will be concurrent development for high-income, and low-income and middle-income countries.[13] The need for maternal group B streptococcus vaccine in low-income and middle-income countries that do not have the infrastructure and resources to implement intrapartum antibiotic prophylaxis strategies is clear.[1,14] The data presented by O'Sullivan and colleagues underscore that high-income countries also have a shared interest in alternatives or adjuncts to intrapartum antibiotic prophylaxis to protect infants from group B streptococcus.

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1 Seale AC, Bianchi-Jassir F, Russell NJ, et al. Estimates of the burden of group B streptococcal disease worldwide for pregnant women, stillbirths, and children. *Clin Infect Dis* 2017; **65** (suppl 2)**:** S200–19.
2 Le Doare K, O'Driscoll M, Turner K, et al. Intrapartum antibiotic chemoprophylaxis policies for the prevention of group B streptococcal disease worldwide: systematic review. *Clin Infect Dis* 2017; **65** (suppl 2)**:** S143–51.
3 O'Sullivan CP, Lamagni T, Patel D, et al. Group B streptococcal disease in UK and Irish infants younger than 90 days, 2014–15: a prospective surveillance study. *Lancet Infect Dis* 2018; published online Nov 26. http://dx.doi.org/10.1016/S1473-3099(18)30555-3.
4 National Institute for Health and Care Excellence. Neonatal infection (early onset): antibiotics for prevention and treatment. 2012. https://www.nice.org.uk/guidance/cg149 (accessed Oct 30, 2018).
5 Hughes RG, Brocklehurst P, Steer PJ, et al. Prevention of early-onset neonatal group B streptococcal disease: green-top guideline no. 36. *BJOG* 2017; **124:** e280–305.
6 Chen JC, Jenkins-Marsh S, Flenady V, et al. Early-onset group B streptococcal disease in a risk factor-based prevention setting: a 15-year population-based study. *Aust N Z J Obstet Gynaecol* 2018; published online Sept 11. DOI:10.1111/ajo.12891.
7 Madrid L, Seale AC, Kohli-Lynch M, et al. Infant group B streptococcal disease incidence and serotypes worldwide: systematic review and meta-analyses. *Clin Infect Dis* 2017; **65** (suppl 2)**:** S160–72.
8 Bekker V, Bijlsma MW, van de Beek D, Kuijpers TW, van der Ende A. Incidence of invasive group B streptococcal disease and pathogen genotype distribution in newborn babies in the Netherlands over 25 years: a nationwide surveillance study. *Lancet Infect Dis* 2014; **14:** 1083–89.
9 Schrag SJ, Zell ER, Lynfield R, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. *N Engl J Med* 2002; **347:** 233–39.
10 Seedat F, Stinton C, Patterson J, et al. Adverse events in women and children who have received intrapartum antibiotic prophylaxis treatment: a systematic review. *BMC Pregnancy Childbirth* 2017; **17:** 247.
11 Centers for Disease Control and Prevention. Active bacterial core surveillance. Bact facts interactive. https://wwwn.cdc.gov/BactFacts/index.html (accessed Oct 30, 2018).
12 Centers for Disease Control and Prevention. National notifiable diseases surveillance system. Notifiable infecious diseases and conditions data tables. https://wwwn.cdc.gov/nndss/infectious-tables.html (accessed Oct 30, 2018).
13 Kobayashi M, Schrag SJ, Alderson MR, et al. WHO consultation on group B streptococcus vaccine development: report from a meeting held on 27-28 April 2016. *Vaccine* 2016; published online Dec 22. DOI:10.1016/j.vaccine.2016.12.029.
14 Schrag SJ, Global Group B Streptococcal Vaccine Working Group. Group B streptococcal vaccine for resource-poor countries. *Lancet* 2011; **378:** 11–12.

Primaquine for all: is it time to simplify malaria treatment in co-endemic areas?

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In most areas endemic for malaria, the major species are *Plasmodium falciparum* and *Plasmodium vivax*. Falciparum malaria is more often lethal, develops resistance to drugs easily, and is responsible for most of the malaria burden in Africa. However, particularly in this second era of malaria elimination efforts,[1] *P vivax* requires increasing attention[2] because of the intrinsic challenges related to its control. This species can lead to severe or even life-threatening disease,[3] can present variable evidence of resistance to chloroquine in relation to geographical area,[4] and has few drug options to prevent relapse. Prevention of relapse is essential because up to 80% of reported cases of *P vivax* malaria could result from hypnozoite-derived relapses, rather than from newly acquired infections.[5] The triggers of relapse are not sufficiently understood, but 8-aminoquinolines (such as primaquine, or the newly registered tafenoquine) are the only effective drugs enabling radical cure.

