmodium vinckei vinckei: relevance to vaccine development. J Immunol 1989; 143:2017–23.
10. Weiss L. Mechanisms of splenic control of murine malaria: cellular reactions of the spleen in lethal (strain 17XL) Plasmodium yoelii malaria in BALB/c mice, and the consequences of pre-infective splenectomy. Am J Trop Med Hyg 1989; 41:144–60.
11. Grun JL, Long CA, Weidanz WP. Effects of splenectomy on antibody-independent immunity to Plasmodium chabaudi adami malaria. Infect Immun 1985; 48:853–8.
12. Zhang HW, Li SJ, Hu T, et al. Prolonged parasite clearance in a Chinese splenectomized patient with falciparum malaria imported from Nigeria. Infect Dis Poverty 2017; 6:44.
13. Demar M, Legrand E, Hommel D, Estere P, Carme B. Plasmodium falciparum malaria in splenectomized patients: two case reports in French Guiana and a literature review. Am J Trop Med Hyg 2004 Sep; 71(3):290–3.
14. Looareesuwan S, Suphutarasami P, Webster HK, Ho M. Malaria in splenectomized patients: report of four cases and review. Clin Infect Dis 1993 Mar; 16(3):361–6.
15. Douglas NM, Pontororing GR, Lampah DA, et al. Mortality attributable to Plasmodium vivax malaria: a clinical audit from Papua, Indonesia. BMC Med 2014; 12:217. doi: 10.1186/s12916-014-0217-z.
16. Anstey NM, Douglas NM, Poepoprodjo JR, Price RN. Plasmodium vivax: clinical spectrum, risk factors and pathogenesis. Adv Parasitol 2012; 80:151–201. doi: 10.1016/B978-0-12-397900-1.00003-7.
17. Tijjra E, Anstey NM, Sugianto P, et al. Multidrug-resistant Plasmodium vivax associated with severe and fatal malaria: a prospective study in Papua, Indonesia. PLoS Med 2008; 5:e218.
18. Karyana M, Burdarm L, Yeung S, et al. Malaria morbidity in Papua Indonesia, an area with multidrug resistant Plasmodium vivax and Plasmodium falciparum. Malar J 2008; 7:418.
19. Pava Z, Burdarm F, Handayuni I, et al. Submicroscopic and asymptomatic Plasmodium parasiteaemia associated with significant risk of anaemia in Papua, Indonesia. PLoS One 2016; 11:e0165340.
20. Douglas NM, Poepoprodjo JR, Patrini D, et al. Unsuspected primaquine for the treatment of Plasmodium vivax malaria relapses in southern Papua: a hospital-based cohort study. PLoS Med 2017; 14:e1002379.
21. Battle KE, Karbunen MS, Bhatt S, et al. Geographical variation in Plasmodium vivax relapse. Malar J 2014; 13:144.
22. Elizalde-Torrent A, Val F, Azevedo ICC, et al. Sudden spleen rupture in a Plasmodium vivax-infected patient undergoing malaria treatment. Malar J 2018; 17:79.
23. Tagariello G, Sartori R, Inojosa WO, et al. Dramatic post-splenectomy onset of malaria caused by latent Plasmodium vivax in a female immigrant with severe immunological anaemia. Blood Transfus 2014; 12:428–30.
24. Bachmann A, Esser C, Peter M, et al. Absence of erythrocyte sequestration and lack of multicopy gene family expression in Plasmodium falciparum from a spleenectomized malaria patient. PLoS One 2009; 4:e7459.
25. Bidegain F, Berry A, Alvarez M, et al. Acute Plasmodium falciparum malaria following splenectomy for suspected lymphoma in 2 patients. Clin Infect Dis 2005; 40:697–100.
26. Vinain VA, Martynov VA, Yasen JV, Orlov VA. Outbreak of latent malaria following splenectomy for trauma. Klin Med (Mosk) 1986; 64:136–7.
27. Barber BE, William T, Grigg MJ, Pararieswanar U, Piera KA, Price RN. Parasite biomass-related inflammation, endothelial activation, microvascular dysfunction and disease severity in vivax malaria. PLoS Pathog 2015; 11.
28. Fonseca LL, Joyner CJ, Galinski MR, Voit EO; MaHPIC Consortium. A model of Plasmodium vivax concealment based on Plasmodium cynomolgi infections in Macaca mulatta. Malar J 2017; 16:375.
29. Machado Siqueira A, Lopes Magalhães BM, Cardoso Melo G, et al. Spleen rupture in a case of untreated Plasmodium vivax infection. PLoS Negl Trop Dis 2012; 6:e1934.
30. Heger T, Sundet M, Van Heng Y, Rattana Y, Husum H. Postinjury malaria: experiences of doctors in Battambang Province, Cambodia. Southeast Asian J Trop Med Public Health 2005; 36:811–5.
31. Husum H, Heger T, Sundet M. Postinjury malaria: a study of trauma victims in Cambodia. J Trauma 2002; 52:259–66.
32. Aina AO. Effect of trauma on malaria infection. World J Surg 1983; 7:527–31.
33. Diako P, Van Langen J, Bonkosungou B, Gazin P. Malaria following surgery in an endemic region. Sante 1994; 4:115–7.
34. Takongmo S, Gaggini J, Malonga E, Leundji H, Same Ekobo A. Malaria and post operative fever in the University Hospital Center of Yaounde (Cameroon). Med Trop (Mars) 1993; 53:97–100.
35. KARK W. Surgery and the relapse rate of malaria. Br Med J 1946; 2:114–7.
36. NTDB. National Trauma Databank 2016 Annual Report. Chicago, IL: American College of Surgeons, 2016.
37. Hansen K, Singer DB. Asplenic hyposplenic overwhelming sepsis: postsplenectomy sepsis revisited. Pediatr Dev Pathol 2001; 4:105–21.
38. Morris DH, Bullock FD. The importance of the spleen in resistance to infection. Ann Surg 1919; 70:513–21.
39. Davidson RN, Wall RA. Prevention and management of infections in patients without a spleen. Clin Microbiol Infect 2001; 7:657–60.
40. Kirikae T, Yoshida M, Sawada H, Tezuka H, Fujita J, Mori K. Effects of splenectomy on the retention of Salmonella enteritidis and on the hemopoietic response to Salmonella infection. Biomed Pharmacother 1984; 40:6–10.