Case study: Evaluation of malaria vaccine introduction into the national immunization program of Cote d'Ivoire

Background

Malaria is a leading cause of morbidity and mortality globally and particularly in sub-Saharan African countries. Acute malaria can lead to cerebral infection, cerebral infarction, and death; sequelae of cerebral malaria may include severe cognitive, neurological, and developmental impairment. Chronically, repeated malaria infections can cause chronic anemia, and contribute to stunting and fatigue. Health care utilization is high and malaria control and treatment may absorb a substantial part of government health budgets.

Unlike most diseases targeted by vaccines, malaria occurs throughout life, although most serious disease occurs in young children. Malaria and malaria outcomes may concentrate among marginalized groups who have less access to prevention and treatment interventions.

Numerous interventions exist to reduce the risk of malaria. Insecticide treated nets (ITN) may reduce overall child mortality by 20%, or 6 child deaths per 1000 children using an ITN per year; despite this success, only one-third of African children sleep under an ITN. Other interventions include intermittent preventive treatment during pregnancy, residual spraying, insect repellants, and removing standing water and other interventions to reduce mosquito habitats. Treatment focuses on artemesin based combination therapy (ACT). Better malaria case management combined with increased access to care has led to an estimated 49% decrease in African malaria mortality rates across all ages and a 54% decrease among children age less than age 5 years. Despite these great successes, malaria continues as one of the primary health problems in some African countries.

An unlicensed vaccine called RTS,S currently exists to prevent malaria caused by Plasmodium falciparum, the primary cause of severe disease in Africa. RTS,S targets the circumsporozoite protein and is given with the AS01 or AS02 adjuvant. It has been evaluated as a 3-dose infant (age 6 to 12 weeks at first dose) or child (age 5 to 17 months at first dose) schedule with vaccine at 1 month intervals with or without a booster. Results have been considered mixed and include the following:

1. At 12 months post vaccination, a primary series among young infants led to
   - approximately 37% VE against severe disease, 30-35% VE against any clinical malaria, and no VE against all cause mortality.
   - prevention of 800 cases of severe malaria and 27,000 cases of any malaria per 100,000 children vaccinated

2. At 12 months post vaccination, a primary series among older infants and young children led to
   - approximately 47% VE against severe disease, 55% VE against any clinical malaria, and no VE against all cause mortality.
   - prevention of 2300 cases of severe malaria and 73,000 cases of any malaria per 100,000 children vaccinated

3. Vaccine efficacy:
   - in Kenya, was zero at four years among children vaccinated at age 5 to 17 months
   - in Mozambique, was close to zero at five years post vaccination.

4. Vaccine safety
   - appears similar to existing EPI vaccines out to 20 months post immunization.
   - has not been evaluated for rare serious events following public health introduction

5. Cost effectiveness. Preliminary CEA suggests RTS,S is a better investment than bednets.

Cote d'Ivoire has not yet elected to introduce RTS,S. The country recently emerged from civil war and is working on rebuilding public health infrastructure. It has many pressing public health needs, including discussion of other important vaccines such as rotavirus, PCV, and MenAfriVac, as well as introduction of IPV.

Task
The MOH asked the Cote d'Ivoire National Immunization Technical Advisory Group (NITAG) – called the National Committee of Independent Experts for Vaccination and Vaccines (CNEIV-CI) – to assess whether RTS,S vaccine should be introduced should it receive WHO pre-qualification. Considerations should include merits relative to other malaria interventions and relative to other vaccines, schedule, logistic issues if delivered outside the routine infant schedule, safety, financial issues and need for impact monitoring. The goal of this exercise is to develop an initial recommendation to the MOH so that the MOH can prepare for vaccine use or not.

