Randomised controlled trial

Phase 3 trial with the RTS,S/AS01 malaria vaccine shows protection against clinical and severe malaria in infants and children in Africa

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Commentary on: RTS,S Clinical Trials Partnership. Efficacy and safety of the RTS,S/AS01 malaria vaccine during 18 months after vaccination: a phase 3 randomized, controlled trial in children and young infants at 11 African sites. *PLoS Med* 2014;11:e1001685.

Context

There is currently no licensed malaria vaccine. Protection against malaria is dependent on use of insecticide-treated nets, other vector control measures and drug treatment. These have reduced the burden of disease over the past decade, but it remains unacceptably high.[1] Malaria transmission is heterogeneous and there are particular challenges presented by hotspots of transmission and by reservoirs of asymptomatic infections that serve to maintain transmission. In addition, there are growing concerns about the spread of drug resistance, and of insecticide resistance that can reduce the benefits of treated bednets or spraying.[2 3]

Methods

This was a phase 3 double-blind trial of the RTS,S/AS01 vaccine which is directed against the pre-erythrocytic stage of *Plasmodium falciparum* malaria. It was conducted in 11 sites in Africa where transmission intensities varied considerably. Six thousand five hundred and thirty-seven infants and 8923 children aged 5–17 months were each vaccinated three times with RTS,S/AS01 or with a control vaccine (meningococcal C vaccine for infants and rabies vaccine for children). The follow-up period was 18 months after the third dose; vaccine efficacy (VE) was determined against clinical malaria, severe malaria, malaria hospitalisation and all-cause hospitalisation. Induction of antibody to the parasite circumsporozoite protein was determined. The impact of the vaccine on burden of disease was assessed as number of clinical and severe cases averted per 1000 children vaccinated.

Findings

VE was better in children than in infants but, waned with time in both groups. Per protocol, the efficacy against clinical malaria was 46% in children (95% CI 42% to 50%) and 27% in infants (95% CI 20% to 32%). VE rates against severe malaria, malaria hospitalisation and all-cause hospitalisation in children, measured as intention to treat, were 34% (95% CI 15% to 48%), 41% (95% CI 30% to 50%) and 19% (95% CI 11% to 27%), respectively; there was no significant protection in infants. VE varied significantly among 11 sites. Equating this directly to transmission intensity was difficult, but there was indication of higher VE at sites with a lower incidence of malaria. The number of clinical cases averted per 1000 children vaccinated also varied considerably from 37 to 2365; the corresponding range among infants was −10 to 1402.

Commentary

Although further results from this trial will be forthcoming, this publication is effectively the culmination of a 20-year programme of development and clinical trials. The RTS,S vaccine has been submitted for regulatory approval by the European Medicines Agency (EMA) and, if approved, will be submitted for evaluation by the WHO. The levels of efficacy in children and infants are in accord with results from phase 2 trials and early stages of phase 3. The particular value of this large, multisite study came from the ability it afforded to make site-specific analyses and determine numbers of cases averted. This provides a valuable measure of the impact on burden of disease and will greatly assist evaluation of how and where the vaccine might be used. On this basis it will be best used in areas of high transmission, but as an addition to existing control and treatment measures, rather than an alternative. In areas where transmission is seasonal, there could be benefits from vaccination in the months preceding the onset of transmission, as protection is highest in the early months of vaccination. Annual booster doses might provide added protection. Operationally speaking, giving children three doses of vaccine does present difficulties, as the vaccine delivery cannot be linked to the WHO Expanded Program on Immunisation (EPI) in the same way that is was with infants.

Adding a partially effective vaccine to ongoing control and treatment measures could provide a valuable improvement in reduction of disease burden. However, this only represents the first phase of malaria vaccine development, and it is vital to continue other promising ongoing studies on pre-erythrocytic, blood-stage, transmission-blocking and combination vaccines in the quest to obtain substantially higher efficacy.[4–7]

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

CrossMark

References

1. **World Health Organization.** *World Malaria Report 2013*. Geneva: World Health Organization, 2013.
2. **Ashley EA,** Dhorda M, Fairhurst RM, *et al.* Spread of artemisinin resistance in *Plasmodium falciparum* malaria. *New Eng J Med* 2014;**371**:411–23.
3. **Protopopoff N,** Matowo J, Malima R, *et al.* High level of resistance in the mosquito *Anopheles gambiae* to pyrethroid insecticides and reduced susceptibility to bendiocarb in north-western Tanzania. *Malar J* 2013;**12**:149.
4. **Hill AVS.** Vaccines against malaria. *Philos Trans R Soc Lond B Biol Sci* 2011;**366**:2806–14.
5. **Seder RA,** Chang LJ, Enama ME, *et al.* Protection against malaria by intravenous immunization with a nonreplicating sporozoite vaccine. *Science* 2013;**341**:1359–65.
6. **Douglas AD,** Williams AR, Knuepfer E, *et al.* Neutralization of *Plasmodium falciparum* by antibodies against PfRH5. *J Immunol* 2014;**192**:245–58.
7. **Theisen M,** Roeffen W, Singh SK, *et al.* A multi-stage malaria vaccine candidate targeting both transmission and asexual parasite life-cycle stages. *Vaccine* 2014;**32**:2623–30.