Operating Characteristics of the Specified Trial Design

Table 1: Probabilities (×100) of reaching each possible trial monitoring outcome and unconditional power (×100) to reject the specified null hypothesis for a 2-arm study design with 1900 placebo and 1700 vaccine recipients

		Weed Out at Interim Analysis			
Average VE(0-18)*	Average HR(0-18)	Potential Harm VE(0-18)<0%	Non-Efficacy VE(0-18)<40%	High Efficacy VE(0-18)>60%	Unconditional Power VE(0-18)>0%
–	3.0	88.0	12.0	0.0	0.0
–	2.5	77.0	23.0	0.0	0.0
–	2.0	52.7	47.3	0.0	0.0
–	1.5	23.8	76.2	0.0	0.0
0%	1.0	4.2	94.8	0.0	1.0
10%	0.9	2.0	88.5	0.1	9.5
20%	0.8	2.3	70.6	0.1	27.1
30%	0.7	1.3	40.7	0.9	58.0
40%	0.6	0.7	14.7	0.9	84.6
50%	0.5	0.2	2.3	3.9	97.3
60%	0.4	0.3	0.4	13.7	99.3
70%	0.3	0.0	0.0	59.3	100.0
80%	0.2	0.1	0.1	98.7	99.8

*VE halved in the first 6 months

N=1900:1700 placebo:vaccine group

4% annual incidence in the placebo group

5% annual dropout

Cumulative incidence-based non-efficacy monitoring incl. post-6 months monitoring

