would reduce blood culture yield by almost 40% [4]—was unusual in their patients, but do not report exactly how many had received antibiotics prior to study enrollment.

In contrast, we found that 13/87 (14.9%) Myanmar adults hospitalized with a positive malaria blood film were bacteremic [5]. The bacteremic patients were sicker and more likely to die, but bacterial coinfection was suspected clinically in only 5 (38%), emphasizing that in the resource-limited setting it may be as difficult to diagnose in adults as in children [2, 6]. Although 42/87 (48%) were at high risk of death (respiratory coma acidosis malaria [RCAM] score ≥ 2, which has an estimated case-fatality rate of 21% in the resource-limited setting [7]), there were only 3 deaths. This may be at least partly explained by the fact that 71/87 (82%) received empirical antibacterial therapy at presentation.

We do not argue that all adults diagnosed with malaria should receive antibacterial therapy, rather that the threshold for its use should be lowered in the resource-limited setting. We have proposed that adults with an RCAM score ≥ 2 should also receive empirical antibacterial therapy, which, in an era of evolving antimicrobial resistance, could be promptly discontinued if bacterial infection were excluded. Almost certainly, some of the Myanmar patients may have been suffering predominantly from bacterial infection, with the parasitemia an incidental finding. However, the pragmatic clinician in a resource-limited setting when faced with a critically ill patient should consider—at least initially—covering both etiologies.

Concomitant bacteremia in children with malaria is hypothesized to be due to intense microvascular sequestration that leads to impaired gut barrier function and bacterial translocation [8]. The fundamental pathology of *falciparum* malaria is the same in adults and children [9], and yet adults have a far higher case-fatality rate. More than 10% of adults with severe malaria develop shock [10]—the still incompletely understood "algid malaria"—and bacterial coinfection appears likely to explain a significant proportion. Until further prospective studies define the frequency of significant bacterial coinfection more precisely, empirical antibacterial therapy for critically ill adults with malaria in resource-limited settings may be more appropriate than Phu et al suggest.

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References

1. Church J, Maitland K. Invasive bacterial co-infection in African children with *Plasmodium falciparum* malaria: a systematic review. BMC Med **2014**; 12:31.
2. Severe malaria. Trop Med Int Health **2014**; 19(Suppl 1):7–131. doi:10.1111/tmi.12313_2. Available at: https://pubmed.ncbi.nlm.nih.gov/25214480/?from_single_result=25214480&show_create_notification_links=False
3. Phu NH, Day NPJ, Tuan PQ, et al. Concomitant bacteremia in adults with severe *falciparum* malaria. Clin Infect Dis **2020**.
4. Cheng MP, Stenstrom R, Paquette K, et al; FABLED Investigators. Blood culture results before and after antimicrobial administration in patients with severe manifestations of sepsis: a diagnostic study. Ann Intern Med **2019**; 171:547–54.
5. Aung NM, Nyein PP, Htut TY, et al. Antibiotic therapy in adults with malaria (ANTHEM): high rate of clinically significant bacteremia in hospitalized adults diagnosed with *falciparum* malaria. Am J Trop Med Hyg **2018**; 99:688–96.
6. Ye Lynn KL, Hanson J, Mon NCN, et al. The clinical characteristics of patients with sepsis in a tertiary referral hospital in Yangon, Myanmar. Trans R Soc Trop Med Hyg **2019**; 113:81–90.
7. Hanson J, Lee SJ, Mohanty S, et al. A simple score to predict the outcome of severe malaria in adults. Clin Infect Dis **2010**; 50:679–85.
8. Church JA, Nyamako L, Olupot-Olupot P, Maitland K, Urban BC. Increased adhesion of *Plasmodium falciparum* infected erythrocytes to ICAM-1 in children with acute intestinal injury. Malar J **2016**; 15:54.
9. White NJ, Turner GD, Day NP, Dondorp AM. Lethal malaria: Marchiafava and Bignami were right. J Infect Dis **2013**; 208:192–8.
10. Dondorp A, Nosten F, Stepniewska K, Day N, White N; South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe *falciparum* malaria: a randomised trial. Lancet **2005**; 366:717–25.

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Reply to Aung et al

To the Editor—Symptomatic malaria is predominantly a disease of childhood in areas of higher transmission (ie, much of sub-Saharan Africa). Most cases of severe malaria occur in children aged <5 years. In these regions, both malaria and sepsis are major causes of childhood death, yet the clinical distinction between the 2 is difficult, particularly if there is no obvious focus of infection [1]. Furthermore, severe malaria predisposes to bacterial infections, particularly with *Salmonella* sp., so a very sick child may have both severe malaria and sepsis. In this epidemiological context, the population prevalence of malaria parasitemia detectable by microscopy or rapid diagnostic tests (RDTs) is high, and on more sensitive testing with polymerase chain reaction assay, a large proportion of the entire population are found to be parasitemic. Thus, when a severely ill febrile child presents to a health facility and the microscopy or RDT are positive for malaria parasites, the admitting clinician is often uncertain. Is this severe malaria, or is it sepsis with an incidental parasitemia, or could it be both severe malaria and sepsis together? Today, an increasing proportion of infections are diagnosed with RDTs, which are not quantitative. With blood film microscopy, finding a malaria parasite count above 10 000/uL is strongly suggestive of malaria as the primary illness in a high-transmission setting [1]. However, the severely ill child could still have both severe malaria and sepsis. In a meta-analysis of 7208 children with severe malaria included in 25 studies across 11 African countries, the mean prevalence of invasive bacterial infections was estimated to

