BIOE 301

Lecture Seventeen

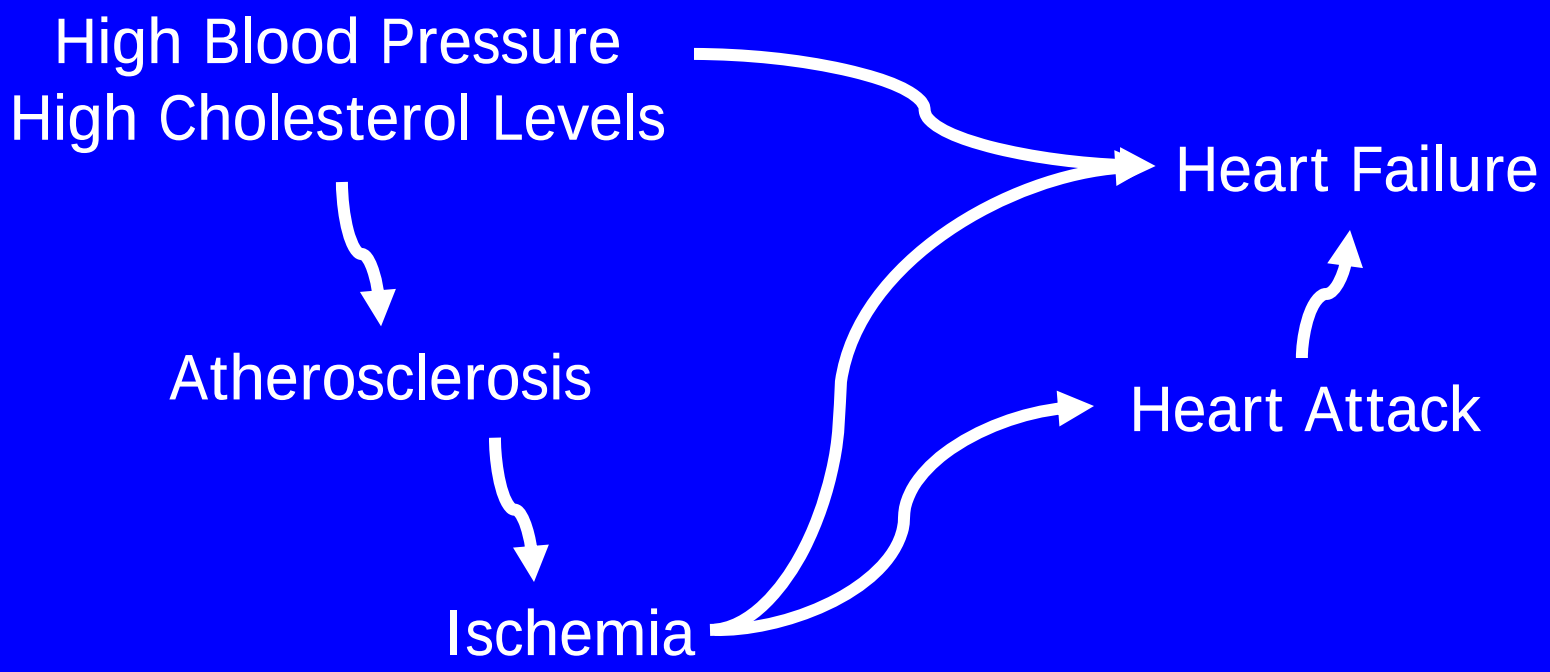
Guest Speaker

- Jay Brollier
  - World Camp Malawi

Update: Health Care Reform

- House passes health care reform bill
  - http://www.npr.org/templates/story/story.php?storyId=120234224
  - http://www.npr.org/templates/story/story.php?storyId=120234413
- Kaiser Family Foundation Comparison Chart
  - http://www.kff.org/healthreform/sidebyside.cfm

Progression of Heart Disease



Review of Last Time

- What is heart failure?
  - Occurs when left or right ventricle loses the ability to keep up with amount of blood flow
- How do we treat heart failure?
  - Heart transplant
    - Rejection, inadequate supply of donor hearts
  - LVAD
    - Can delay progression of heart failure
  - Artificial heart

Prevention of Heart Disease

- 1990s:
  - Small series of trials suggested that high doses of Vitamin E might reduce risk of developing heart disease by 40%
- 1996: Randomized clinical trial:
  - 1035 patients taking vitamin E
  - 967 patients taking placebo
  - Vitamin E provides a protective effect

Prevention of Heart Disease

- 2000: pivotal clinical trial
  - 9,541 patients
  - No benefit to Vitamin E
  - Followed for 7 years: may increase risk of heart disease
- What happened?