Composition of the CNEIV-CI
CNEIV-CI deals with both adult and childhood immunizations. It consists of the following core members:
- ♦ Chairman (professor of public health)
- ♦ Vice chair (professor of infectious diseases)

Additional expertise:
- Public health and health policy
- Microbiology
- Pediatrics
- Infectious diseases
- Pharmacy/logistics
- Applied vaccinology
- Epidemiology and biostatistics
- Health economics
- Sociology/anthropology
- Gynecology and obstetrics
- Workplace medicine
- Paramedical associations

Advice on the group work process
- Choose the chairman. Choose the rapporteur.
- Address the key topic first, that is, is there any role for RTS,S vaccine in the country. If the answer is yes, address specific questions on how it should be used. If the answer is no because additional data are needed, identify the needed studies. If the answer is no and sufficient data exist to make this a final decision, provide a rationale that will convince the MOH (many of whose family members have suffered from malaria!).

The meeting should last no longer than 1 hour 20 minutes, after which the MOH has arranged for the chairman of the expert group to give a summary of their advice to the Ministry of Finance who presently is drafting the 5-year financial plan of the country.

Infant immunization program of Cote d'Ivoire

Vaccine	Full vaccine name	Schedule
BCG	Bacille Calmette-Guérin vaccine	Birth
DTwPHibHep	Diphtheria and tetanus toxoid with whole cell pertussis, Hib and HepB vaccine	6,10,14 weeks
Measles	Measles vaccine	9 months
OPV	Oral polio vaccine	Birth; 6, 10, 14 weeks
VitaminA	Vitamin A supplementation	6, 12, 18, 24, 30, 36 months
YF	Yellow fever vaccine	9 months

Cote d'Ivoire country indicators

Under 5 mortality rate	123/1000 live births
Infant mortality rate	86/1000 live births
Life expectancy	55 years
Annual number of births	673,000
Total population	19.7 million
DPT3 coverage estimate	85%
Adult (age 15-49 years) HIV prevalence	3.4%
GNI per capita	1070 USD

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ABSTRACTS

1. Background

An ongoing phase 3 study of the efficacy, safety, and immunogenicity of candidate malaria vaccine RTS,S/AS01 is being conducted in seven African countries.

Methods

From March 2009 through January 2011, we enrolled 15,460 children in two age categories — 6 to 12 weeks of age and 5 to 17 months of age — for vaccination with either RTS,S/AS01 or a non-malaria comparator vaccine. The primary end point of the analysis was vaccine efficacy against clinical malaria during the 12 months after vaccination in the first 6000 children 5 to 17 months of age at enrollment who received all three doses of vaccine according to protocol. After 250 children had an episode of severe malaria, we evaluated vaccine efficacy against severe malaria in both age categories.

Results

In the 14 months after the first dose of vaccine, the incidence of first episodes of clinical malaria in the first 6000 children in the older age category was 0.32 episodes per person-year in the RTS,S/AS01 group and 0.55 episodes per person-year in the control group, for an efficacy of 50.4% (95% confidence interval [CI], 45.8 to 54.6) in the intention-to-treat population and 55.8% (97.5% CI, 50.6 to 60.4) in the per-protocol population. Vaccine efficacy against severe malaria was 45.1% (95% CI, 23.8 to 60.5) in the intention-to-treat population and 47.3% (95% CI, 22.4 to 64.2) in the per-protocol population. Vaccine efficacy against severe malaria in the combined age categories was 34.8% (95% CI, 16.2 to 49.2) in the per-protocol population during an average follow-up of 11 months. Serious adverse events occurred with a similar frequency in the two study groups. Among children in the older age category, the rate of generalized convulsive seizures after RTS,S/AS01 vaccination was 1.04 per 1000 doses (95% CI, 0.62 to 1.64).

Conclusions

The RTS,S/AS01 vaccine provided protection against both clinical and severe malaria in African children.

2. Background

The candidate malaria vaccine RTS,S/AS01 reduced episodes of both clinical and severe malaria in children 5 to 17 months of age by approximately 50% in an ongoing phase 3 trial. We studied infants 6 to 12 weeks of age recruited for the same trial.