Cumulative incidence-based high efficacy monitoring

Cumulative incidence-based unconditional power

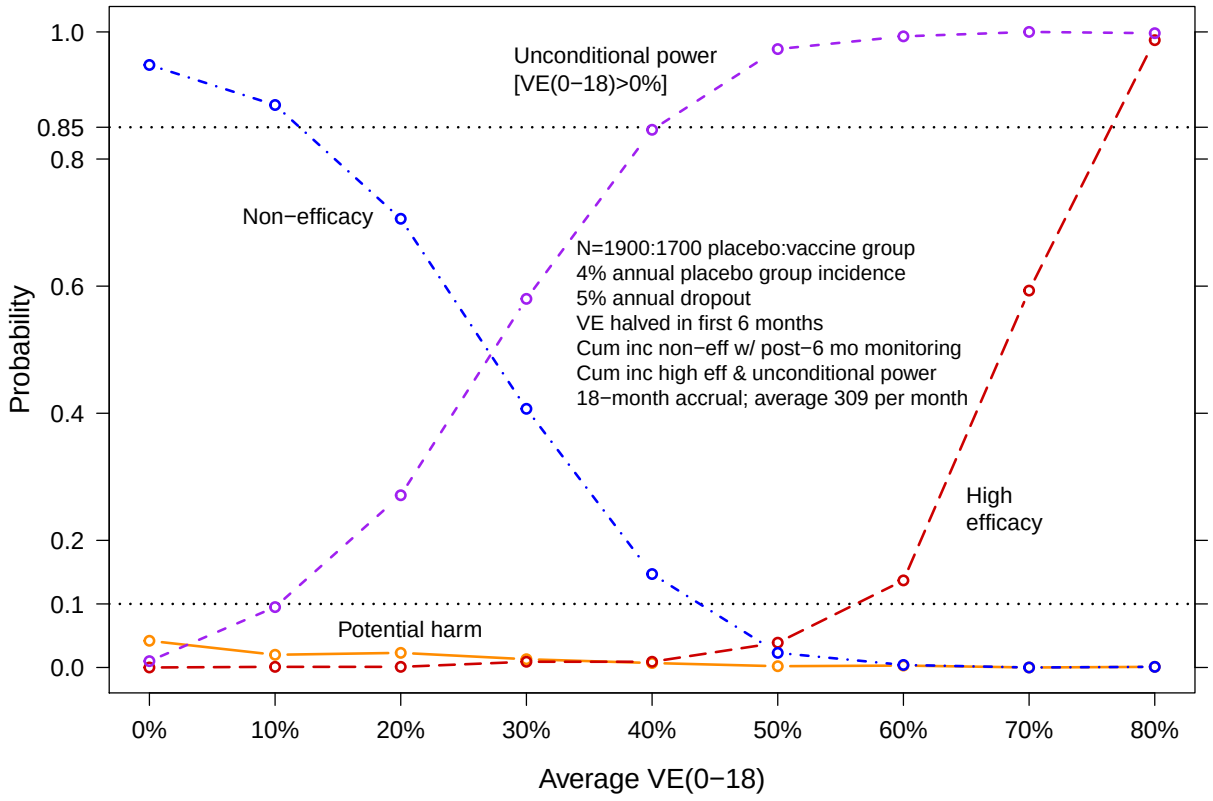


Figure 1: Probabilities of reaching each possible trial monitoring outcome, and unconditional power to reject the specified null hypothesis for a 2-arm study design with 1900 placebo and 1700 vaccine recipients

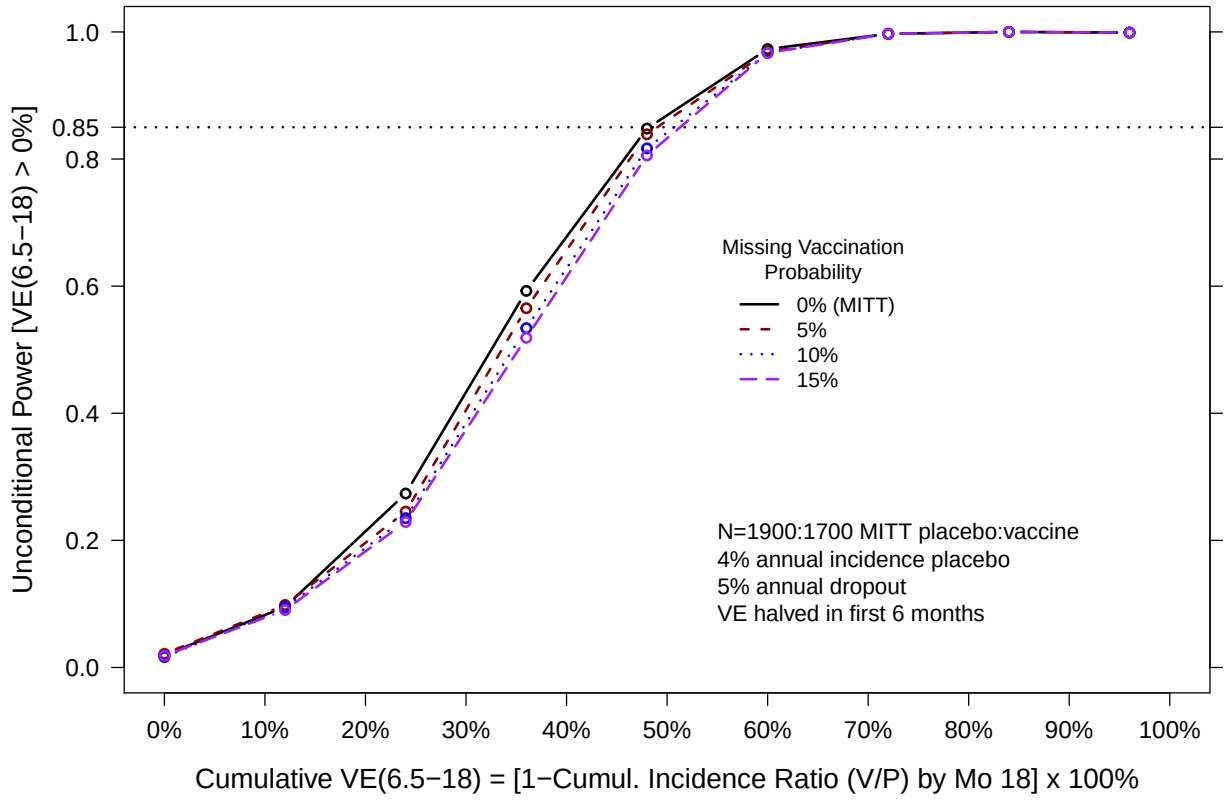


Figure 2: Unconditional power to reject the null hypothesis H_0: VE(6.5–18)$\leq$0% in per-protocol cohorts with a varying probability of a missing vaccination