Challenges: Clinical Research

- Early studies, small # patients:
  - Generate hypotheses
- Larger studies
  - Rigorously test hypotheses
- Due to biological variability:
  - Larger studies often contradict early studies
- Recent study:
  - 1/3 of highly cited studies - later contradicted!
  - More frequent if patients aren't randomized

Types of Clinical Studies

- Hypothesis Generation
  - Case study, case series: examine patient or group of patients with similar illness

- Hypothesis Testing:
  - Observational:
    - Identify group of patients with and without disease. Collect data. Use to test our hypothesis.
    - Advantage: Easy, cheap.
    - Disadvantage: Bias. Can't control the interventional to decisively show cause and effect.

Types of Clinical Studies

- Hypothesis Testing:
  - Experimental:
    - Clinical trial: Research study to evaluate effect of an intervention on patients.
    - Isolate all but a single variable and measure the effect of the variable.
    - Done prospectively: Plan, then execute.
    - Single arm study: Take patients, give intervention, compare to baseline. Can suffer from placebo effect.
    - Randomized clinical trials: Different subjects are randomly assigned to get the treatment or the control.

Planning a Randomized Clinical Trial

- Two arms:
  - Treatment group
  - Control group
- Outcome:
  - Primary outcome
  - Secondary outcomes
- Sample size:
  - Want to ensure that any differences between treatment and control group are real
  - Must consider $$ available

Example – Planning a Clinical Trial

- New drug eluting stent
- Treatment group:
- Control group:
- Primary Outcome:
- Secondary Outcomes:

Sample Size Calculation

- There will be some statistical uncertainty associated with the measured restenosis rate
- Goal:
  - Uncertainty << Difference in primary outcome between control & treatment group
  - Choose our sample size so that this is true

Types of Errors in Clinical Trial

- Type I Error:
  - We mistakenly conclude that there is a difference between the two groups, when in reality there is no difference
- Type II Error:
  - We mistakenly conclude that there is not a difference between the two, when in reality there is a difference
- Choose our sample size:
  - Acceptable likelihood of Type I or II error
  - Enough $$ to carry out the trial

Types of Errors in Clinical Trial

- Type I Error:
  - We mistakenly conclude that there IS a difference between the two groups
  - p-value – probability of making a Type I error
  - Usually set p = 1% - 5%
- Type II Error:
  - We mistakenly conclude that there IS NOT a difference between the two
  - Beta – probability of making a Type II error
  - Power
    - = 1 – beta
    - = 1 – probability of making a Type II error
  - Usually set beta = 10 - 20%

How do we calculate n?