Methods

We administered RTS,S/AS01 or a comparator vaccine to 6537 infants who were 6 to 12 weeks of age at the time of the first vaccination in conjunction with Expanded Program on Immunization (EPI) vaccines in a three-dose monthly schedule. Vaccine efficacy against the first or only episode of clinical malaria during the 12 months after vaccination, a coprimary end point, was analyzed with the use of Cox regression. Vaccine efficacy against all malaria episodes, vaccine efficacy against severe malaria, safety, and immunogenicity were also assessed.

Results

The incidence of the first or only episode of clinical malaria in the intention-to-treat population during the 14 months after the first dose of vaccine was 0.31 per personyear in the RTS,S/AS01 group and 0.40 per person-year in the control group, for a vaccine efficacy of 30.1% (95% confidence interval [CI], 23.6 to 36.1). Vaccine efficacy in the per-protocol population was 31.3% (97.5% CI, 23.6 to 38.3). Vaccine efficacy against severe malaria was 26.0% (95% CI, −7.4 to 48.6) in the intention-totreat population and 36.6% (95% CI, 4.6 to 57.7) in the per-protocol population. Serious adverse events occurred with a similar frequency in the two study groups. One month after administration of the third dose of RTS,S/AS01, 99.7% of children were positive for anti-circumsporozoite antibodies, with a geometric mean titer of 209 EU per milliliter (95% CI, 197 to 222).

Conclusions

The RTS,S/AS01 vaccine coadministered with EPI vaccines provided modest protection against both clinical and severe malaria in young infants.

3. BACKGROUND

The candidate malaria vaccine RTS,S/AS01E has entered phase 3 trials, but data on long-term outcomes are limited.

METHODS

For 4 years, we followed children who had been randomly assigned, at 5 to 17 months of age, to receive three doses of RTS,S/AS01E vaccine (223 children) or rabies vaccine (224 controls). The end point was clinical malaria (temperature of ≥37.5°„C and Plasmodium falciparum parasitemia density of >2500 parasites per cubic millimeter). Each child's exposure to malaria was estimated with the use of the distance-weighted local prevalence of malaria.

RESULTS

Over a period of 4 years, 118 of 223 children who received the RTS,S/AS01E vaccine and 138 of 224 of the controls had at least 1 episode of clinical malaria. Vaccine efficacies in the intention-to-treat and per-protocol analyses were 29.9% (95% confidence interval [CI], 10.3 to 45.3; P = 0.005) and 32.1% (95% CI, 11.6 to 47.8; P = 0.004), respectively, calculated by Cox regression. Multiple episodes were common, with 551 and 618 malarial episodes in the RTS,S/AS01E and control groups, respectively; vaccine efficacies in the intention-to-treat and per-protocol analyses were 16.8% (95% CI, −8.6 to 36.3; P = 0.18) and 24.3% (95% CI, 1.9 to 41.6; P = 0.04), respectively, calculated by the Andersen–Gill extension of the Cox model. For every 100 vaccinated children, 65 cases of clinical malaria were averted. Vaccine efficacy declined over time (P = 0.004) and with increasing exposure to malaria (P = 0.001) in the per-protocol analysis. Vaccine efficacy was 43.6% (95% CI, 15.5 to 62.3) in the first year but was −0.4% (95% CI, −32.1 to 45.3) in the fourth year. Among children with a malaria-exposure index that was average or lower than average, the vaccine efficacy was 45.1% (95% CI, 11.3 to 66.0), but among children with a malaria-exposure index that

was higher than average it was 15.9% (95% CI, −11.0 to 36.4).
CONCLUSIONS
The efficacy of RTS,S/AS01E vaccine over the 4-year period was 16.8%. Efficacy declined over time and with increasing malaria exposure. (Funded by the PATH

