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 study design with 1 vaccine arm with 1900 placebo recipients 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	99.3	0.7	0.0	0.0
–	2.5	94.7	5.3	0.0	0.0
–	2.0	76.3	23.7	0.0	0.0
–	1.5	34.8	65.2	0.0	0.0
0%	1.0	7.2	90.7	0.0	2.1
10%	0.9	4.1	87.8	0.0	8.1
20%	0.8	2.6	69.5	0.1	27.9
30%	0.7	0.9	38.8	0.0	60.3
40%	0.6	0.6	13.6	0.6	85.8
50%	0.5	0.3	2.3	0.7	97.4
60%	0.4	0.2	0.3	4.7	99.5
70%	0.3	0.0	0.1	32.5	99.9
80%	0.2	0.0	0.0	76.5	100.0

*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

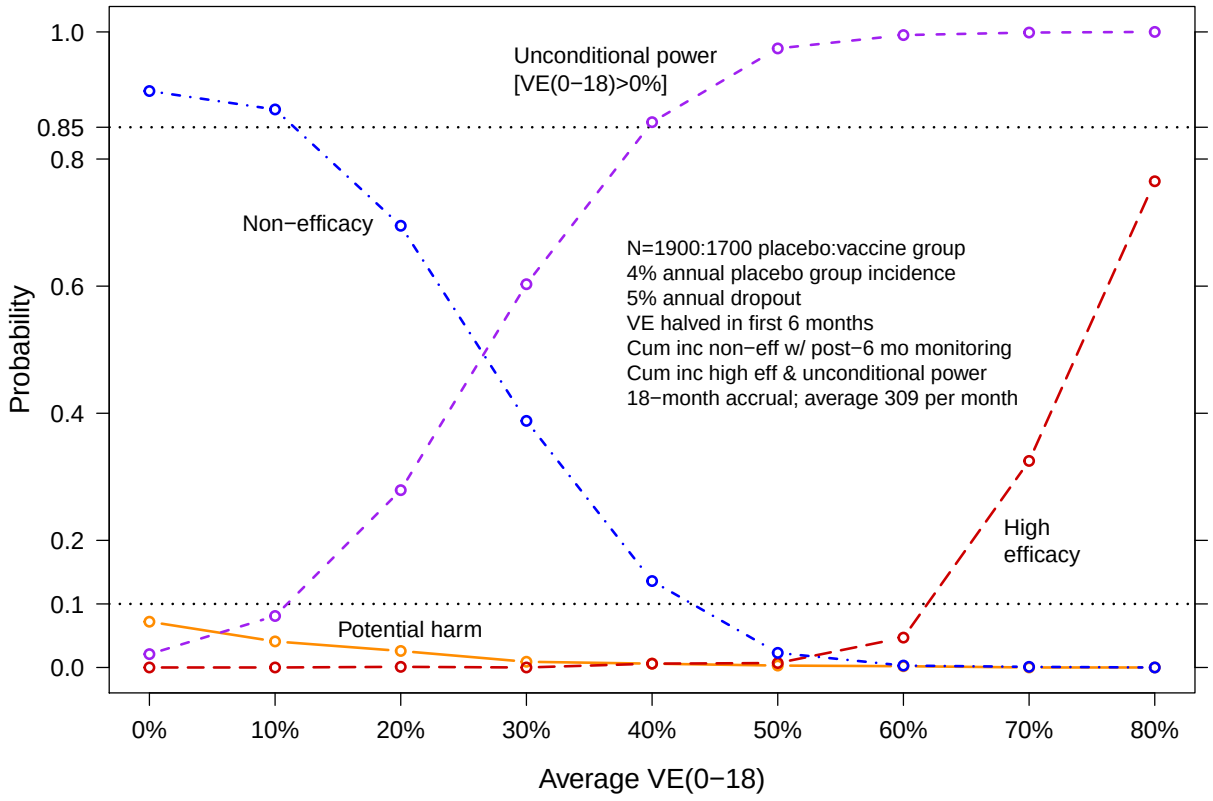


Figure 1: Probabilities of reaching each possible trial monitoring outcome, and unconditional power to reject the specified null hypothesis for a study design with 1 vaccine arm with 1900 placebo recipients and 1700 vaccine recipients