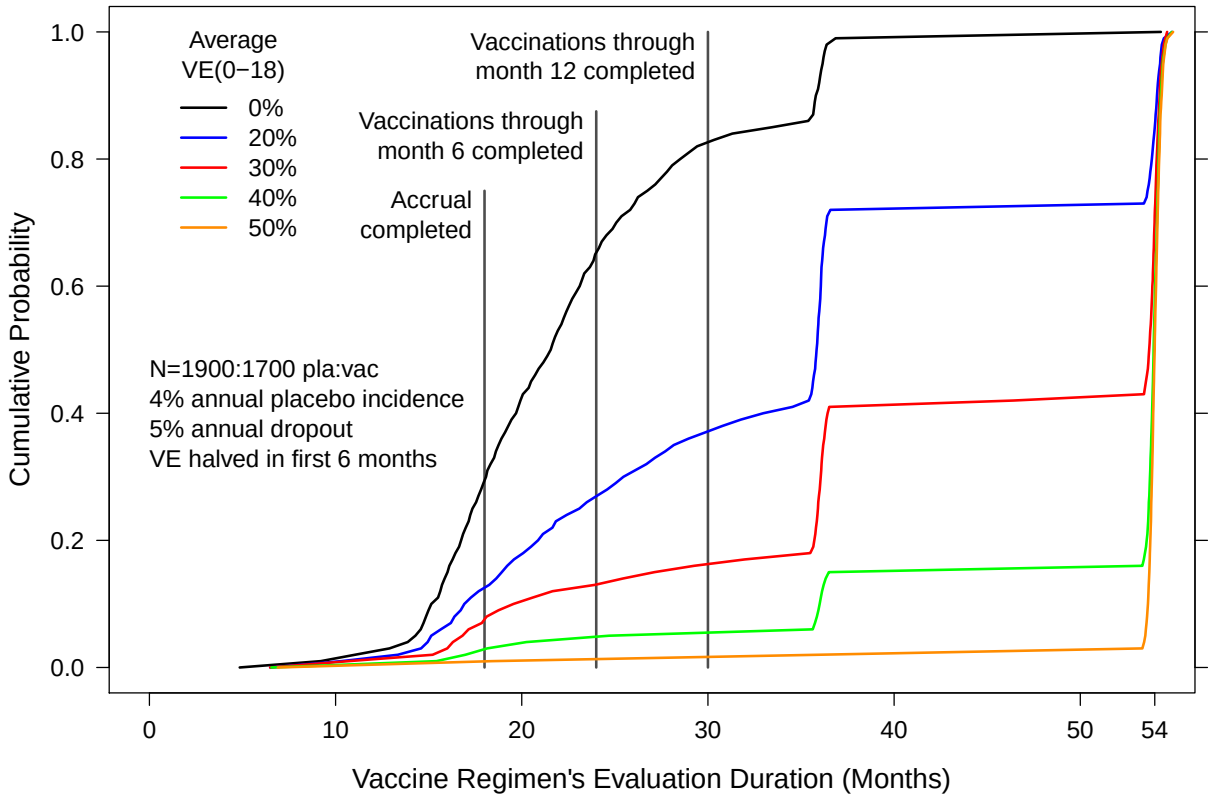


Figure 3: Duration of a vaccine regimen's evaluation (n =1900 in the placebo arm and n =1700 in the vaccine arm)

