	PaO_2/F_IO_2 post bypass	$PaCO_2$ after extubation	Time to rewarm (h)	3 h drains loss	Time to discharge (days)
Control (n=14)	243 (36)	6·3 (0·7)	3·5 (0·79)	218 (50)	8·4 (0·5)
Remifentanil (n=13)	292 (34)	6·1 (0·6)	2·1 (0·2)	241 (54)	6·6 (0·26)
p	0·33	0·41	0·11	0·76	0·015

Table: **Results**

[SE]) for oxygen exchange (ratio of partial pressure of oxygen in arterial blood to inspired oxygen, PaO_2/F_IO_2), arterial carbon dioxide tension ($PaCO_2$), time to rewarming, and early drains loss. All these data were similar between groups as were the preoperative cardiovascular status, duration of surgery, and ischaemic period during bypass. The time to extubation was shorter (p=0·025) in patients anaesthetised with the remifentanil-based TIVA method. On average these patients were extubated 2·5 hours earlier than patients given inhalational anaesthetic with fentanyl. The range in times to extubation was 3–7 hours in this TIVA group and 3·5–11 hours in the other patients. One of us (T S) suggested that earlier extubation was also associated with an earlier discharge from hospital. This clinical impression was confirmed in this small group of patients.

These observations are difficult to explain. However, these data show that it is possible to achieve early postoperative extubation with TIVA alone. The data also suggest that variations in anaesthetic technique affects subsequent rate of recovery.

*R Bacon, V Chandrasekan, A Haigh, B D Royston, D Royston, T Sundt
Harefield Hospital, Harefield, Middlesex UB9 6JH, UK

1 Chong JL, Grebenik C, Sinclair M, Fisher A, Pillai R, Westaby S. The effect of a cardiac surgical recovery area on the timing of extubation. *J Cardiothoracic Vasc Anesth* 1993; 7: 137–41.
2 Shapiro BA, Lichtenthal PR. Inhalation-based anesthetic techniques are the key to early extubation of the cardiac surgical patient. *J Cardiothoracic Vasc Anesth* 1993; 7: 156–36.
3 Glass PS, Hardman D, Kamiyama Y, et al. Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanil (GI87084B). *Anesth Analg* 1993; 77: 1031–40.
4 Rosow C. Remifentanil: a unique opioid analgesic. *Anesthesiology* 1993; 79: 875–76.
5 Westmoreland CL, Hoke JF, Sebel PS, Hug C Jr, Muir KT. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. *Anesthesiology* 1993; 79: 893–903.

Efficacy of SPf66 vaccine against *Plasmodium falciparum* malaria in children

Sir—Alonso and colleagues (Oct 29, p 1175) report a decrease in the frequency of clinical malaria among Tanzanian children who had received the SPf66 malaria vaccine developed by Pattaroyo. These results were obtained in an area where malaria transmission rate is one of the highest in the world, with about 300 infective bites per person each year. It therefore seems surprising that such a small number of malaria attacks—0·35 annual incidence rate—was recorded in the placebo group. Malarial morbidity was measured by passive case detection at the dispensary. In a subgroup consisting of about a third of children, active case detection was also done by weekly home visits. As the investigators point out, these methods can detect only a certain number of malaria attacks among the study population.

What percentage of malaria episodes was actually detected? Two surveys that we did in areas of similar malaria endemicity in tropical Africa could help to answer this question, since they consisted of daily clinical monitoring of

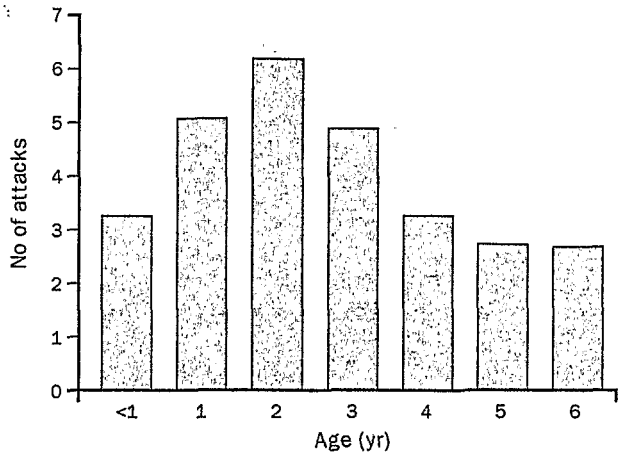

Figure: **Annual incidence of malaria attacks by age, Dielmo (Senegal), June, 1990, to May, 1992**

