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Review

Could the RTS,S/AS01 meningitis safety signal really be a protective effect of rabies vaccine?

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ABSTRACT

The RTS,S/AS01 malaria vaccine has been associated with meningitis and cerebral malaria safety signals. Key characteristics of the meningitis signal include presence, in the 5–17 month but not the 6–12 week age group, of delayed and variable meningitis onset after vaccination, and multiple etiologies. For both meningitis and cerebral malaria, the 5–17 month old age group control arm had abnormally low incidences while other arms in both age groups had meningitis and cerebral malaria incidences similar to background rates. No single hypothesis postulating an adverse effect from RTS,S/AS01 unites these observations. Unlike the 6–12 week group, the control population in the 5–17 month old age group received rabies vaccine. This raises the possibility that non-specific rabies vaccine effects had a protective effect against central nervous system infection, a hypothesis consistent with the epidemiologic data. The lack of a confirmed biologic mechanism for such an effect emphasizes the need for additional studies.

Contents

1. Introduction

The RTS,S malaria vaccine combined with the novel AS01 adjuvant has received a positive opinion from the European Medicines Agency. One of the concerns before rollout within endemic areas of Africa is the higher incidence of meningitis reported in the RTS,S intervention group than among controls in the pivotal clinical trial [1]. Although the absolute numbers were relatively small, the magnitude of the observed effect among children enrolled at age 5–17 months was large, with 11 cases occurring in the 2976 children enrolled in the R3R group (three RTS,S/AS01 primary doses at 0, 1,

Abbreviations: BCG, Bacillus Calmette–Guérin vaccine; C3C, group in the RTS,S trial that received three primary and one booster control vaccines (meningococcal conjugate in younger group [612 weeks], rabies vaccine in older group [517 months]); CNS, central nervous system; MCV-C, Menjugate serogroup C meningococcal conjugate vaccine; R3C, group in the RTS,S trial that received three primary RTS,S doses and a control booster of meningococcal conjugate vaccine; R3R, group in the RTS,S trial that received three primary and one booster RTS,S vaccines.

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and 2 months and one booster dose at 20 months) (Table 1), 10 cases in the 2972 children enrolled in the R3C group (three primary doses of RTS,S/AS01 plus control vaccine booster [Menjugate serogroup C meningococcal conjugate, Novartis, Basel, Switzerland]) and one case in the 2974 children enrolled in the control (C3C) group (three primary doses and one booster dose of Verorab rabies vaccine [Sanofi Pasteur, Paris, France]). Although not reported in the trial manuscript, the estimated crude risk ratio was 10.5; using the number of children enrolled as the denominator, the 95% confidence interval (CI) around this value was 1.4 to 78 (Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 3.01. www.OpenEpi.com, updated 2013/04/06, accessed 2016/09/14) (calculations done using 2 × 2 tables, risk ratios, and Taylor series 95% CI) (Table 2).

There are several intriguing characteristics of this signal, which we presented in abbreviated form in a recent communication [2]. This paper presents an expanded systematic review and evaluation of the hypothesis that rabies vaccine might induce non-specific protection against central nervous system (CNS) infections and discusses existing evidence concerning possible immunological mechanisms of such an effect.

2. Review of the RTS,S/AS01 data

The following summarize the data from the RTS,S/AS01 clinical trial as it relates to the meningitis safety signal:

