CVIVA Research Center for Vitamins & Vaccines

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Dear SAGE, MPAC, JTEG, GMP, SAGE's WG on the non-specific effects of vaccines, IVB, and GACVS,

During the SAGE-MPAC discussion of RTS,S malaria vaccine on 21 October 2015 at WHO, a GSK representative presented data from the recent randomised controlled trials (RCTs) on the number of deaths by sex and randomisation group (Table 1). We have previously asked for these numbers (1,2), and the RTS-consortium promised to include them in the final report from the study (3). Assuming that boys and girls are equally distributed in all groups, an analysis of these deaths suggests that RTS,S is associated with a significantly increased mortality among females. This effect was seen in both the 6-12-weeks and the 5-17-months age groups.

To assure that the numbers have been recorded accurately from the brief power point presentation, these numbers and the number of boys and girls in each randomisation group should be carefully checked by the responsible investigators. If the final analysis is similar to Table 1, there are two important conclusions. First, two RCTs among both younger and older children have shown that RTS,S is associated with an increase in female mortality, the combined estimate being 86% (27% to 173%) higher mortality. Second, the effect of RTS,S for mortality differs significantly by sex (test of interaction, p=0.003).

There is precedence for such results. In the late 1980s two RCTs showed that high-titre measles vaccine (HTMV) prevented measles infection, but was associated with a two-fold increase in all-cause mortality in girls, with no effect in boys (4-6). The last dose of DTP is usually given before standard-titre measles vaccine, but HTMV was given at an earlier age, and many children received DTP after HTMV; it turned out that the increased mortality was confined to children who received DTP after HTMV (7). I believe the RTS,S-trial data should be analysed carefully for similar interactions with other interventions that might modulate the immune system. There were probably many of those interventions during the conduct of the RTS,S trials, such as administration of other vaccines, IPTi, vitamin A supplementation (VAS) with vaccines (8), VAS campaigns, OPV campaigns (9,10), measles vaccine campaigns (11), H1N1 campaigns (10), and mebendazole campaigns. If the negative effect of RTS,S in females is due to interaction with other health interventions there may be ways of preventing it. For example, many studies have shown that co-administration of BCG with the first dose of DTP

reduces the negative effect of DTP for females (12-16); thus, it might be worth examining whether the administration of BCG with RTS,S could mitigate its adverse effect on females.

If no preventable interaction can be found which explains the excess mortality among female RTS,S-recipients, the research community should think carefully before pursuing the SAGE-MPAC meeting decision to launch demonstration projects in which hundreds of thousands of children would be given a vaccine that increases female mortality, and is associated with significant increases in meningitis and cerebral malaria.

Best regards

Peter Aaby

Bandim Health Project

Guinea-Bissau

Table 1. RTS,S malaria vaccine and mortality by sex

	Number of deaths/persons by group				**Risk ratio (95%CI)**
	R3R	R3C	RTS combined	C3C	
Number 5-17 months	2976	2972		2974	
Number 6-12 weeks	2180	2178		2179	
Males					
5-17 months	26	19	45/2974	29/1487	0.78 (0.49-1.23)
6-12 weeks	24	26	50/2179	26 /1089	0.96 (0.60-1.54)
Total			95/5153	55/2576	0.86 (0.62-1.20)
Females					
5-17 months	35	32	67/2974	17/1487	1.97 (1.16-3.34)
6-12 weeks	27	29	56/2179	16/1089	1.75 (1.01-3.03)
Total			123/5153	33/2576	1.86 (1.27-2.73)

The table assumes that there was an equal number of boys and girls in each group.

The table has 306 deaths, consistent with the 158 deaths in the older group and 148 death reported in the Lancet paper (Lancet 2015;386:31-45), "*158 of 8922 (1.8%, 95% CI 1.5-2.1 children and 148 of 6537 (2.3%, 1.9-2.7) young infants died during follow-up (month 0 to study end; appendix pp 49, 59)*". However, the tables presented at the SAGE-MPAC meeting by JTEG had only 305 deaths, as did the mortality tables in the supplement to the Lancet paper. The "excess" or "missing" death is in the RTS,S group. It is unlikely to change any of the conclusions.

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