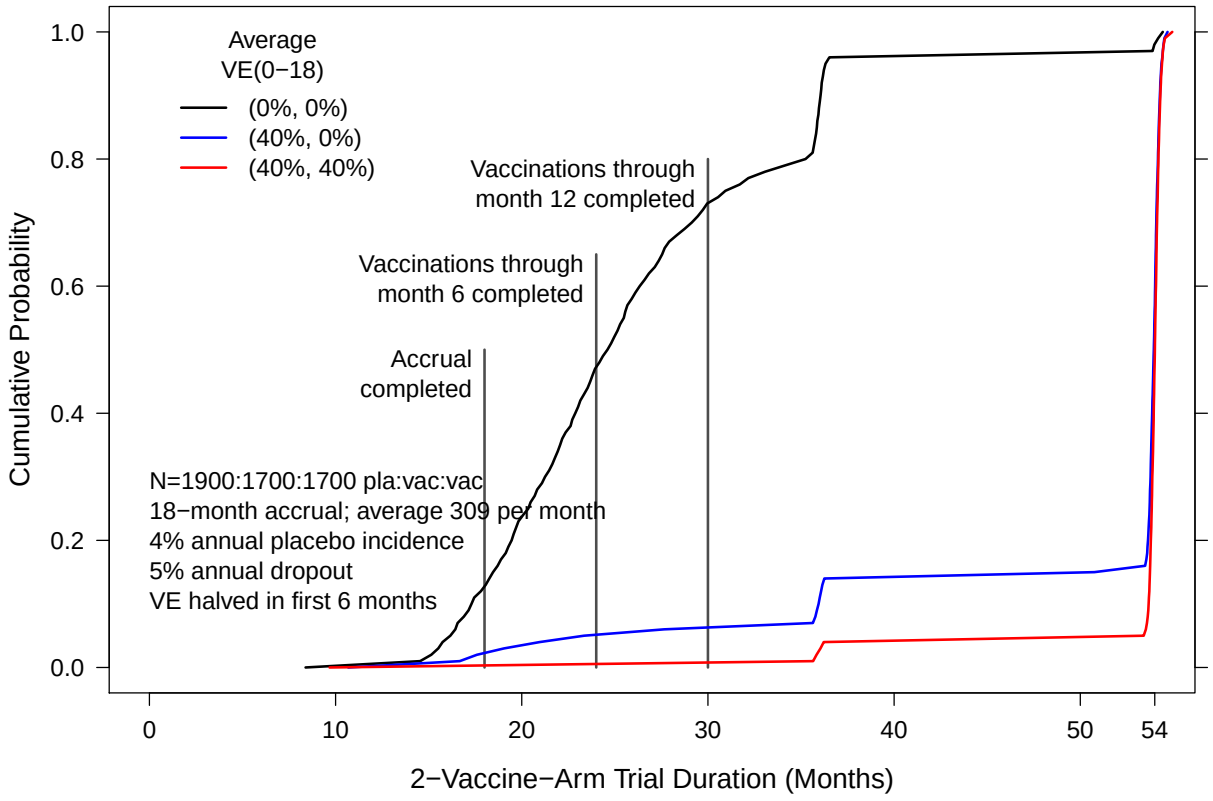


Figure 4: Total trial duration for the evaluation of 2 vaccine regimens ($N = 1700$ per arm) versus one placebo arm ($N = 1900$)

Table 2: Distribution of the number of month 6.5–18 infections per vaccine group for use in the immune correlates analysis, for vaccine regimens with average VE of 40%, halved in the initial 6 months ($N = 1900$ in the placebo group, $N = 1700$ in each vaccine group, and 5% conditional probability of having missed a vaccination given HIV-negative and ongoing at the Month 6 [Week 26] visit).

	Percentiles of distribution of number of month 6.5–18 infections per vaccine arm						
Mean	1%	5%	25%	50%	75%	95%	99%
Month 6.5–18 infections in MITT cohort							
32	8	21	28	32	36	41	44
Month 6.5–18 infections in per-protocol cohort							
30	7	19	27	31	34	39	43

N=1900:1700 MITT placebo:vaccine

5% probability of a missing vaccination

4% annual placebo group incidence

5% annual dropout

Average VE=40%, halved VE in the first 6 months

Table 3: Distribution of the number of month 6.5–24 infections per vaccine group for use in the immune correlates analysis, for vaccine regimens with average VE of 40%, halved in the initial 6 months ($N = 1900$ in the placebo group, $N = 1700$ in each vaccine group, and 5% conditional probability of having missed a vaccination given HIV-negative and ongoing at the Month 6 [Week 26] visit).

	Percentiles of distribution of number of month 6.5–24 infections per vaccine arm						
Mean	1%	5%	25%	50%	75%	95%	99%
Month 6.5–24 infections in MITT cohort							
48	8	29	44	49	54	61	65
Month 6.5–24 infections in per-protocol cohort							
46	7	29	42	47	51	58	63

N=1900:1700 MITT placebo:vaccine

5% probability of a missing vaccination

4% annual placebo group incidence

5% annual dropout

Average VE=40%, halved VE in the first 6 months

Table 4: Distribution of the number of month 6.5–36 infections per vaccine group for use in the immune correlates analysis, for vaccine regimens with average VE of 40%, halved in the initial 6 months ($N = 1900$ in the placebo group, $N = 1700$ in each vaccine group, and 5% conditional probability of having missed a vaccination given HIV-negative and ongoing at the Month 6 [Week 26] visit).