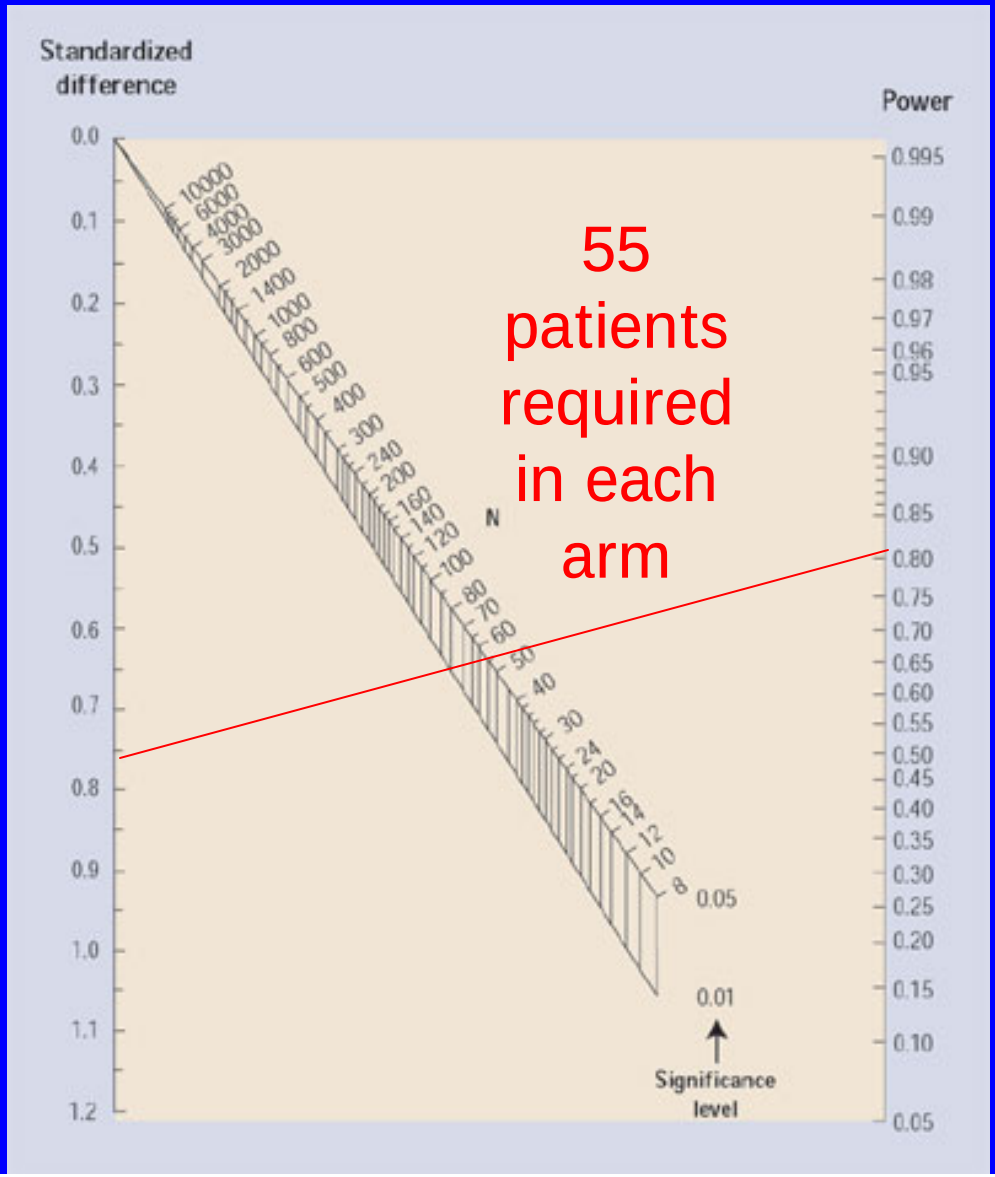
- Select primary outcome
- Estimate expected rate of primary outcome in:
  - Treatment group
  - Control group
- Set acceptable levels of Type I and II error
  - Choose p-value
  - Choose beta

How do we calculate n?

- Calculate standardized difference:
  - SD = P_1-P_2/sqrt(p(1-p))
  - p = (P_1+P_2)/2
  - P_1 = fraction of patients in treatment group who experience primary outcome
  - P_2 = fraction of patients in control group who experience primary outcome
- Use Altman's nomogram to determine n

Drug Eluting Stent – Sample Size

- Treatment group:
  - Receive stent
- Control group:
  - Get angioplasty
- Primary Outcome:
  - 1 year restenosis rate
- Expected Outcomes:
  - Stent: 10%
  - Angioplasty: 45%
- Error rates:
  - p = 0.05
  - Beta = 0.2
- SD = 0.78



Data & Safety Monitoring Boards

- DSMB:
  - Special committees to monitor interim results in clinical trials.
  - Federal rules require all phase III trials be monitored by DSMBs.
  - Can stop trial early:
    - New treatment offered to both groups.
    - Prevent additional harm.

DSMBs

- New treatment for sepsis:
  - New drug
  - Placebo
  - n = 1500
- Interim analysis after 722 patients:
  - Mortality in placebo group: 38.9%
  - Mortality in treatment group: 29.1%
  - Significant at the p = 0.006 level!
- Should the study be stopped?