be 6.4% (95% confidence interval [CI], 5.81% to 6.98%) [2]. For these reasons, it is recommended that in areas of higher malaria transmission, children suspected of having severe malaria should also receive empirical broad-spectrum antibiotics [1, 3]. In practice, this usually means ceftriaxone.

The situation is different in areas of low malaria transmission. In these areas, it is adults, particularly men, who are more likely to present with severe malaria. The malaria blood smear has greater predictive value, and the diagnosis is therefore easier. In managing adult patients with severe malaria, the World Health Organization (WHO) currently recommends that physicians have a low threshold for starting antibiotics, but that routine empirical treatment with broad-spectrum antibiotics is not necessary [1, 3]. This perspective has been challenged in a recent series from Myanmar. In 2 combined series, 13 (14.9%) of 87 adult patients hospitalized with a positive malaria blood film were bacteremic [4, 5]. It was concluded that "empirical antibiotics may also be appropriate in adults hospitalized with falciparum malaria in low transmission settings, until bacterial infection is excluded" [4]. In contrast, a recent large prospective study of sequential adult patients with strictly defined severe falciparum malaria from Vietnam found only 9 (1.07%) of 845 patients were bacteremic [6].

In this issue of *Clinical Infectious Diseases*, the authors of the original series from Myanmar propose that the marked difference between the 2 studies might be explained by unreported antibiotic pretreatment and by blood culture insensitivity, although similar blood volumes were cultured in both studies. As described in Phu et al [7], antibiotic self-treatment was unusual in the Vietnamese patients with severe malaria but cannot be excluded completely, and blood culture is certainly insensitive in the diagnosis of septicemia. Nevertheless, the majority of patients in the Vietnam series did not receive antibiotics during their hospital stay and recovered uneventfully. How then can this marked difference between the 2 studies be reconciled? The adult patients hospitalized in Myanmar with a diagnosis of malaria who were bacteremic had fever, neutrophil leukocytosis, and low malaria parasite counts [4, 5]. Indeed, their semiquantitative malaria parasite counts were significantly lower than in the nonbacteremic malaria patients, and they were orders of magnitude lower than the bacteremic patients in the Vietnam study. It is also unclear how many of the Myanmar patients fulfilled the WHO criteria for severe malaria [1]. In contrast, the patients in the Vietnam series all had strictly defined severe falciparum malaria, and concomitant bacteremias were associated with very high parasitemias, no neutrophil leukocytosis, and a high mortality [7]. The prevalence of bacteremia on admission was 0.65% (95% CI, .08% to 1.2%) in the Vietnamese patients with malaria parasitemias less than 20% (20% of erythrocytes containing one or more malaria parasites), which is 23 times lower than in the Myanmar series.

The simplest and most plausible explanation for these marked differences is that the adult Myanmar patients with bacteremia did not have severe falciparum malaria but instead had bacterial sepsis as their primary illness, and they had incidental low density malaria parasitemia (a common finding in malaria endemic areas). Recent epidemiological studies across the Greater Mekong subregion, an area of low seasonal malaria transmission, show that asymptomatic parasite carriage in adults is more common than thought previously [6]. It is therefore not unexpected that adults living in these areas who develop bacterial infections might sometimes also have incidental low-density parasitemias. With the exception of enteric fever, neutrophil leukocytosis is another pointer to a primary bacterial infection. Emphasizing this diagnostic distinction is clearly of clinical importance. Thus, the current WHO guidelines that adults with severe falciparum malaria do not require empirical antibacterial drugs on admission seems reasonable based on current evidence. The one important exception is patients with very high parasite counts. In the Vietnamese patients with >20% malaria parasitemia, the prevalence of concomitant bacteremia was 5.2% (95% CI, .2% to 10.3%), a risk ratio of 8.1 (2.2 to 29.5). Whether 20% parasitemia is the optimum threshold for giving empirical broad spectrum antibiotics was not determined. This argues for rapid thin blood film assessment with accurate parasite counts in all patients suspected of having severe malaria [1, 7]. Severe malaria is a risk factor for bacterial infections, and there should be a low threshold for starting antibiotics in adults with severe falciparum malaria [1, 3], but those who are not hyperparasitemic do not require empirical antibiotics on admission.

