It is reassuring that these data support the idea of no preexisting increase in \textit{pfmdr1} copy number in parasites from these 2 West African countries. It would have been useful to have an estimate of the degree of polyclonality of infections, because multiple clones can lead to underestimation of the frequency of increased \textit{pfmdr1} copy number [2]. Nonetheless, the relatively large sample size provides a useful baseline against which molecular surveillance can be implemented to detect emerging resistance to drugs such as mefloquine (MQ) and lumefantrine.

These findings are from an area with no MQ pressure and strengthen the hypothesis that MQ is the principal agent for selection of \textit{pfmdr1} amplification in field isolates (making quinine a less likely selective agent). Quinine has been implicated as a possible cause of cross-resistance to MQ [3]. Of note, our study from Gabon was performed at a time when low-dose MQ studies were being performed in that area [3].

Previous studies show that \textit{pfmdr1} amplification and the N86Y point mutation in this gene are inversely related [4], for reasons that remain incompletely understood. In African isolates, the \textit{pfmdr1} 86Y allele may occur infrequently by itself or more frequently in association with the \textit{pfcrt} K76T allele, depending on the endemic setting [5–7]. This combined genotype (N86Y and K76T) has been strongly associated, in some but not all studies, with resistance to CQ. It has been proposed that N86Y is selected for because of CQ pressure, either to augment resistance or to compensate for altered functional properties of mutant \textit{pfcrt} harboring K76T. The N86Y mutation may in turn have rendered the parasites hypersensitive to MQ [2]. If so, then in areas with MQ pressure, wild-type 86N could be favored and predispose to \textit{pfmdr1} amplification. Multicopy \textit{pfmdr1} is highly associated with MQ resistance and may also increase CQ susceptibility in some parasite genetic backgrounds.

Ursing et al. report that \( \geq \)60% of their samples carry the \textit{pfmdr1} 86N allele, suggesting that \textit{pfmdr1} amplification is theoretically possible [1]. Although present at lower levels, CQ resistance is not as widespread in Guinea-Bissau as it is in Gabon [7, 8]. Perhaps the lack of high-level CQ resistance provides a protective role for the development of MQ resistance by \textit{pfmdr1} amplification. Monitoring for these amplifications will become increasingly important as African countries move away from using CQ and instead use MQ and other agents in artemisinin-based combination therapy.

\begin{flushright}
\textit{Anne-Catrin Uhlemann* and Sanjeev Krishna}
\end{flushright}

\begin{flushright}
Division of Cellular and Molecular Medicine, Centre for Infection, St. George’s, University of London, London, United Kingdom.
\end{flushright}

References


---

\*Correspondence: Dr. Johan Ursing, Dept. of Infectious Diseases, Karolinska Institute, Roslagstulls sjukhus, Stockholm, Sweden (johan.ursing@ki.se).

Reprints or correspondence: Dr. Johan Ursing, Dept. of Infectious Diseases, Karolinska Institute, Roslagstulls sjukhus, Stockholm, Sweden (johan.ursing@ki.se).

The Journal of Infectious Diseases 2006;194:716–8 © 2006 by the Infectious Diseases Society of America. All rights reserved. 0022-1899/2006/19402-0015/00

\begin{flushleft}
\textbf{Reply to Ursing et al.}
\end{flushleft}

\textbf{To the Editor—}Ursing et al. report on a study from Guinea-Bissau that analyzes the prevalence of \textit{pfmdr1} copy number in \textit{Plasmodium falciparum} infections [1]. They genotyped parasite samples obtained from 523 of 560 children who received either chloroquine (CQ) or amodiaquine, collected between 2001 and 2004. Analysis was extended to samples from an in vitro surveillance study for CQ resistance from the early 1990s (\( n = 73 \)), as well as to samples derived from a study in Liberia from as early as 1981 (\( n = 34 \)). None of these samples showed \textit{pfmdr1} amplification.
**Neonatal Vitamin A Supplementation: Sex-Differential Effects on Mortality?**

To the Editor—Humphrey et al. [1] and Malaba et al. [2] recently presented the results of a large vitamin A supplementation (VAS) study in Zimbabwe. In this study, neonates and their mothers were randomized to receive either vitamin A (50,000 IU for infants and 400,000 IU for mothers) or placebo, in a 2-by-2 factorial design. In contrast to the findings of 2 previously published studies of neonatal VAS conducted in Indonesia [3] and India [4], the Zimbabwe study found no beneficial effect of neonatal VAS on mortality among infants of HIV-negative mothers [2], and, among infants of HIV-positive mothers, neonatal VAS was associated with increased mortality in infants who remained negative by polymerase chain reaction at 6 weeks of age [1]. The results of the Zimbabwe study were not reported by sex.

In both previous studies [3, 4], the mortality-reducing effect of VAS seemed to be stronger in boys (table 1). Hence, these studies suggest a highly significant beneficial effect in boys but no effect in girls. In fact, the very first randomized VAS study, which was conducted by Sommer et al. and which included very young infants, reported a beneficial effect in boys but no effect in girls among the youngest children [5]. We have previously reported that boys had a stronger antibody response to measles vaccine administered with VAS than girls [6]. Recently, we also reported that boys benefited more from receiving the standard dose of vitamin A, compared with a smaller dose, than did girls [7]. We are currently analyzing data from a neonatal VAS study conducted in Guinea-Bissau, and we have found that the effect of VAS was better in boys than in girls (authors’ unpublished data).

It can be speculated that boys benefit more from VAS because they are more vitamin A deficient than girls, and there are indeed indications that boys are born with lower vitamin A levels [8, 9]. It may also be that infant boys and girls have underlying immunological differences that determine a differential response. Irrespective of the underlying mechanisms, if the effect of VAS differs between the sexes, it could potentially be very important for designing the optimal VAS policy. A presentation of the results of the Zimbabwe study by sex would provide indications as to the consistency of the observation of a sex-differential effect of VAS in infants of HIV-negative as well as HIV-positive mothers.

Christine Stabell Benn, Ane Bærent Fisker, Birgitte Rode Diness, and Peter Aaby
Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark, and Bissau, Guinea-Bissau

Table 1. Mortality ratios and 95% confidence intervals (CIs) for neonatal vitamin A supplementation compared with placebo, by sex.

<table>
<thead>
<tr>
<th>Country</th>
<th>Mortality ratio (95% CI)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia [3]</td>
<td>0.15 (0.03–0.68)</td>
<td>0.84 (0.26–2.77)</td>
<td></td>
</tr>
<tr>
<td>India [4]</td>
<td>0.70 (0.52–0.94)</td>
<td>0.87 (0.65–1.17)</td>
<td></td>
</tr>
</tbody>
</table>


Potential conflicts of interest: none reported.

Reprints or correspondence: Dr. Christine Stabell Benn, Bandim Health Project, Statens Serum Institut, Artilerne 5, 2300 Copenhagen, Denmark (cb@ssi.dk).

The Journal of Infectious Diseases 2006; 194:719
© 2006 by the Infectious Diseases Society of America. All rights reserved. 0022-1899/2006/19405-0030$15.00