DSMBs

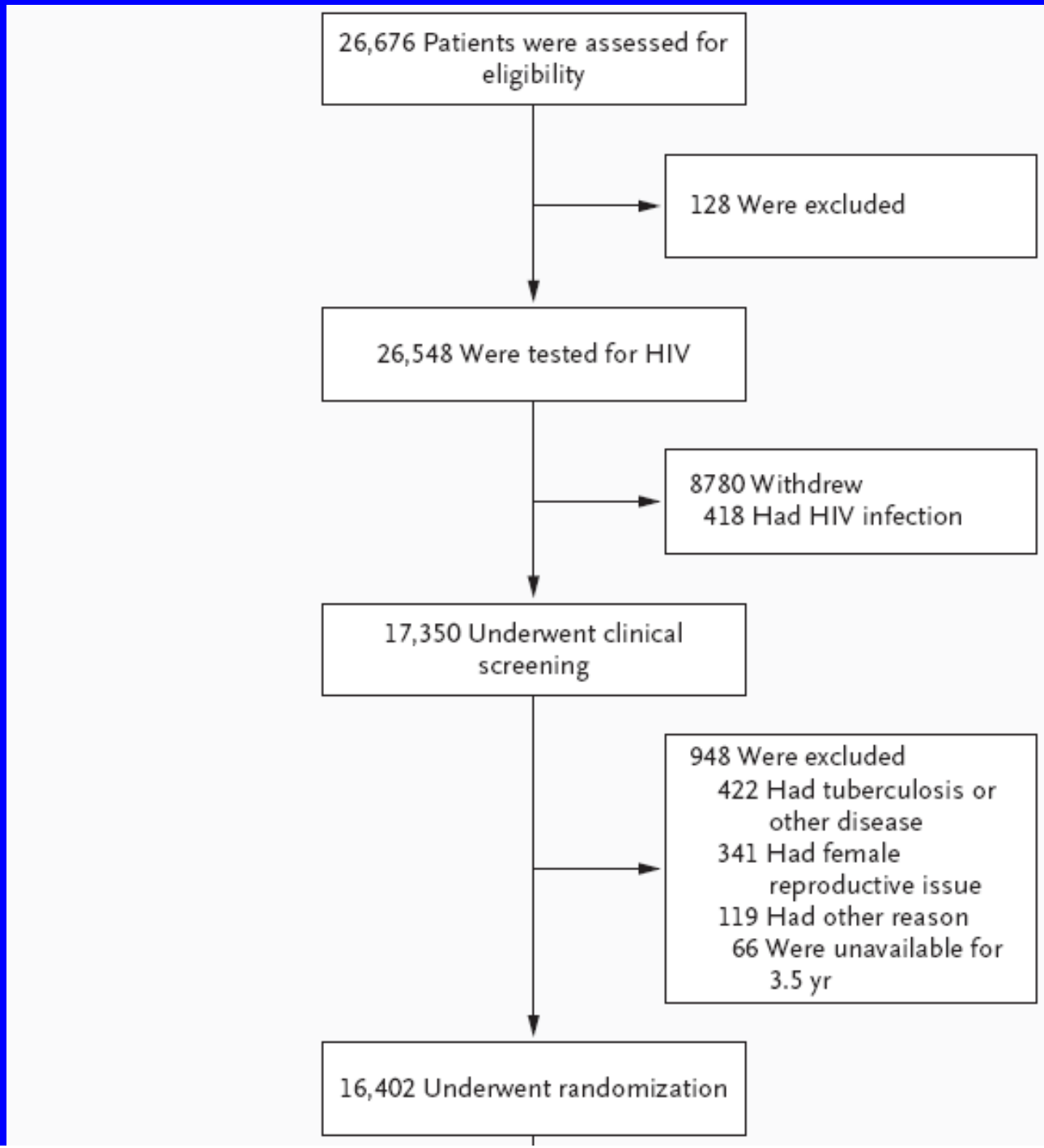
- Decision:
  - No
  - Neither researchers nor subjects were informed
- Outcome:
  - Mortality in placebo group: 33.9%
  - Mortality in treatment group: 34.2%
  - Difference was neither clinically nor statistically significant!
- Informed consents should be modified to indicate if a trial is monitored by a DSMB.