Notes

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References

1. World Health Organization. Severe malaria. Trop Med Int Health **2014**; 19(Suppl 1):7–131.
2. World Health Organization. Guidelines for the treatment of malaria. 3rd ed. Geneva, Switzerland: WHO; **2015**.
3. Church J, Maitland K. Invasive bacterial co-infection in African children with *Plasmodium falciparum* malaria: a systematic review. BMC Med **2014**; 12:31.
4. Nyein PP, Aung NM, Kyi TT, et al. High frequency of clinically significant bacteremia in adults hospitalized with falciparum malaria. Open Forum Infect Dis **2016**; 3:ofw028.
5. Aung NM, Nyein PP, Htut TY, et al. Antibiotic Therapy in Adults with Malaria (ANTHEM): high rate of clinically significant bacteremia in hospitalized adults diagnosed with falciparum malaria. Am J Trop Med Hyg **2018**; 99:688–96.
6. Imwong M, Stepniewska K, Tripura R, et al. Numerical distributions of parasite densities during asymptomatic malaria. J Infect Dis **2016**; 213:1322–9.
7. Phu NH, Day NPJ, Tuan PQ, et al. Concomitant bacteremia in adults with severe falciparum malaria. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa191

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It Is Not a Case-control Study

To the Editor—I read the recent study by Li et al with great interest [1]. The study investigated the association between coronavirus disease 2019 (COVID-19) infection during pregnancy and the risk of maternal and neonatal outcomes. It extends our knowledge regarding the potential risks of COVID-19 infection during pregnancy that may impose on birth outcomes. However, the study design was not case-control as stated in the title.

The investigators examined 16 pregnant women confirmed with COVID-19 infection and another 18 as suspected cases, and then compared them with a group of pregnant women without the infection ("controls"). The study examined the association between infection status and pregnancy outcomes. This study design was truly a cohort study.

A case-control study is a retrospective study design, which is to recruit participants based on outcome status, rather than on risk exposure status [2]. As this study was to examine whether COVID-19 infection affects risks of pregnancy outcomes, a case-control study should recruit women with adverse pregnancy outcomes as cases and women without the indicated outcomes as controls. Then, the status of exposure to COVID-19 infection beforehand is retrospectively assessed and compared between the groups. A case-control study is a useful study design that can be used to quickly investigate the possible causes of a certain outcome [3]. A recent emergent example was about the risk of Zika virus infection on newborn microcephaly [4].

Although the misnomer of "case-control" study was not rare before and may still exist in the future [5], preventing the misuse of study design terms is imperative in the scientific community, for 2 reasons. The first is about scientific communication. Nowadays, dissemination of scientific findings is much easier than a century ago. Scientific publications can be accessed from every corner of the world as long as the internet is working. A standardized, clear-cut and well-defined study design classification can promote readers' accurate appraisal of the research findings. The second reason is about scientific progress. The systematic review and meta-analysis has been regarded as a top method of medical evidence generation, but it builds on individual standalone studies. When the naming system of study design is not standardized, it causes confusion among the systematic review researchers and makes it troublesome to correctly archive the data.

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References

1. Li N, Han L, Peng M, et al. Maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia: a case-control study [manuscript published online ahead of print 30 March 2020]. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa352.
2. Schulz KF, Grimes DA. Case-control studies: research in reverse. Lancet **2002**; 359:431–4.
3. Musso D, Baud D. Zika virus: time to move from case reports to case control. Lancet Infect Dis **2016**; 16:620–1.
4. de Araújo TVB, Ximenes RAA, Miranda-Filho DB, et al; Investigators from the Microcephaly Epidemic Research Group; Brazilian Ministry of Health; Pan American Health Organization; Instituto de Medicina Integral Professor Fernando Figueira; State Health Department of Pernambuco. Association between microcephaly, Zika virus infection, and other risk factors in Brazil: final report of a case-control study. Lancet Infect Dis **2018**; 18:328–36.
5. Marshall T. What is a case-control study? Int J Epidemiol **2004**; 33:612–3.

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Reply to Chen

To the Editor—We thank Dr Hsin-Jen Chen for his comments on our article [1, 2]. We understand his concern was the result of seeing our study from a different angle. He thought our study was a cohort study, as coronavirus disease 2019 (COVID-19) infection ("exposure" in his opinion) occurred before maternal and neonatal outcomes. However, when we initiated the study, we first grouped patients based on their disease status (confirmed with COVID-19 or not), so COVID-19 infection was a disease outcome rather than an exposure. We compared their medical history and laboratory profile on admission to identify the potential risk factors of infection ("exposure"). We found that coexisting chronic illness and maternal complications might be associated with an increased risk of COVID-19 infection. From this perspective, our study is a case-control study [3].

Given the serious concerns about potential vertical transmission and adverse events in pregnant women with COVID-19, we further compared the maternal and neonatal outcomes of COVID-19 and non–COVID-19 patients. It is of note that our study included 2 vulnerable populations (pregnant women and neonates), and COVID-19 infection coincided with prelabor and delivery. Although our initial design was for a case-control study to explore the risk factors in pregnant women, from the perspective of neonates, our study was more like a cohort study. However, since the exact onset dates of COVID-19 infection (so-called exposure in a cohort study) were uncertain in some patients, we hesitate to call this a cohort study in the perspective of pregnant women. We recruited the pregnant women when they had acute