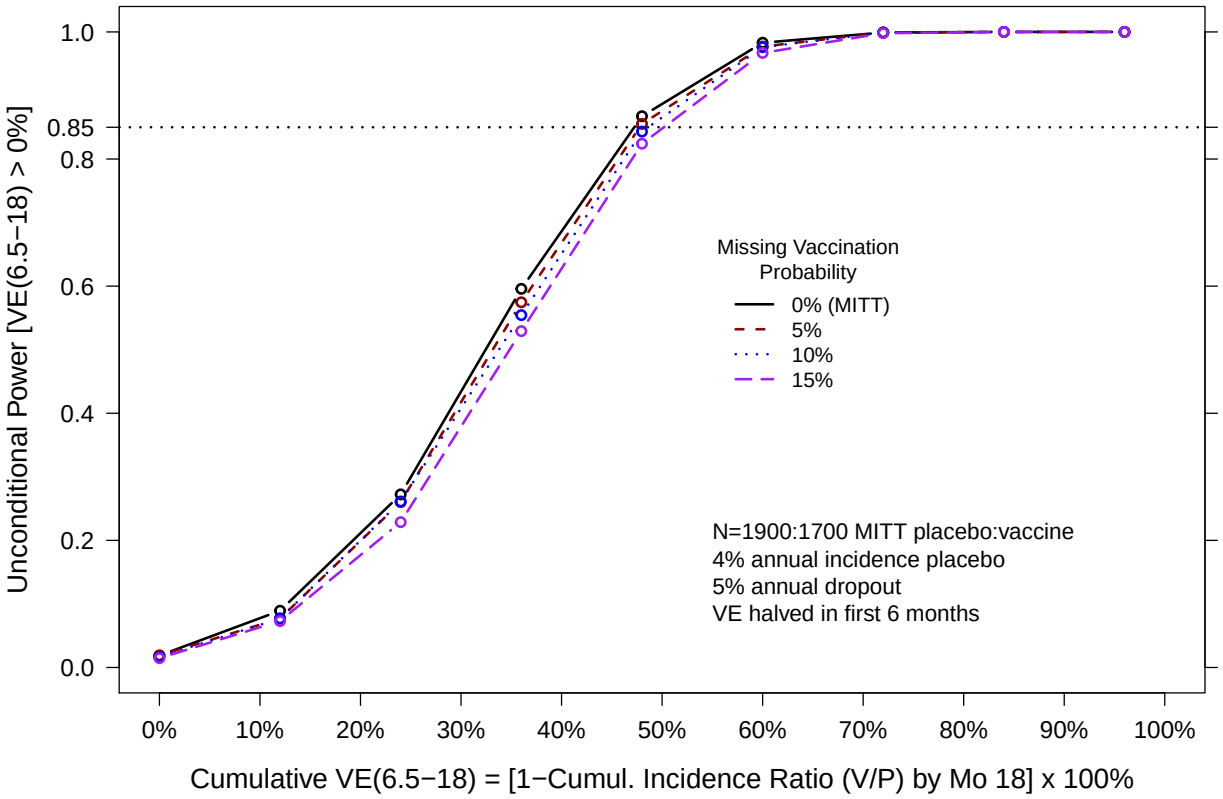


Figure 2: Unconditional power to reject the null hypothesis H_0: VE(6.5–18)$\leq$0% in per-protocol cohorts with a varying probability of a missing vaccination

