Antimalarial resistance: is vivax left behind?

Frédéric Ariey, Richard E. Paul

post-exposure prophylaxis to more than 10 000 people. In Europe, active vaccination against hepatitis A is currently recommended mainly for travelers visiting countries endemic for hepatitis A virus. International travel is a risk factor, accounting for about a third of cases in Austria and Germany. In 2013, 80 cases of hepatitis A were statutorily reported in Austria and 779 in Germany, of which 25 in Austria and 278 in Germany were imported infections. By contrast with Germany, the Austrian national vaccination plan since 2008 has included a recommendation of hepatitis A virus vaccination for all seronegative food handlers in food production and gastronomy companies.

According to Sprenger, the recent foodborne outbreaks of hepatitis A in Europe raise the question whether the member states should consider options for even broader vaccination recommendations against hepatitis A.[9] However, the ultimate aim should be food product safety—ie, to secure the absence of hepatitis A virus from food. Viral contamination of food can occur anywhere in the production process, but most foodborne viral infections can be traced back to infected people who handled food that is not heated or otherwise treated afterwards.[10] Experimental studies have shown that the virus can be transferred from contaminated hands to food and surfaces.[11]

Appropriate and regular hand hygiene practices are the mostly effective measure to prevent transmission of hepatitis A virus. Ensuring adequate hygiene in the countries producing the food will be a major challenge in the endeavor to prevent foodborne hepatitis A. In the meantime, physicians and public health officers should consider hepatitis A infections as possibly foodborne until proven otherwise. Routine collection and preservation of serum and stool samples from all patients with hepatitis A within 28 days of the date of symptom onset would improve detection and control outbreaks. In this way, the treating physician can have a paramount role in disease prevention in high-income countries.

*Jürgen J Wenzel, *Franz Allerberger*
Institute of Clinical Microbiology and Hygiene, Regensburg University Medical Center, Regensburg, Germany (JJW), Department of Public Health, Austrian Agency for Health and Food Safety, Vienna, Austria (FA)
franz.allerberger@ages.at

We declare no competing interests.

1 Collier MG, Khudyakov YE, Selvage D, et al, for the Hepatitis A Outbreak Investigation Team. Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study. *Lancet Infect Dis* 2014; published online Sept 4. http://dx.doi.org/10.1016/S1473-3099(14)70883-7.
2 ECDC. Outbreak of hepatitis A in EU/EEA countries—second update, April 11, 2014. Stockholm: European Centre for Disease Prevention and Control, 2014. http://www.ecdc.europa.eu/en/publications/Publications/ROA-Hepatitis%20A%20virus-Italy%20Ireland%20Netherlands%20Norway%20France%20Germany%20Sweden%20United%20Kingdom%20-%20final.pdf (accessed Aug 5, 2014).
3 Schmid D, Fretz R, Buchner G, et al. Foodborne outbreak of hepatitis A, November 2007–January 2008, Austria. *Eur J Clin Microbiol Infect Dis* 2009; **28:** 385–91.
4 Schenkel K, Bremer V, Grabe C, et al. Outbreak of hepatitis A in two federal states of Germany: bakery products as vehicle of infection. *Epidemiol Infect* 2006; **134:** 1292–98.
5 Nordic outbreak investigation team. Joint analysis by the Nordic countries of a hepatitis A outbreak, October 2012 to June 2013: frozen strawberries suspected. *Euro Surveill* 2013; **18:** 20520.
6 Carvalho C, Thomas HL, Balogun K, et al. A possible outbreak of hepatitis A associated with semi-dried tomatoes, England, July–November 2011. *Euro Surveill* 2012; **17:** 20083.
7 Fournet N, Baas D, van Pelt W, et al. Another possible food-borne outbreak of hepatitis A in the Netherlands indicated by two closely related molecular sequences, July to October 2011. *Euro Surveill* 2012; **17:** 20079.
8 ECDC. Viral hepatitis in Europe: undiagnosed and under-reported. Stockholm: European Centre for Disease Prevention and Control, 2014. http://www.ecdc.europa.eu/en/press/news/_layouts/forms/News_DispForm.aspx?List=8db7286c-fe2d-476c-9133-18ff4cb1b568&ID=1037 (accessed Aug 5, 2014).
9 Sprenger M. More can be done to stop 'silent disease' of hepatitis. *The Parliament Magazine* **394/395:** 9. http://viewer.zmags.com/publication/39b84223#/39b84223/9 (accessed Aug 5, 2014).
10 Koopmanns M, Duizer E. Foodborne viruses: an emerging problem. *Int J Food Microbiol* 2003; **90:** 23–41.
11 Bidawid S, Farber JM, Sattar SA. Contamination of foods by food handlers: experiments on hepatitis A transfer to food and its interruption. *Appl Environ Microbiol* 2000; **66:** 2759–63.

Antimalarial resistance: is vivax left behind?

Published **Online** September 9, 2014
http://dx.doi.org/10.1016/S1473-3099(14)70921-1

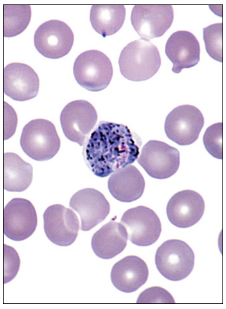
See **Articles** page 982

Despite the necessary and major goal of containment of artemisinin resistance in *Plasmodium falciparum*,[1–4] not all malaria is caused by *P falciparum* and outside of Africa the greatest malaria burden is attributable to *Plasmodium vivax*.[1] In *The Lancet Infectious Diseases*, Ric Price and colleagues[5] report a systematic review of the resistance of *P vivax* to chloroquine, examining published studies from 1960 to 2014. They conclude that chloroquine-resistant *P vivax* is now present across most of vivax-endemic regions. In addition to containing their high-quality analysis, their Article proposes a set of methods to explore resistance to antimalarial drugs in vivax malaria and highlights a surprising scarcity of data and methods available to work on *P vivax*.