There are several sources of variation in relapse rates. Different strains of vivax have distinct relapse patterns,[6] and pharmacogenetics also seems to have a role in primaquine metabolism, which could affect relapse as primaquine only becomes active once metabolised (CYP 2D6 pathway) into its active metabolites.[7] However, acute infections may also trigger relapses.[8] Data showing possible *P vivax* relapses after *P falciparum* infection were obtained first in Thailand,[9] but an analysis reported in *The Lancet Infectious Diseases* by Robert Commons and colleagues[10] provides statistical robustness regarding this observation. Their impressive meta-analysis, which included 31 262 patients from 153 studies done over more than four decades, supports that such relapses are not just local, but rather occur

globally in all settings co-endemic for *P vivax* and *P falciparum*. The overall risk of *P vivax* parasitaemia by day 42 after *P falciparum* treatment was 5·6% (95% CI 4·0–7·4). Although the investigators found some short-term significant differences in the risk of recurrence depending on regional relapse periodicity and the half-lives of the drugs used to treat the initial *P falciparum* infection, the differential effect seemed to wane by day 63, when nearly a quarter (24%) of all patients treated for *P falciparum* had developed a *P vivax* relapse, detectable in peripheral blood. Importantly, *P vivax* predominated among all parasite recurrences following *P falciparum* treatment, representing about 70% of recurrences at day 63.

The mechanisms behind such relapses are still unknown, but one could argue, from a public health standpoint, that the time has come to propose an innovative move in the treatment of malaria, promoting the universal use of primaquine for both species in areas where they co-exist and remain prevalent. Indeed, the number of cases of *P falciparum* needed to treat with radical cure to prevent one *P vivax* recurrence by day 63—ranging between 4·7 and 5·0 as proposed by the study investigators—would seem to amply justify this radical change in malaria treatment. The additional *P falciparum* gametocidal effect that 8-aminoquinolines exert, which should also substantially reduce malaria transmission, might be another advantage of such a bold programmatic change.

In areas where primaquine is routinely used for all patients with *P vivax*, such as Latin America,[11] this change would not pose major difficulties, with the exception of ensuring adequate compliance for a usually 2-week treatment course. Nevertheless, in areas where glucose-6-phosphate dehydrogenase (G6PD) deficiency is prevalent, such as southeast Asia, primaquine use would need to be expanded carefully on account of the potential hazards that such a prohaemolytic drug might have in individuals lacking full functionality of the G6PD enzyme.[12] The availability of point-of-care tests to detect G6PD deficiency (ie, G6PD activity lower than 30%) might help the safe use of primaquine against both malaria species.[13]

In the real world, however, the switch from a simple 3-day *P falciparum* treatment regimen with an artemisinin-based combination therapy (ACT) to a 14-day course including primaquine might be met with some reluctance among health providers and even the general population. In this respect, tafenoquine could be an exciting alternative to bypass these barriers, because it only requires a single dose, and is considered safe and efficacious for individuals with G6PD activity higher than 70%.[14]

Studies such as the one by Commons and colleagues highlight the relevance of meta-analytical approaches to answer questions that remain difficult to solve with single studies. The results of this study hint at the exciting potential of simplifying malaria treatment in areas co-endemic for *P falciparum* and *P vivax*. Use of an ACT plus primaquine (or tafenoquine) regimen irrespective of the underlying species could have huge operational advantages, but the overall impact of such an approach needs to be thoroughly evaluated.

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1 Bassat Q, Velarde M, Mueller I, et al. Key knowledge gaps for *Plasmodium vivax* control and elimination. *Am J Trop Med Hyg* 2016; **95** (suppl 6)**:** 62–71.
2 Bassat Q. The importance of being vivax. *J Trop Pediatr* 2014; **60:** 335–37.
3 Siqueira AM, Lacerda MV, Magalhães BM, et al. Characterization of *Plasmodium vivax*-associated admissions to reference hospitals in Brazil and India. *BMC Med* 2015; **13:** 57.
4 Siqueira AM, Alencar AC, Melo GC, et al. Fixed-dose artesunate-amodiaquine combination vs chloroquine for treatment of uncomplicated blood stage *P. vivax* infection in the Brazilian Amazon: an open-label randomized, controlled trial. *Clin Infect Dis* 2017; **64:** 166–74.
5 Robinson LJ, Wampfler R, Betuela I, et al. Strategies for understanding and reducing the *Plasmodium vivax* and *Plasmodium ovale* hypnozoite reservoir in Papua New Guinean children: a randomised placebo-controlled trial and mathematical model. *PLoS Med* 2015; **12:** e1001891.
6 Battle KE, Karhunen MS, Bhatt S, et al. Geographical variation in *Plasmodium vivax* relapse. *Malar J* 2014; **13:** 144.
7 Brasil LW, Rodrigues-Soares F, Santoro AB, et al. CYP2D6 activity and the risk of recurrence of *Plasmodium vivax* malaria in the Brazilian Amazon: a prospective cohort study. *Malar J* 2018; **17:** 57.
8 Shanks GD, White NJ. The activation of vivax malaria hypnozoites by infectious diseases. *Lancet Infect Dis* 2013; **13:** 900–06.
9 Looareesuwan S, White NJ, Chittamas S, Bunnag D, Harinasuta T. High rate of *Plasmodium vivax* relapse following treatment of falciparum malaria in Thailand. *Lancet* 1987; **2:** 1052–55.