	Percentiles of distribution of number of month 6.5–36 infections per vaccine arm						
Mean	1%	5%	25%	50%	75%	95%	99%
Month 6.5–36 infections in MITT cohort							
77	8	31	73	81	88	98	105
Month 6.5–36 infections in per-protocol cohort							
74	7	29	69	77	84	93	102

N=1900:1700 MITT placebo:vaccine

5% probability of a missing vaccination

4% annual placebo group incidence

5% annual dropout

Average VE=40%, halved VE in the first 6 months

Table 5: Power (×100) to detect that relative VE(0–18) > 0% comparing head-to-head vaccine regimens 1 vs. 2 and VE(0–18) > 0% for vaccine regimen 1, and probability (×100) of correct ranking and selection of the winning most efficacious vaccine regimen

True average VE (%)[1] (Vx1, Vx2)	Power (×100) Vx1 vs. Vx2 & Vx1 vs. Placebo[2]	Probability (×100) select best vaccine[3]
(40, 0)	74.1	82.5
(40, 20)	36.7	82.6
(40, 30)	13.4	73.7
(50, 30)	42.3	94.4
(50, 40)	15.2	86.0
(60, 30)	78.9	98.4
(60, 40)	47.5	98.7

[1] VE halved in the first 6 months

[2] Cumulative incidence-based Wald tests of both Vx1/Vx2 and Vx1/Placebo VE(0–18) with 1-sided $\alpha = 0.025$

[3] Correct selection = Vx1 has highest estimated VE(0–36) and VE(0–18) significantly > 0%

N=1900:1700:1700 pla:vac:vac group

18-month accrual; average 309 per month

4% annual incidence in the placebo group

5% annual dropout

Cumulative incidence-based monitoring

Table 6: Distribution of the number of Stage 1 infections pooled over the placebo group and the vaccine group with the maximum number of infections, ignoring sequential monitoring for potential harm, non-efficacy, and high efficacy (n=1900 in the placebo group and n=1700 in each vaccine group)

Ave VE	Percentiles of distribution of number of Stage 1 infections														
(0-18)*	1%	2.5%	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%	95%	97.5%	99%
0%	176	181	184	189	195	200	203	206	209	213	217	224	229	234	238
40%	142	145	149	152	158	162	165	168	171	174	178	184	187	194	198

*VE halved in the first 6 months

N=1900:1700:1700 pla:vac:vac group

18-month accrual; average 309 per month

4% annual incidence in the placebo group

5% annual dropout

Table 7: Distribution of the number of Stage 1 infections pooled over the placebo group and the vaccine group with the maximum number of infections, accounting for sequential monitoring for potential harm, non-efficacy, and high efficacy (n=1900 in the placebo group and n=1700 in each vaccine group)

Ave VE	Percentiles of distribution of number of Stage 1 infections														
(0-18)*	1%	2.5%	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%	95%	97.5%	99%
0%	60	60	65	80	101	120	140	152	167	183	200	211	220	225	234
40%	138	144	148	152	158	162	165	168	171	174	177	184	187	194	198