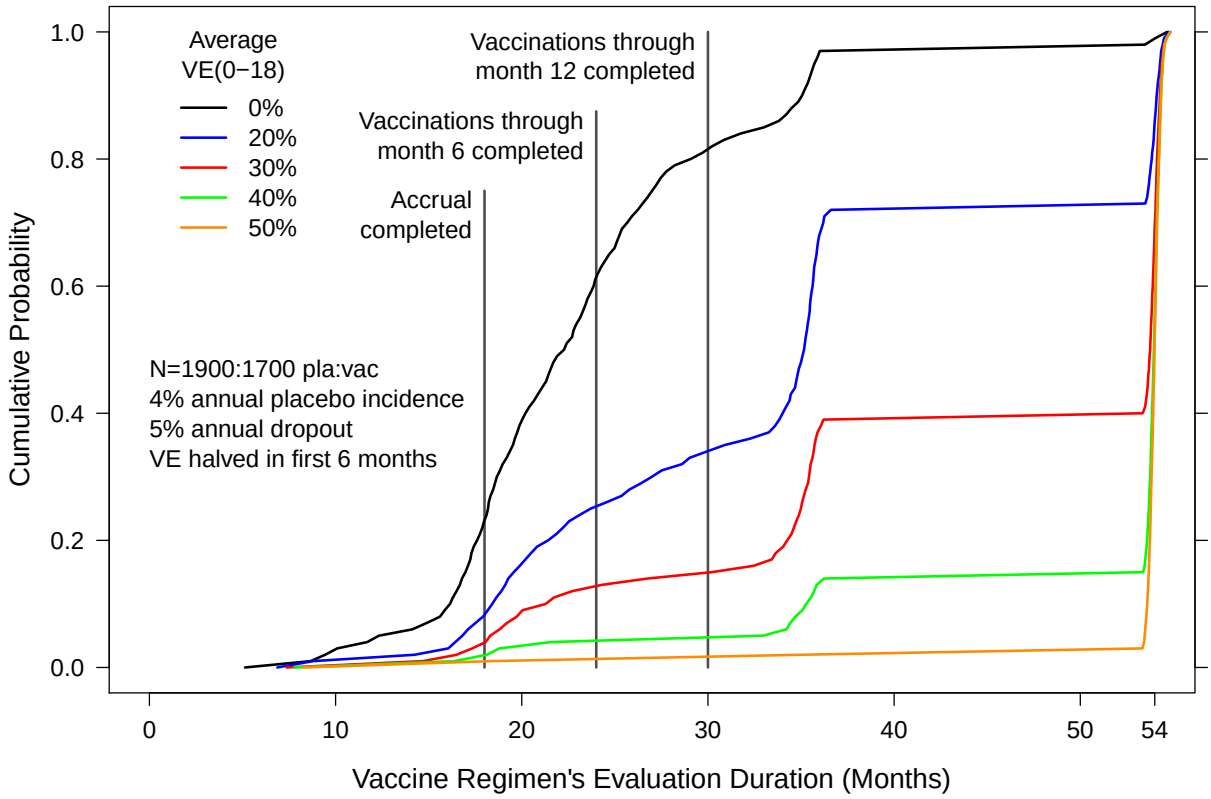


Figure 3: Duration of a vaccine regimen's evaluation (n =1900 in the placebo arm and n =1700 in the vaccine arm)