the children. In one village in the Congo where malaria transmission was 246 infective bites per person per year,[1] we recorded a minimum of 3 attacks per year among children aged 5–6 years.[2] Since 1990 in Senegal, we have been monitoring the population in a village where *Plasmodium falciparum* transmission is permanent, and varies yearly from 101 to 273 infective bites per person.[3] Each child is visited daily at home, his temperature is recorded three times a week, and a medical team is on call day and night in the research station in the village to diagnose and treat every pathological episode.[3,4] The figure shows that the frequency of malaria attacks among children from 0 to 6 years varies according to age from 2·6 to 6·1 attacks per year, which is an average of 4·1 attacks per year in children of the same age as the Tanzanian group. The diagnostic criteria used were practically identical for the three surveys.[3,5] The Tanzanian vaccine trial may therefore have only detected 1 in 8–12 cases of actual malaria, dependent on the subgroup. The reason for this is the very short duration (usually one or two days even without treatment) of most clinical malaria episodes in children exposed to intense perennial transmission, and the erratic nature of peaks of fever during these episodes.

We believe that the malaria attacks detected by Alonso and colleagues include most of the potentially severe cases, but only a small percentage of other cases. The decrease in the frequency of episodes detected in vaccinated children could result from a decrease in intensity of the symptoms rather than the number of attacks, and it is possible that the vaccine reduces malaria mortality in a higher proportion than the 31% recorded for the clinical episodes that were detected. The results of the Tanzanian trial justify further trials on a larger scale, to establish the impact of SPf66 on malaria mortality in highly endemic areas; such trials should take into account the potential effect of the vaccine on the intensity of symptoms.

*Jean-François Trape, Christopher Rogier
*Laboratoire de Paludologie, ORSTOM, BP 1386, Dakar, Senegal; and Service d'Epidémiologie, Institut Pasteur, Dakar

1 Trape JF, Zoulani A. Etudes sur le paludisme dans une zone de mosaïque forêt-savane d'Afrique Centrale, la région de Brazzaville. *Bull Soc Pathol Exot* 1987; 80: 84–99.
2 Trape JF, Zoulani A, Quinet MC. Assessment of the incidence and prevalence of clinical malaria in semi-immune children exposed to intense and perennial transmission. *Am J Epidemiol* 1987; 126: 193–201.
3 Trape JF, Rogier C, Konate K, et al. The Dielmo Project: a longitudinal study of natural malaria infection and the mechanisms of protective immunity in a community living in a holoendemic area of Senegal. *Am J Trop Med Hyg* 1994; 51: 123–37.

4 Rogier C, Trape JF. Malaria attacks in children exposed to high transmission: who is protected? *Trans R Soc Trop Med Hyg* 1993; **87**: 245–46.
5 Trape JF, Peelman P, Morault-Peelman B. Criteria for diagnosing clinical malaria among a semi-immune population exposed to intense and perennial transmission. *Trans R Soc Trop Med Hyg* 1985; **79**: 435–42.

Authors' reply

SIR—Trape and Rogier rightly point out that in the Tanzanian SPf66 trial the reported annual incidence of clinical episodes was lower than the number of episodes expected in an area of such high malaria transmission. There are probably several reasons for this.

The highest risk of clinical malaria in the Kilombero population occurs around the first birthday. In areas like this one, where transmission is so intense, the frequency of clinical malaria declines very rapidly with age. Indeed 1-year-old children have twice the risk of 2-year-olds. For regulatory reasons we could not vaccinate children less than 1 year of age. Consequently, most of the time, at risk refers to children who were older (up to 7 years by the end of the trial) and had much lower risk of symptomatic episodes. Furthermore, the study cohorts were ageing as the trial progressed and the risk of malaria therefore decreased. At the same time, primary data analysis depended on passive case detection at the village dispensary. Even though the dispensary staff and supplies were re-enforced during the study period, and free medical services were offered around the clock for the entire duration of the trial, it is quite likely that children with mild, short-duration, and self-limited episodes did not attend the dispensary for consultation, and were therefore not reported. The dispersed structure of the village could have also contributed to the low recorded frequency (mean distance from the dispensary 1·9 km; interquartile range 0·9–4·8). The recorded frequency was higher in children who lived nearest the dispensary, suggesting that reporting rates were lower from more remote parts of the village.