*VE halved in the first 6 months

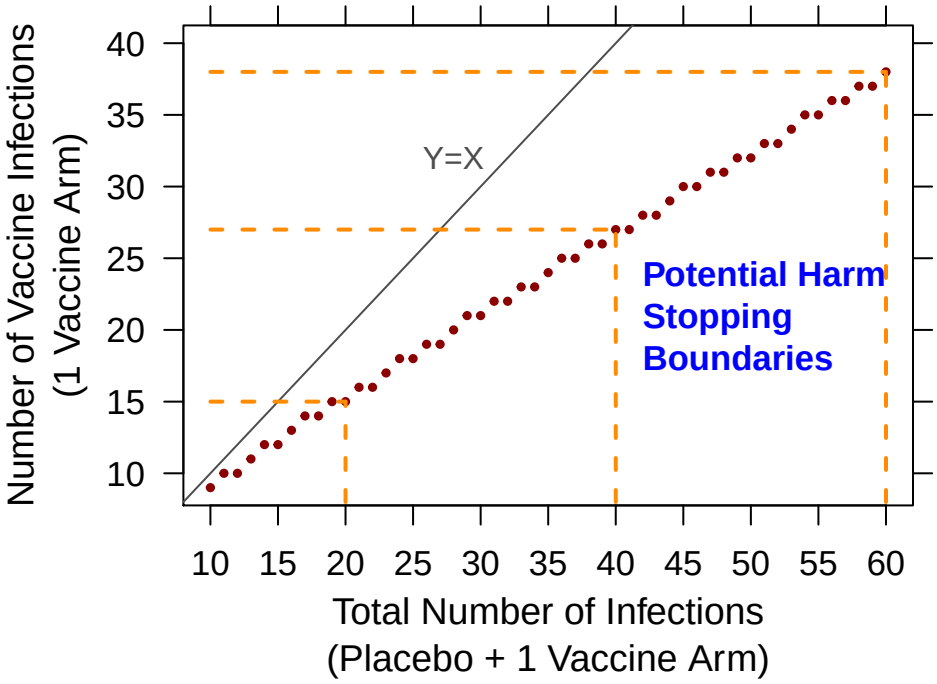
N=1900:1700:1700 pla:vac:vac group

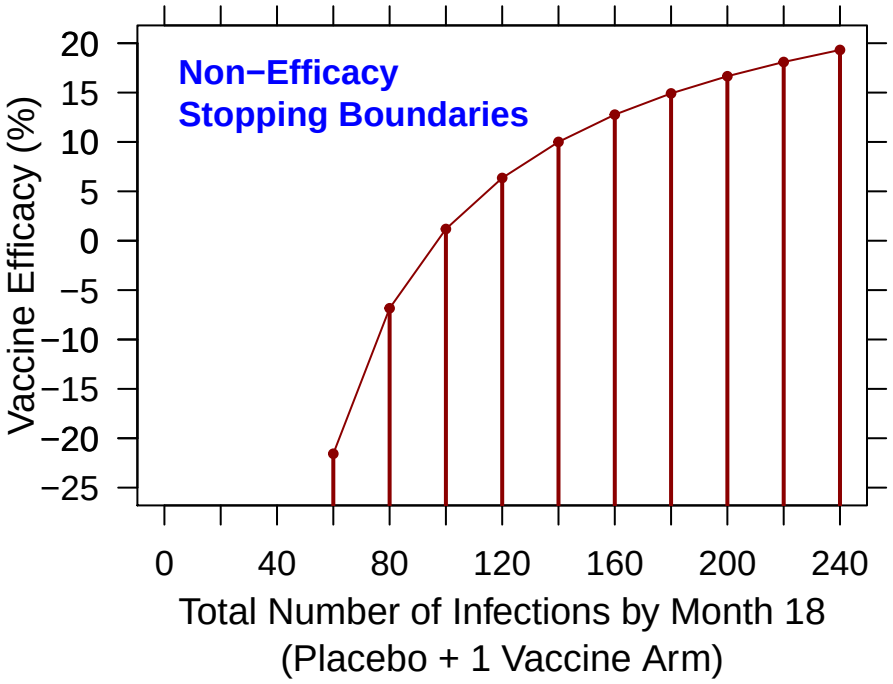
18-month accrual; average 309 per month

4% annual incidence in the placebo group

5% annual dropout

Cumulative incidence-based monitoring


Number of Vaccine Infections
(1 Vaccine Arm)
40
35
30
25
20
15
10
Y=X
Potential Harm
Stopping
Boundaries
10
15
20
25
30
35
40
45
50
55
60
Total Number of Infections
(Placebo + 1 Vaccine Arm)



Non-Efficacy Stopping*		
Total Infections	Infections Split V:P	$\widehat{\text{VE}}^{\dagger}$ (%)
60	31:29	-22
80	39:41	-7
100	47:53	1
120	55:65	6
140	62:78	10
160	70:90	13
180	78:102	15
200	85:115	17
220	93:127	18
240	101:139	19

*Ave VE=20%, halved in first 6 mo.

†Based on a binomial model