Malaria vaccination and rebound malaria

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A large phase 3 trial of the RTS,S/AS01 malaria vaccine, done in 11 centres in sub-Saharan Africa, showed moderate efficacy against severe and uncomplicated malaria,[1] but also raised a number of safety concerns.[1,2] For these reasons, WHO recommended new large scale pilot implementation studies.[3] Infants and children recruited to the phase 3 trial were followed for an initial period of 3 years or 4 years, respectively, because it was uncertain whether the efficacy observed in the trial would be sustained. Two other studies[4,5] provided further information on the long-term efficacy and safety of RTS,S/AS01.

In Kenya, Olotu and colleagues[4] followed children who had been enrolled in a small phase 2 RTS,S/AS01 trial for a period of 7 years. These children had received three doses of RTS,S/AS01 when aged 5–17 months, but not a fourth booster dose. Vaccine efficacy against clinical episodes of malaria was observed for an initial period of 2–3 years[5] was not maintained during the later period of follow-up, and, in year 5, a negative efficacy of −34·4% (95% CI −83·9 to 1·8) was measured in the overall cohort and of −56·8% (−118·7 to −12·3) among children who lived in the area with the highest malaria transmission.[4]

In *The Lancet Infectious Diseases*, Halidou Tinto and colleagues[6] report findings from children enrolled in three of the initial phase 3 trial centres, who were followed for an additional 3 years. Encouragingly, vaccine efficacy against severe malaria was sustained; vaccine efficacy against severe malaria during the 6-year or 7-year post-vaccination period in children who had received a booster dose was 36·7% (95% CI 14·6–53·1) in the older age group (5–7 years) and 31·0% (4·7–50·0) in the younger age group (3–5 years). Vaccine efficacy against uncomplicated malaria during the full follow-up period was 23·7% (15·9–30·7) and 15·5% (6·7–23·5) in the older age and younger age groups, respectively. No protection against clinical malaria was measured during the extension period and, in the centre with the highest transmission, a statistically significant increase in the incidence of clinical malaria was measured for older children during the extension period (vaccine efficacy −30·3% [−59·5 to −6·4]).

15 deaths were recorded in RTS,S/AS01 vaccinated children (ten girls and five boys) and seven in the control group (four girls and three boys). Five cases of meningitis were reported, two in children who received RTS,S/AS01 vaccine and three in the control group. Limitations of the study include a gap of nearly 2 years during which surveillance data were dependent on retrospective analysis of routinely collected data and the fact that only 70% of children in the original trial were enrolled in the extended follow-up. Nevertheless, this study provides strong evidence that RTS,S/AS01 can provide sustained protection against severe malaria and some reassurance on its safety, although numbers of serious adverse events and deaths were small and the gender imbalance in deaths noted previously in the overall phase 3 trial population was still present.

In both studies, an increase in the incidence of uncomplicated clinical malaria was observed during the extended follow-up period, with the greatest effect in children exposed to the highest level of malaria transmission. This increase was not measured for severe malaria, although in Kenya, the peak age incidence of severe malaria was delayed in RTS,S/AS01 vaccinated children. These findings are not surprising because strong evidence suggests that repeated exposure to malaria is necessary to establish and sustain naturally acquired immunity, although the intensity of infection needed to achieve this immunity is not known. However, some information comes from studies of chemoprevention. When malaria was prevented in Tanzanian infants during the first year of life, a significant increase in cases of clinical malaria was reported in the following year.[7] However, in children aged 3–59 months protected for 1 year by seasonal malaria chemoprevention, only a small increase in cases of uncomplicated malaria was reported during the following year.[8,9]

Longer periods of protection might be followed by a substantial, although short-lasting, increase in susceptibility to clinical malaria,[10] but in all cases the benefits of protection exceeded those of the subsequent period of enhanced risk. A highly effective malaria vaccine that provides only a relatively short period of protection will probably lead to some degree of so-called rebound malaria because its efficacy wanes unless the force of infection has been reduced during the period of follow-up. Booster vaccinations might delay the period

of risk, but vaccinated children might need to receive additional support during the period of enhanced risk through education, improved access to treatment, and regular distribution of insecticide-treated bed nets.

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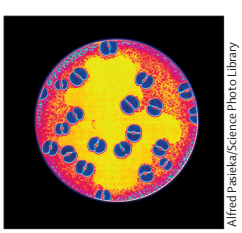
Solithromycin for the treatment of drug-resistant gonorrhoea

In *The Lancet Infectious Diseases*, Marcus Chen and colleagues[1] report on the efficacy of solithromycin, a novel fourth generation macrolide, as a treatment option for urogenital gonorrhoea. In the SOLITAIRE-U trial, solithromycin was compared with a combination of ceftriaxone plus azithromycin, which is the standard therapy in many countries. To date, *Neisseria gonorrhoeae*, the pathogen that causes gonorrhoea, has acquired antimicrobial resistance against all available first-line antibiotic treatment options, including penicillin, tetracycline, ciprofloxacin, and spectinomycin, leading to treatment failure.[2] WHO recommends a minimum cure rate of 95% for an antibiotic to be used as first-line treatment.[3] Therefore, the current first-line option, ceftriaxone (given as monotherapy or in combination with azithromycin), is considered a safe option since the ceftriaxone cure rate remains above 95%. However, the number of strains with decreased susceptibility for ceftriaxone is increasing[4] and treatment failure with both monotherapy and dual therapy has been reported.[5,6] Since all previous treatment options for gonorrhoea have been abandoned, and resistance to ceftriaxone might soon become a problem, alternative antibiotics are urgently needed.

The SOLITAIRE-U trial assessed solithromycin as an alternative treatment option for gonorrhoea. In the microbiological intention-to-treat population, solithromycin was not non-inferior to standard first-line treatment: genital gonorrhoea was eradicated in 99 (80%) of 123 patients in the solithromycin group compared with 109 (84%) of patients in the ceftriaxone plus azithromycin group (difference −4·0%, 95% CI −13·6 to 5·5). In this analysis, patients lost to follow-up or those who did not return for assessment at test-of-cure (on day 7 or 21) were considered to have treatment failure. In a secondary analysis restricted to patients from whom a test of cure sample was obtained (microbiologically evaluable population), the eradication rate with solithromycin was 92% compared with 100% for ceftriaxone plus azithromycin. In all analyses, less than 95% of patients had eradication with solithromycin, which is below the minimum cure rate recommended by WHO, and was not found to be non-inferior to the first-line treatment.

Treatment failures were not associated with resistance to solithromycin. Moreover, whole genome sequencing was used to type strains cultured before and after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