1. The proportion of children with meningitis identified in the R3R, R3C, and control groups (C3C) for both children enrolled at age 5–17 months and 6–12 weeks varied from 0.2% to 0.4% for all groups except the 5–17 month old control group among whom it was nearly 0%. Note that for children enrolled at 6–12 weeks of age, vaccines and vaccine schedules were identical to children enrolled at age 5–17 months for the R3R and R3C groups while the control group received three primary doses and one booster dose of Menjugate serogroup C meningococcal conjugate vaccine (Table 1).
2. Overall meningitis rates for the 5–17 months age stratum were low in the control group rather than high in the malaria-vaccinated group. With just one case among 3000 children enrolled at age 5–17 months over the 48 month study duration, the annual incidence of all-cause meningitis hospitalization among this control group was 8 per 100,000 per year while among the combined R3R + R3C intervention groups it was approximately 92 per 100,000, of which 42 per 100,000 were bacterial meningitis. Previous studies suggest that the incidence in the intervention group was consistent with rates generally seen in other countries, while the control group incidence was unusually low. For example, a previous study estimated annual hospitalization incidences for suspected meningitis among children age <5 years as 43 and 110 per 100,000 in The Gambia and Senegal, respectively [3]. Additionally, all-cause annual bacterial meningitis incidence in Africa among children age <5 years during the *Haemophilus influenzae* type B (Hib) and pneumococcal conjugate vaccine eras has been reported as 20–40 per 100,000 [4,5].
3. No between-group differences in meningitis rates were seen in the 6–12 week age group among whom a meningococcal conjugate vaccine, rather than a rabies vaccine, was used in controls (Table 2).
4. For children enrolled aged 5–17 months, multiple meningitis etiologies were identified including diverse bacterial causes in 10 children (three *Haemophilus influenzae*, five meningococcus, one pneumococcus, and one tuberculosis, all in the intervention group), viral causes (one case, in the intervention group), and cases identified only on clinical grounds (11 cases, 10 in the intervention group) [1,6]. Publicly available data on the characteristics of meningitis cases (such as distribution of etiologies by location and age) have not been published.
5. There was no consistent time period following vaccination after which cases clustered, with this delay extending out to approximately 1100 days after doses 1, 2, and 3 and almost 500 days after dose 4 (Fig. 1).

Table 1
Vaccine schedules for children enrolled in the RTS,S/AS01 malaria vaccine clinical trial.

Age group	Intervention group			Control group	
	Primary series	Active booster (R3R group)	Control booster (R3C group)	Primary series	Control booster (C3C group)
Age 5–17 months at enrollment	RTS,S/AS01 at 0, 1, 2 months	RTS,S/AS01 at 20 months	MCV-C[a] at 20 months	Verorab rabies vaccine at 0, 1, 2 months	Verorab rabies vaccine at 20 months
Age 6–12 weeks at enrollment	RTS,S/AS01 at 0, 1, 2 months	RTS,S/AS01 at 20 months	MCV-C[a] at 20 months	MCV-C[a] at 0, 1, 2 months	MCV-C[a] at 20 months

[a] Menjugate serogroup C meningococcal conjugate vaccine.

Table 2
Meningitis cases in children who received 4 doses of RTS,S at months 0, 1, 2, and 20 (R3R group); 3 doses of RTS,S at months 0, 1, and 2 followed by a dose of meningococcal serogroup C conjugate vaccine at 20 months (R3C group); or four doses of control vaccine (C3C group), specifically rabies vaccine for children age 5–17 months at enrollment and meningococcal serogroup C conjugate for children age 6–12 weeks at enrollment. Raw data from reference 6; risk ratios and 95% confidence interval (CI) were calculated by the authors.

Age group and study phase	4-dose schedule		3-dose schedule		Controls		Risk ratio (95% CI) for total intervention vs. controls
	Cases	No. enrolled	Cases	No. enrolled	Cases	No. enrolled	
Age 5–17 mo.							
0–20 mo.	9	2976	7	2972	1	2974	8.0 (1.1 to 60)
21 mo. to study end	2	2681	3	2719	0	2702	Undefined
Total[a]	11	2976	10	2972	1	2974	10.5 (1.4 to 78)
Age 6–12 weeks: 0 mo. to study end[b]	5	2976	7	2178	6	2179	0.85 (0.32 to 2.3)

[a] Original enrollment was used as the denominator assuming none of those lost to follow-up had meningitis.
[b] Data stratified by study period were not presented for the younger age group.

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