4. A primary concern for the RTS,S malaria vaccine candidate is duration of protection. The ongoing Phase IIItrial reported evidence of waning efficacy within the first year following vaccination. Multiple Phase IIbtrials demonstrated early waning of efficacy. The longest duration of protection for RTS,S recorded to datewas in a trial of a cohort of 1605 Mozambican children age 1–4 yr at the time of immunization (C1), whichshowed an overall efficacy against clinical malaria of 30.5% over 43 subsequent months of surveillance.A significant reduction in parasite prevalence in RTS,S vaccinees indicated that the vaccine continued toprotect at the end of this period. Although follow-up for recording incident cases of clinical malaria wasstopped at 45 months, we were interested in evidence of further durability of protection, and revisited thecohort at 63 months, recording the secondary trial endpoint, prevalence of asexual Plasmodium falciparumparasitemia, in the RTS,S and comparator vaccine groups as a proxy for efficacy. As a comparator, we alsovisited the contemporaneous cohort of 417 children (C2), which showed waning efficacy after 6 monthsof follow-up. We also assessed anti-circumsporozoite antibody titers. These results were compared withthose of other Phase IIb trials. Prevalence of parasitemia was not significantly lower in the RTS,S/AS02group compared to comparator groups in C1 (57 [119%] Vs 62 [128%]; p = 0.696) or C2 (30 [226%] Vs35 [276%]; p = 0.391), despite elevated antibody titers, suggesting that protection did not extend to 5years after vaccination. This is in contrast to the earlier assessment of parasitemia in C1, where a 34%lower prevalence of parasitemia was observed in the RTS,S/AS02 group at month 45. Comparison withother Phase II trials highlights a complex relationship between efficacy, age and transmission intensity.RTS,S/AS02 provided partial protection from clinical malaria for at least 3.5 years in C1. Duration ofprotection may depend on environmental circumstances, such as changing malaria transmission, andspecial attention should be given in the Phase III trial to identifying factors that modify longevity ofprotection.

5. The malaria vaccine candidate, RTS,S/AS01E, showed promising protective efficacy in a trial of Kenyan and Tanzanian children aged 5 to 17 months. Here we report on the vaccine's safety and tolerability. The experimental design was a Phase 2b, two-centre, double-blind (observer- and participant-blind), randomised (1:1 ratio) controlled trial. Three doses of study or control (rabies) vaccines were administered intramuscularly at 1 month intervals. Solicited adverse events (AEs) were collected for 7 days after each vaccination. There was surveillance and reporting for unsolicited adverse events for 30 days after each vaccination. Serious adverse events (SAEs) were recorded throughout the study period which lasted for 14 months after dose 1 in Korogwe, Tanzania and an average of 18 months post-dose 1 in Kilifi, Kenya. Blood samples for safety monitoring of haematological, renal and hepatic functions were taken at baseline, 3, 10 and 14 months after dose 1. A total of 894 children received RTS,S/AS01E or rabies vaccine between March and August 2007. Overall, children vaccinated with RTS,S/AS01E had fewer SAEs (51/447) than children in the control group (88/447). One SAE episode in a RTS,S/AS01E recipient and nine episodes among eight rabies vaccine recipients met the criteria for severe malaria. Unsolicited AEs were reported in 78% of subjects in the RTS,S/AS01E group and 74% of subjects in the rabies vaccine group. In both vaccine groups, gastroenteritis and pneumonia were the most frequently reported unsolicited AE. Fever was the most frequently observed solicited AE and was recorded after 11% of RTS,S/AS01E doses compared to 31% of doses of rabies vaccine. The candidate vaccine RTS,S/AS01E showed an acceptable safety profile in children living in a malaria-endemic area in East Africa. More data on the safety of RTS,S/AS01E will become available from the Phase 3 programme.