10 Commons RJ, Simpson JA, Thriemer K, et al. Risk of *Plasmodium vivax* parasitaemia after *Plasmodium falciparum* infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2019; **19:** 91–101.
11 Recht J, Siqueira AM, Monteiro WM, Herrera SM, Herrera S, Lacerda MVG. Malaria in Brazil, Colombia, Peru and Venezuela: current challenges in malaria control and elimination. *Malar J* 2017; **16:** 273.
12 Thriemer K, Bobogare A, Ley B, et al. Quantifying primaquine effectiveness and improving adherence: a round table discussion of the APMEN Vivax Working Group. *Malar J* 2018; **17:** 241.
13 Brito MA, Peixoto HM, Almeida AC, et al. Validation of the rapid test Carestart(tm) G6PD among malaria vivax-infected subjects in the Brazilian Amazon. *Rev Soc Bras Med Trop* 2016; **49:** 446–55.
14 Llanos-Cuentas A, Lacerda MV, Rueangweerayut R, et al. Tafenoquine plus chloroquine for the treatment and relapse prevention of *Plasmodium vivax* malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. *Lancet* 2014; **383:** 1049–58.

Improving the provision of rabies post-exposure prophylaxis

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In 2015, WHO and its partners set the ambitious objective[1] to reach zero human deaths from dog-mediated rabies by 2030, after the concept of effective One Health interventions.[2] Mass dog vaccination is expected to be an important part of any successful strategy.[3,4] In *The Lancet Infectious Diseases*, the WHO Rabies Modelling Consortium[5] reminds us that effective and timely post-exposure prophylaxis, administered to humans bitten by rabid dogs to prevent the fatal onset of rabies, is another essential tool for success.[5] Through the analysis of a wide range of data collected in multiple countries and the use of multilayer mathematical models, the authors show that increased investment in post-exposure prophylaxis by Gavi, the Vaccine Alliance, would be extremely cost-effective and could substantially reduce disease burden. The study is particularly timely because Gavi is currently reconsidering rabies vaccine investment.

Preparation of such assessment required the Consortium[5] to overcome several major challenges. First, any assessment of post-exposure prophylaxis needs to account for a very diverse set of factors.[6] For example, it must be based on a good understanding of dog populations, how they are structured, how they interact with humans, how they can be affected by the spread of rabies, and how that spread might be mitigated by dog vaccination.[7] Furthermore, the likelihood that a bitten person will seek, obtain access to, and complete post-exposure prophylaxis treatment depends on cultural, economic, geographical, and logistical factors (eg, awareness in the population, accessibility to post-exposure prophylaxis centres, direct and indirect costs, effective stockpiling, and delivery of vaccines). Several of these factors have historically been poorly characterised and might exhibit strong spatial heterogeneities. A major strength of the analysis[5] is that it benefited from tremendous efforts by Gavi to reduce some of these knowledge gaps by supporting rabies field studies. Consequently, the diversity of data the authors used to build their assessment is quite impressive, both in terms of data type and geographical coverage. A second achievement of the paper is that the authors developed a multidisciplinary modelling framework in which these data could be integrated in a coherent way, making it possible to generate rabies incidence dynamics in dogs and the associated human exposures under various epidemiological scenarios, while also capturing economic, behavioural, and logistical aspects.[5]

The new data and modelling framework therefore constitute an important improvement to past studies; future iterations of the work are likely to lead to additional refinements. Of course, still too many countries have little or no data available, and more field studies targeting these places are needed. Some aspects of the assessment could also be improved further. For example, in some circumstances, free provision alone might be insufficient to increase health-care seeking and accessibility. Indeed, the lack of infrastructure might make it impossible for exposed populations (especially those living in rural remote areas) to travel to clinics and access post-exposure prophylaxis,[8] even if vaccines are freely available. To this regard, further investments are needed to improve the accessibility to post-exposure prophylaxis via point-of-care and decentralised integrated dog bite management centres (IDBCs).[9] The geographical distribution of these IDBCs is a crucial issue in many developing countries and will require important efforts from national authorities.[8] The education of populations to increase awareness and perception of the risks related to dog bite exposure and rabies is another complex issue that is starting to be addressed by stakeholders but should be promoted further.[10]

Hopefully, Gavi and other national and international stakeholders and donors will keep on supporting field studies so that all these aspects can be better