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RTS,S Malaria Vaccine and Increased Mortality in Girls

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Malaria was estimated to result in 214 million clinical cases and 438,000 deaths in 2015, primarily in children under 5 years of age. In Africa, malaria causes approximately 10% of all deaths in children under 5 years of age. The RTS,S/AS01 malaria vaccine has been tested in young children in phase III clinical trials and shown to be 18 to 36% efficacious against clinical malaria (1). Although the vaccine may be efficacious against clinical malaria, it does not however reduce overall mortality.

The WHO has speculated that the increased mortality in girls was “largely due to the low female mortality in the control arm” and “could be due to chance” (2), despite the P value of 0.0006 for sex of group and 0.0005 for sex and age group. The WHO has also acknowledged that increased mortality in girls was “largely due to the low female mortality in the control arm” and “could be due to chance” (2), despite the P value of 0.0006 for sex of group and 0.0005 for sex and age group. The WHO has further speculated that the increased mortality in girls was “due to chance” (2), despite the P value of 0.0006 for sex of group and 0.0005 for sex and age group.

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girls need lower doses of the RTS,S/AS01 vaccine or should receive the vaccine with or separately from other vaccines or at different ages than boys.

Preclinical studies in animal models can help provide insights into the biological basis of these observations, but here too, analysis of potential sex effects has been lacking. Published studies of RTS,S or recombinant circumsporozoite protein in mice and non-human primates have only reported using adult females or have not reported the sex of the animals (7–9). Generally, in the fields of immunology, vaccinology, and infectious diseases, investigators either do not report the sex of their animals or predominately use female animals (10). This “one size fits all” approach to vaccine research is not working. Preclinical studies should consider how both age and sex affect vaccine responses and outcomes. RTS,S vaccine could also be used to uncover immunological mechanisms for a possible increase in mortality after RTS,S vaccination among girls but not boys.

The RTS,S vaccine is modestly effective at reducing clinical malaria in children, but the sex differences in all-cause mortality should be rigorously studied in both clinical trials and experimental animal models, particularly in light of prior experience with the HTMV. We seek to raise awareness about the need for additional research into how the RTS,S vaccine and, possibly, other vaccines are associated with greater mortality in girls but not boys. This will only be achieved if age and sex are considered in a priori hypotheses in vaccine trials to identify and address potential risks early in the vaccine development process.

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REFERENCES


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