6. Background: The RTS,S/AS malaria candidate vaccine is being developed with the intent to be delivered, if approved, through the Expanded Programme on Immunization (EPI) of the World Health Organization. Safety, immunogenicity and efficacy of the RTS,S/AS02D vaccine candidate when integrated into a standard EPI schedule for infants have been reported over a nine-month surveillance period. This paper describes results following
20 months of follow up.
Methods: This Phase IIb, single-centre, randomized controlled trial enrolled 340 infants in Tanzania to receive three doses of RTS,S/AS02D or hepatitis B vaccine at 8, 12, and 16 weeks of age. All infants also received DTPw/Hib (diphtheria and tetanus toxoids, whole-cell pertussis vaccine, conjugated Haemophilus influenzae type b vaccine) at the same timepoints. The study was double-blinded to month 9 and single-blinded from months 9 to 20.
Results: From month 0 to 20, at least one SAE was reported in 57/170 infants who received RTS,S/AS02D (33.5%;
95% confidence interval [CI]: 26.5, 41.2) and 62/170 infants who received hepatitis B vaccine (36.5%; 95% CI: 29.2, 44.2). The SAE profile was similar in both vaccine groups; none were considered to be related to vaccination. At month 20, 18 months after completion of vaccination, 71.8% of recipients of RTS,S/AS02D and 3.8% of recipients of hepatitis B vaccine had seropositive titres for anti-CS antibodies; seroprotective levels of anti-HBs antibodies remained in 100% of recipients of RTS,S/AS02D and 97.7% recipients of hepatitis B vaccine. Anti-HBs antibody GMTs were higher in the RTS,S/AS02D group at all post-vaccination time points compared to control. According to protocol population, vaccine efficacy against multiple episodes of malaria disease was 50.7% (95% CI: -6.5 to 77.1, p = 0.072) and 26.7% (95% CI: -33.1 to 59.6, p = 0.307) over 12 and 18 months post vaccination, respectively. In the Intention to Treat population, over the 20-month follow up, vaccine efficacy against multiple episodes of malaria disease was 14.4% (95% CI: -41.9 to 48.4, p = 0.545).
Conclusions: The acceptable safety profile and good tolerability of RTS,S/AS02D in combination with EPI vaccines previously reported from month 0 to 9 was confirmed over a 20 month surveillance period in this infant population. Antibodies against both CS and HBsAg in the RTS,S/AS02D group remained significantly higher compared to control for the study duration. Over 18 months follow up, RTS,S/AS02D prevented approximately a quarter of malaria cases in the study population.

7. Background: New RTS,S malaria vaccines may soon be licensed, yet its cost-effectiveness is unknown. Before the widespread introduction of RTS,S vaccines, cost-effectiveness studies are needed to help inform governments in resource-poor settings about how best to prioritize between the new vaccine and existing malaria interventions.
Methods: A Markov model simulated malaria progression in a hypothetical Malawian birth cohort. Parameters were based on published data. Three strategies were compared: no intervention, vaccination at one year, and long-lasting, insecticide-treated nets (LLINs) at birth. Both health service and societal perspectives were explored. Health outcomes were measured in disability-adjusted life years (DALYs) averted and costed in 2012 US$. Incremental cost-effectiveness ratios (ICERs) were calculated and extensive sensitivity analyses were conducted. Three times GDP per capita ($1,095) per DALY averted was used for a cost-effectiveness threshold, whilst one times GDP ($365) was considered 'very cost-effective'.
Results: From a societal perspective the vaccine strategy was dominant. It averted 0.11 more DALYs than LLINs and 0.372 more DALYs than the no intervention strategy per person, while costing $10.04 less than LLINs and $59.74 less than no intervention. From a health service perspective the vaccine's ICER was $145.03 per DALY averted, and thus can be considered very cost-effective. The results were robust to changes in all variables except the

vaccine and LLINs' duration of efficacy. Vaccines remained cost-effective even at the lowest assumed efficacy levels of 49.6% (mild malaria) and 14.2% (severe malaria), and the highest price of $15. However, from a societal perspective, if the vaccine duration efficacy was set below 2.69 years or the LLIN duration of efficacy was greater than 4.24 years then LLINs became the more cost-effective strategy.
Conclusion: The results showed that vaccinating Malawian children with RTS,S vaccines was very cost-effective from both a societal and a health service perspective. This result was robust to changes in most variables, including vaccine price and vaccine efficacy, but was sensitive to the duration of efficacy of the vaccine and LLINs. Given the best evidence currently available, vaccines can be considered as a very cost-effective component of Malawi's future malaria control programmes. However, long-term follow-up studies on both interventions are needed.