Moreover, symptomless infections occur at a high frequency in the Tanzanian study area, and this complicates the analysis of any trial of interventions against malaria morbidity. Children with fevers of non-malarial aetiology can have concurrent symptomless parasitaemia, and therefore we can never be entirely sure that the parasites are the cause of the fever; this is especially so when sick children are not necessarily examined at either the peak of fever or peak parasitaemia of the episode. In the Kilombero vaccine trial, many such episodes would not, at the time of sampling, have satisfied our primary case definition, which included only episodes presenting with an axillary temperature of 37·5°C or more and a parasite density greater than 20 000/μL. The risk of fever does, however, increase with the density of parasitaemia. We have lately used this observation to show how the sensitivity and specificity of different parasitaemia cutoffs can be determined.[1,2] The case definition used for the primary analysis was established before the randomisation code was broken, with the data obtained during the 6 months of follow-up between the first and third dose. A definition with a high specificity was chosen to avoid the dilution of the vaccine effect by inclusion of fever cases with non-malarial aetiology.

All these considerations combined with the known time-dependent variability on the frequency of clinical malaria as indicated by the reduction over time in the age-standardised rates of malaria morbidity in both the vaccine and placebo cohorts, might have contributed to the lower-than-expected incidence of malaria recorded in the Kilombero vaccine trial. Finally, we agree with Trape and Rogier that it is likely that the episodes detected include most of the potentially severe cases. We also agree that the vaccine-related reduction in the number of episodes recorded could be due to a decrease in the intensity of symptoms rather than number of the attacks—ie, shifting the spectrum of clinical severity towards the more benign presentations. If this is so, the vaccine might have a substantial impact on mortality that needs to be documented.

*Pedro L Alonso, Tom Smith, Marcel Tanner
*Unidad de Epidemiologia y Bioestadistica, Hospital Clinic I Provincial, 08036 Barcelona, Spain; and Department of Epidemiology and Public Health, Swiss Tropical Institute, Basel, Switzerland

1 Smith TA, Armstrong Schellenberg JRM, Hayes R. Attributable fraction estimates and case definitions for malaria in endemic areas. *Stat Med* 1994; **13**: 2345–58.
2 Armstrong Schellenberg JRM, Smith T, Alonso PL, et al. What is clinical malaria? Finding case definitions for malaria in endemic areas. *Parasitol Today* 1994; **10**: 429–42.

Regional variations in medium-chain acyl-CoA dehydrogenase deficiency

SIR—Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is an autosomal recessive disorder of mitochondrial fatty acid oxidation. About 90% of patients are homozygous for the same mutation (G985). Affected individuals are at risk of metabolic decompensation, especially during infancy, and may present with hypoglycaemia, encephalopathy, hepatomegaly, and sudden death or near-miss episodes, though some remain symptom-free.[1] Preliminary studies from the West Midlands[2] and Trent[3] regions of the UK found heterozygosity for G985 in 12 of 479 and 6 of 410 babies, respectively, suggesting that in these areas 1 in 10 000 individuals have MCAD deficiency and supporting anecdotal evidence that this is a relatively common disorder, and one that may be widely underdiagnosed.[1] However, the statistical limitations of these small surveys left unanswered many questions about the impact of the disease and the case for routine neonatal screening. We have now examined over 10 000 samples and have compared the predicted frequencies of MCAD deficiency with the rates of diagnosis in the two regions.

The West Midlands study covered the Herefordshire, Shropshire, and North and South Worcestershire health districts. In Trent eleven of the thirteen districts participated. Dried blood surplus to routine screening was tested for G985 by polymerase chain amplification and allele-specific hybridisation.[4] All samples in the heterozygous range were then examined by *Sty*I restriction enzyme digestion followed by gel electrophoresis. (Details of assay performance will be reported elsewhere but if there is any bias it will be to underestimate heterozygote frequency.) The results (table) confirm previous indications[2,3] that gene frequency is higher in the selected West Midlands districts than in Trent and that there is significant regional variation in the frequency of MCAD deficiency. A lower frequency of G985 MCAD mutation has been reported from the west of Scotland.[5]

There has been a long-standing interest in MCAD deficiency in Sheffield (Trent) and a high index of suspicion is to be expected. The rate of diagnosis in the West Midlands is much lower, although using the gene frequency from a selected area to calculate the expected number of cases for the whole region may have introduced some bias. Explanations for the apparently missing cases in the West Midlands could include a lower awareness of MCAD deficiency and its presenting features, failure to detect the