Many national control programmes are quite insensitive to concerns about vivax elimination in the face of the threat of falciparum. However, vivax, and the threat of resistance in that organism, needs to be considered in its own right. The *P vivax* lifecycle has important differences to that of *P falciparum*, which are expected to slow down the development of resistance to chloroquine.[6] The parasite stays as latent forms (hypnozoites) in the liver, from which regular relapses can occur. Treatment with chloroquine alone cannot prevent relapses and hence the interest in hypnozoiticidal drugs such as primaquine. Vivax can produce gametocytes (stages that are infectious to mosquitoes) rapidly after emergence from the liver and invasion of the blood. This contrasts with falciparum, which not only does not have latent liver stages, but also takes a minimum of 10 days to generate infectious gametocytes in the blood.[7] Both these lifecycle differences should expose vivax parasites to less selection pressure from drug treatment. However, vivax parasites might have been exposed to sublethal concentrations of chloroquine after treatment for falciparum malaria during coinfection; treatment of falciparum cases in Thailand was often followed by a clinical case of vivax malaria.[8] Now that chloroquine is no longer the first-line drug for treating falciparum malaria, this collateral effect will be alleviated. Thus, the probability of the spread of resistance is expected to be lower for vivax than that for falciparum. Lower but not null, and this risk must be taken into account when considering vivax national treatment policies.

Obstacles specific to addressing of *P vivax* chloroquine resistance need to be overcome: it is very difficult to do standardised in-vitro culture (and therefore have a reproducible phenotype of drug sensitivity); it is impossible to distinguish between relapse and recrudescence; we have little information on the population genetic structure of *P vivax* (gene flow, selfing rate, etc); and so far no molecular marker of resistance has been proposed for large epidemiological studies. The absence of molecular markers is, of course, a major obstacle for use in the assessment of the spread of resistance and, thus, optimisation of therapeutic strategies. A key step for the identification of a molecular marker is development of a clear-cut phenotype of resistance. Price and colleagues propose parasite clearance time as a proxy to study antimalarial resistance. Indeed, accurate characterisation of this clearance time would enable differentiation of clinical resistance from relapse.[9]

There has been much conjecture on whether *P vivax* and *P falciparum* affect one another and thus whether targeting one species might lead to the emergence of the other.[10,11] Focus is now on the fight against *P falciparum*, which seems to have had little effect on the vivax burden.[1] For public health care, vivax malaria must be considered as a disease distinct from falciparum malaria,[12,13] and will benefit from a dedicated control programme strategy. Malaria elimination will not be able to ignore vivax, which should no longer be the least of our worries.


Gladden Willis, Visuals Unlimited/Science Photo Library

*Frédéric Ariey, Richard E Paul
Genetics and Genomics of Insect Vectors Unit (FA) and Functional Genetics of Infectious Diseases Unit (REP), Institut Pasteur, Paris 75724, France
frederic.ariey@pasteur.fr

We declare no competing interests.

1 WHO. World Malaria Report 2013. http://www.who.int/malaria/publications/world_malaria_report_2013/en/ (accessed Aug 24, 2014).
2 Dondorp AM, Nosten F, Poravuth Y, et al. Artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med* 2009; **361:** 455–67.
3 Ariey F, Witkowski B, Amaratunga C, et al. A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. *Nature* 2014; **505:** 50–55.
4 Ashley EA, Dhorda M, Fairhurst RM, et al. Spread of artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med* 2014; **371:** 411–23.
5 Price RN, von Seidlein L, Valecha N, Nosten F, Baird JK, White NJ. Prevalence of chloroquine-resistant *Plasmodium vivax*: a systematic review. *Lancet Infect Dis* 2014; published online Sept 9. http://dx.doi.org/10.1016/S1473-3099(14)70855-2.
6 Garnham PCC. Malaria parasites and other haemosporidia. Oxford: Blackwell, 1966: 1132.
7 Talman AM, Domarle O, McKenzie FE, et al. Gametocytogenesis: the puberty of *Plasmodium falciparum*. *Malar J* 2004; **3:** 24.
8 Looareesuwan S, White NJ, Chittamas S, et al. High rate of *Plasmodium vivax* relapse following treatment of falciparum malaria in Thailand. *Lancet* 1987; **2:** 1052–55.
9 Pukrittayakamee S, Imwong M, Looareesuwan S, et al. Therapeutic responses to antimalarial and antibacterial drugs in vivax malaria. *Acta Trop* 2004; **89:** 351–56.
10 Sattabongkot J, Tsuboi T, Zollner GE, et al. *Plasmodium vivax* transmission: chances for control? *Trends Parasitol* 2004; **20:** 192–98.
11 Snounou G, White NJ. The co-existence of *Plasmodium*: sidelights from *falciparum* and *vivax* malaria in Thailand. *Trends Parasitol* 2004; **20:** 333–39.
12 Vogel G. The forgotten malaria. *Science* 2013; **342:** 684–687.
13 Cotter C, Sturrock HJ, Hsiang MS, et al. The changing epidemiology of malaria elimination: new strategies for new challenges. *Lancet* 2013; **382:** 900–11.