CVIVA Research Center for Vitamins & Vaccines

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Non-live vaccines are associated with increased female mortality

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

A letter sent to you and your committees on October 26, 2015 expressed concern about a possible negative effect of the RTS,S vaccine on overall female mortality. None of the committees have answered. IVB is trying to find sites for pilot implementation of the RTS,S as discussed at the SAGE meeting in October 2015.

The sex-differential effects of RTS,S have now been clarified since GSK has published the mortality data by sex (1). As portrayed in table 1, female recipients of RTS,S had significantly increased mortality in both the 6-12 weeks and the 5-17 months age groups; the combined effect being 91% (30-179%) higher female mortality among RTS,S recipients. Since RTS,S is associated with 16% (-17-39%) lower male mortality, this is a highly significant sex-differential effect of RTS,S (p for same effect in the two sexes=0.001).

In the recent reports in Weekly Epidemiological Record, both SAGE and GACVS seem to ascribe the excess female mortality in the RTS,S group to "too low mortality" in the female control group. In GAVCS' words it was "largely due to the low female mortality in the control arm (the female mortality in the RTS,S/AS01 arm was similar to male mortality in control and vaccine arms)"(3). In the WHO position paper: "largely due to the low female mortality in the control arm (the female mortality in the RTS,S/AS01 arm was similar to male mortality in control and vaccine arms). These findings could be due to chance"(4).

The same unexpected "chance" twice in two different trials would usually suggest "cause". Furthermore, it is not correct to say that "the female mortality in the RTS,S/AS01 arm was similar to male mortality in control and vaccine arms". The female-male mortality risk ratio among RTS,S recipients (stratified for age group, and number of doses) was 1.33 (1.02-1.74) (Table 1). This excess female mortality was significant in its own right with a mortality risk ratio of 1.50 (1.03-2.18) in the 5-17-month-age group where the RTS,S is going to be tested (Table 1).

Table 1. RTS,S malaria vaccine and mortality by sex (1,2)

	Number of deaths/persons by group (percent)				**RTS,S/controls Risk ratio (95%CI)**
	R3R	R3C	RTS combined	C3C	
Males					
5-17 months	26/1509 (1.72%)	19/1472 (1.29%)	45/2981 (1.51%)	29/1471 (1.97%)	0.77 (0.48-1.22)
6-12 weeks	24/1116 (2.15%)	26/1118 (2.33%)	50/2234 (2.24%)	26 /1079 (2.41%)	0.93 (0.58-1.48)
Total			95/5215 (1.82%)	55/2550 (2.16%)	0.84 (0.61-1.17)
Females					
5-17 months	35/1467 (2.39%)	32/1500 (2.13%)	67/2967 (2.26%)	17/1503 (1.13%)	2.00 (1.18-3.39)
6-12 weeks	27/1064 (2.54%)	29/1060 (2.74%)	56/2124 (2.64%)	16/1100 (1.45%)	1.81 (1.04-3.14)
Total			123/5091 (2.42%)	33/2603 (1.27%)	1.91 (1.30-2.79)
Female-male mortality risk ratio					
5-17 months	1.38 (0.84-2.29)	1.65 (0.94-2.90)	1.50 (1.03-2.18)		
6-12 weeks	1.18 (0.69-2.03)	1.18 (0.70-1.98)	1.18 (0.81-1.72)		
Total	1.33 (1.02-1.74)				

R3R= 3*RTS,S+booster RTS,S; R3C=3*RTS,S +comparator vaccine; C3C = controls (comparator vaccines)

In the plans presented at the SAGE meeting in October 2015, the RTS,S pilot implementation projects would involve 5 sites with 200,000 children, for a total of 1,000,000. The pilot implementation projects are going to be conducted in the 5-17 months age group, where RTS,S had its best vaccine efficacy against clinical malaria. To our knowledge, the design is not clear yet, but presumably at least 250,000 girls in the age group 5-17 months will receive 4 doses of RTS,S. Based on the existing data (Table 1), these girls will have a 2-fold increased risk of dying during follow-up. If the female mortality risk in the future reference population is 1.13% (Table 1), then 2825 girls will die unnecessarily. However, since the RTS,S trial participants had good access to health care during the trial, it is more likely that the mortality rate will be considerably higher and a much larger group of girls will die due to the pilot experiment.

It should be remembered that all non-live vaccines which have been tested for possible sex-differential effects so far have found excess female mortality (Table 2). DTP, Hepatitis B vaccine (HBV), inactivated polio vaccine (IPV) and pentavalent vaccine are all associated with excess female mortality. This is unlikely to be due to "chance". Hence, to ascribe RTS,S excess female mortality to "chance" could be interpreted as ignoring existing knowledge.

Table 2. The mortality rate ratios (MRR) or risk ratios (RR) for non-live vaccine recipients compared with children unvaccinated with the same vaccine

Vaccine	Studies	Vaccinated/unvaccinated MRR for all [N]	Vaccinated/unvaccinated MRR for females	Female/male (F/M) MRR among vaccinated children [N]
DTP (5-7)	Observational studies and natural experiments	2.00 (1.50-2.67) [N=8]		1.50 (1.21-1.85) [N=16]
Pentavalent vaccine (8)	Observational study of mortality after 17,313 penta vaccination at health centres			1.73 (1.11-2.70) [1]
IPV (9)	IPV as comparator vaccine in 3 RCTS			1.52 (1.02-2.28) [3]
HBV (10)	Natural experiment	1.81 (1.19-2.75)		2.20 (1.07-4.54)
H1N1 influenza vaccine (11)	Campaign (natural experiment – mortality after vs before)	1.86 (1.02-3.42)	Vaccinated/control for females MRR 2.32 (1.19-4.52)	
RTS,S malaria vaccine (1,3,12)	2 RCTs	Overall: 1.24 (0.97-1.58) Long-term follow-up after 1st year: 1.50 (1.01-2.24)	Vaccinated/control RR for females RCT-1: 1.81 (1.04-3.14) RCT-2: 2.00 (1.18-3.39)	1.33 (1.02-1.74)[2]

[N]=number of studies where more than one.

If there is any justification for testing the RTS,S vaccine further in girls, because it is believed that the excess female mortality in the two previous trials was due to "chance" (3,4), to too much medical care in the previous trials (2), to the first trials not having been planned to measure mortality (13) etc., then the design has to considered very carefully. Given the danger signal for girls and the need to minimise the number of girls exposed to the risk, maybe other designs rather than large pilot implementation projects should be used.

Best regards

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