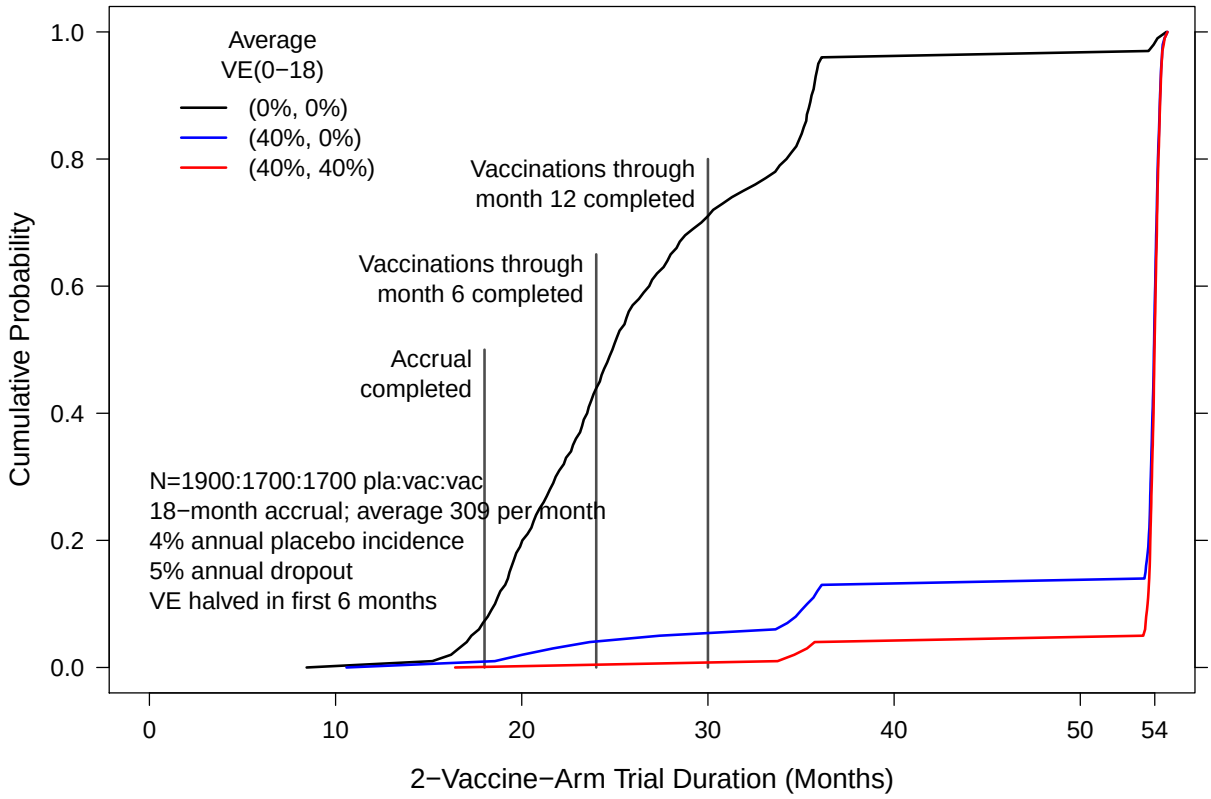


Figure 4: Total trial duration for the evaluation of 2 vaccine regimens ($N = 1700$ per arm) versus one placebo arm ($N = 1900$)

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	6	21	29	32	36	42	46
Month 6.5–18 infections in per-protocol cohort							
30	6	20	27	31	35	40	44

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							
49	6	34	45	50	55	62	68
Month 6.5–24 infections in per-protocol cohort							
47	6	33	43	48	52	59	64

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							
80	6	47	75	84	90	99	106
Month 6.5–36 infections in per-protocol cohort							
76	6	43	71	80	86	95	101

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)	77.0	84.7
(40, 20)	35.3	83.9
(40, 30)	12.2	73.1
(50, 30)	41.5	95.4
(50, 40)	14.1	85.7
(60, 30)	80.2	98.9
(60, 40)	48.0	98.4

[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%	178	182	186	189	195	200	204	207	210	214	218	224	229	233	237
40%	141	146	149	152	157	161	164	167	170	173	177	182	186	190	196

*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%	48	64	76	90	111	128	143	157	172	186	199	213	221	226	232
40%	138	145	149	152	157	161	164	167	170	173	176	182	186	190	196

*VE halved in the first 6 months

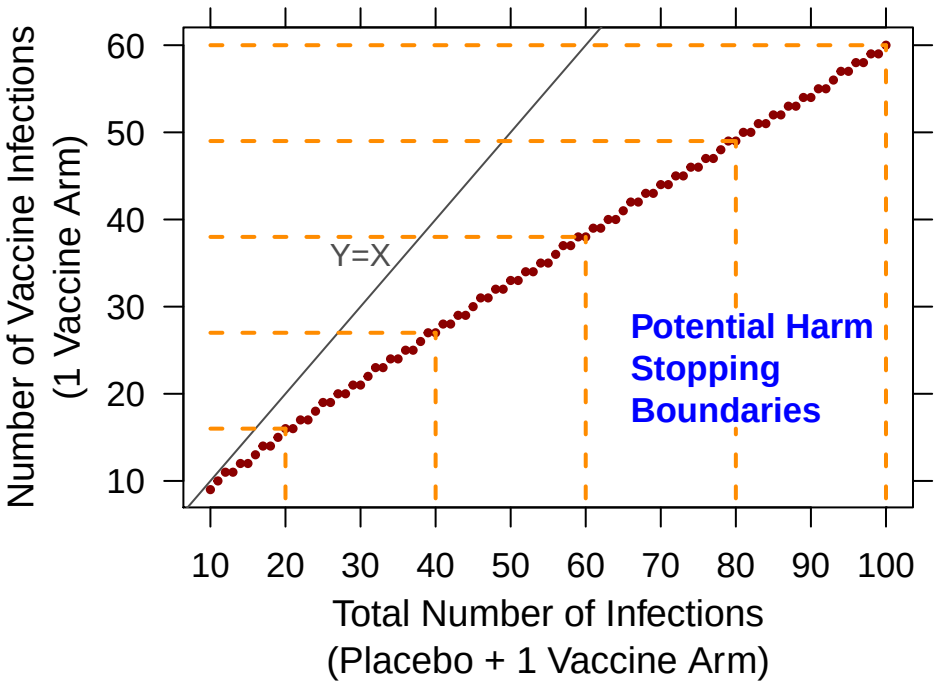
N=1900:1700:1700 pla:vac:vac group

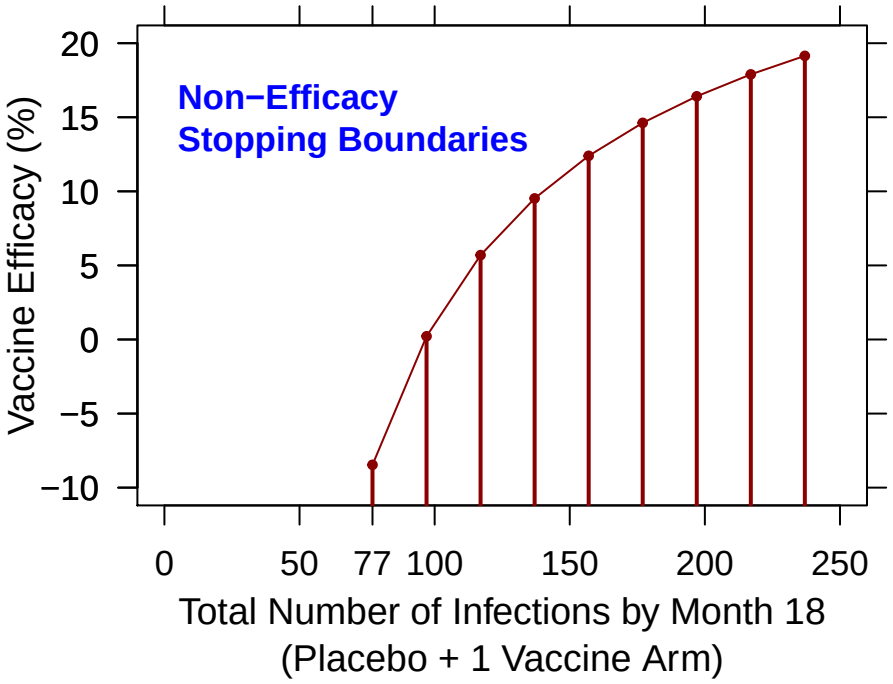
18-month accrual; average 309 per month

4% annual incidence in the placebo group

5% annual dropout

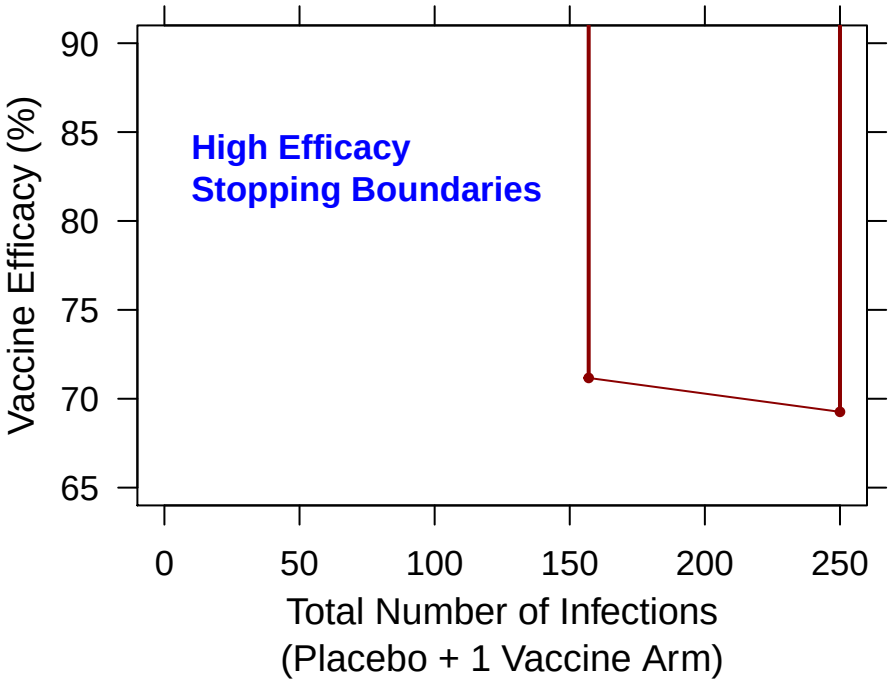
Cumulative incidence-based monitoring


Number of Vaccine Infections
(1 Vaccine Arm)
60
50
40
30
20
10
Y=X
Potential Harm
Stopping
Boundaries
10
20
30
40
50
60
70
80
90
100
Total Number of Infections
(Placebo + 1 Vaccine Arm)



Non-Efficacy Stopping*		
Total Infections	Infections Split V:P	$\widehat{\text{VE}}$ (%)
77	38:39	-8
97	46:51	0
117	54:63	6
137	61:76	10
157	69:88	12
177	77:100	15
197	84:113	16
217	92:125	18
237	99:138	19

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



High Efficacy Stopping*		
Total Infections	Infections Split V:P	$\widehat{\text{VE}}$ (%)
157	32:125	71
250	54:196	69

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