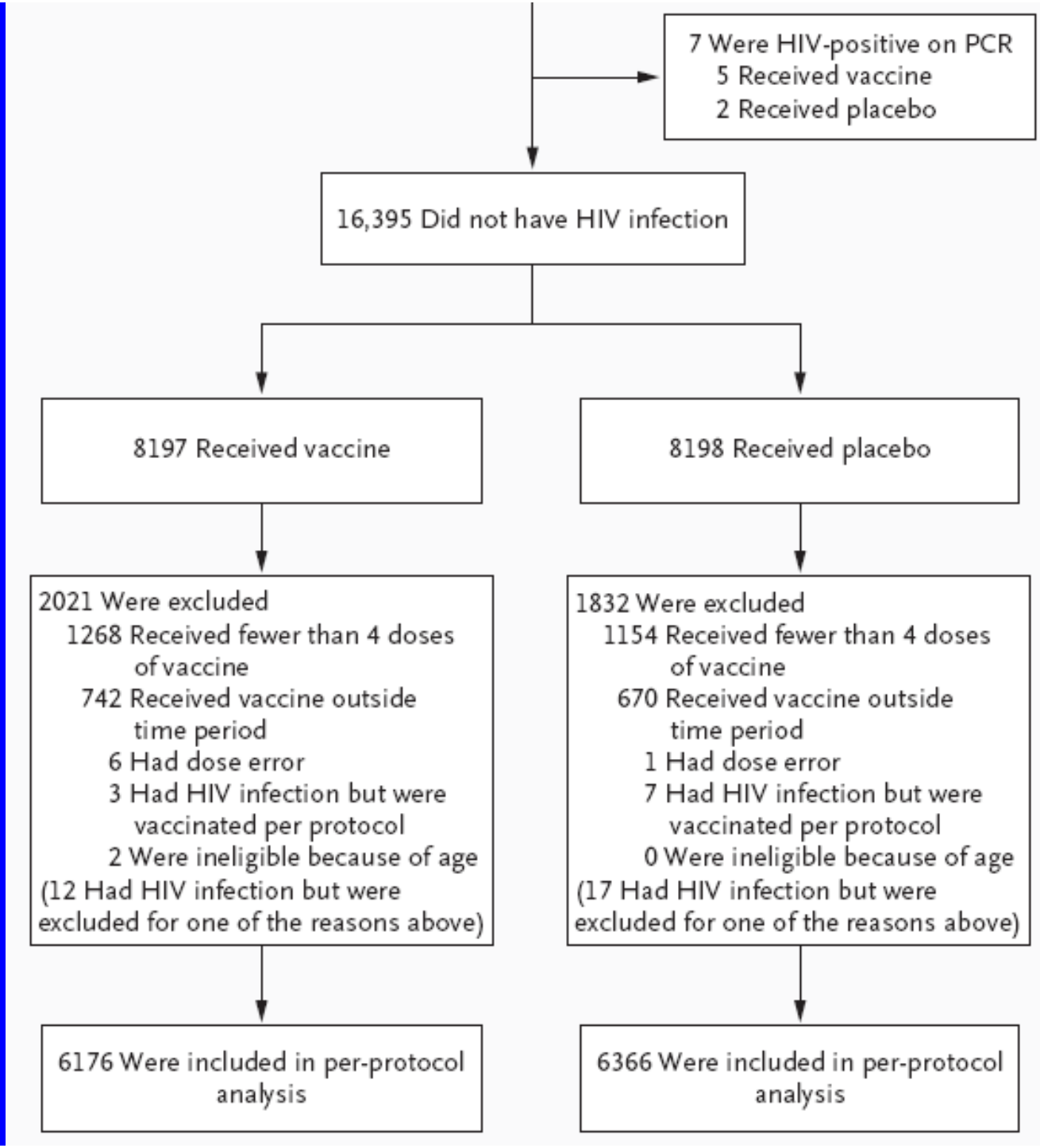
The NEW ENGLAND JOURNAL of MEDICINE

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

RESULTS

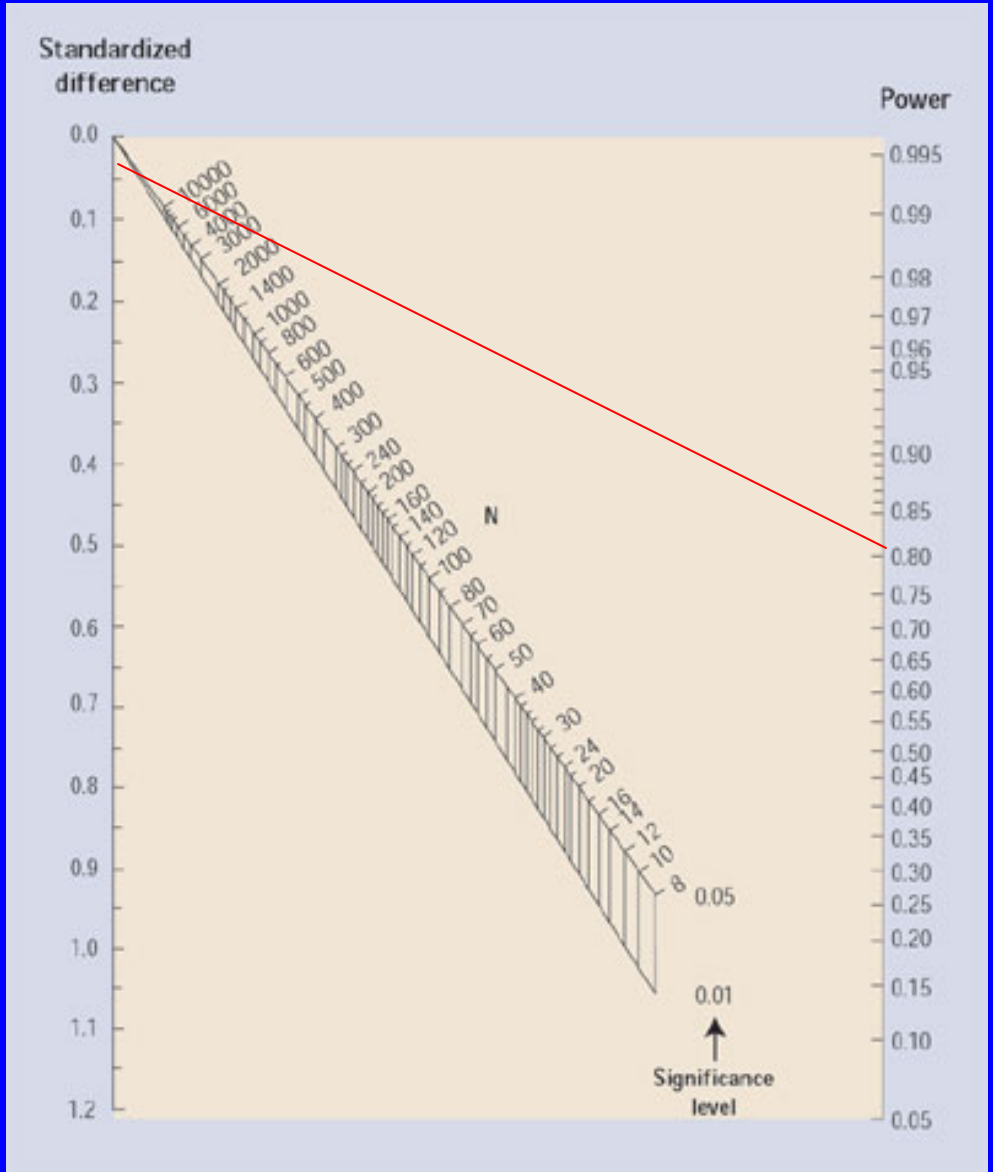
In the intention-to-treat analysis involving 16,402 subjects, there was a trend toward the prevention of HIV-1 infection among the vaccine recipients, with a vaccine efficacy of 26.4% (95% confidence interval [CI], −4.0 to 47.9; P=0.08). In the per-protocol analysis involving 12,452 subjects, the vaccine efficacy was 26.2% (95% CI, −13.3 to 51.9; P=0.16). In the modified intention-to-treat analysis involving 16,395 subjects (with the exclusion of 7 subjects who were found to have had HIV-1 infection at baseline), the vaccine efficacy was 31.2% (95% CI, 1.1 to 51.2; P=0.04). Vaccination did not affect the degree of viremia or the CD4+ T-cell count in subjects in whom HIV-1 infection was subsequently diagnosed.


26,676 Patients were assessed for eligibility
128 Were excluded
26,548 Were tested for HIV
8780 Withdrew
418 Had HIV infection
17,350 Underwent clinical screening
948 Were excluded
422 Had tuberculosis or other disease
341 Had female reproductive issue
119 Had other reason
66 Were unavailable for 3.5 yr
16,402 Underwent randomization

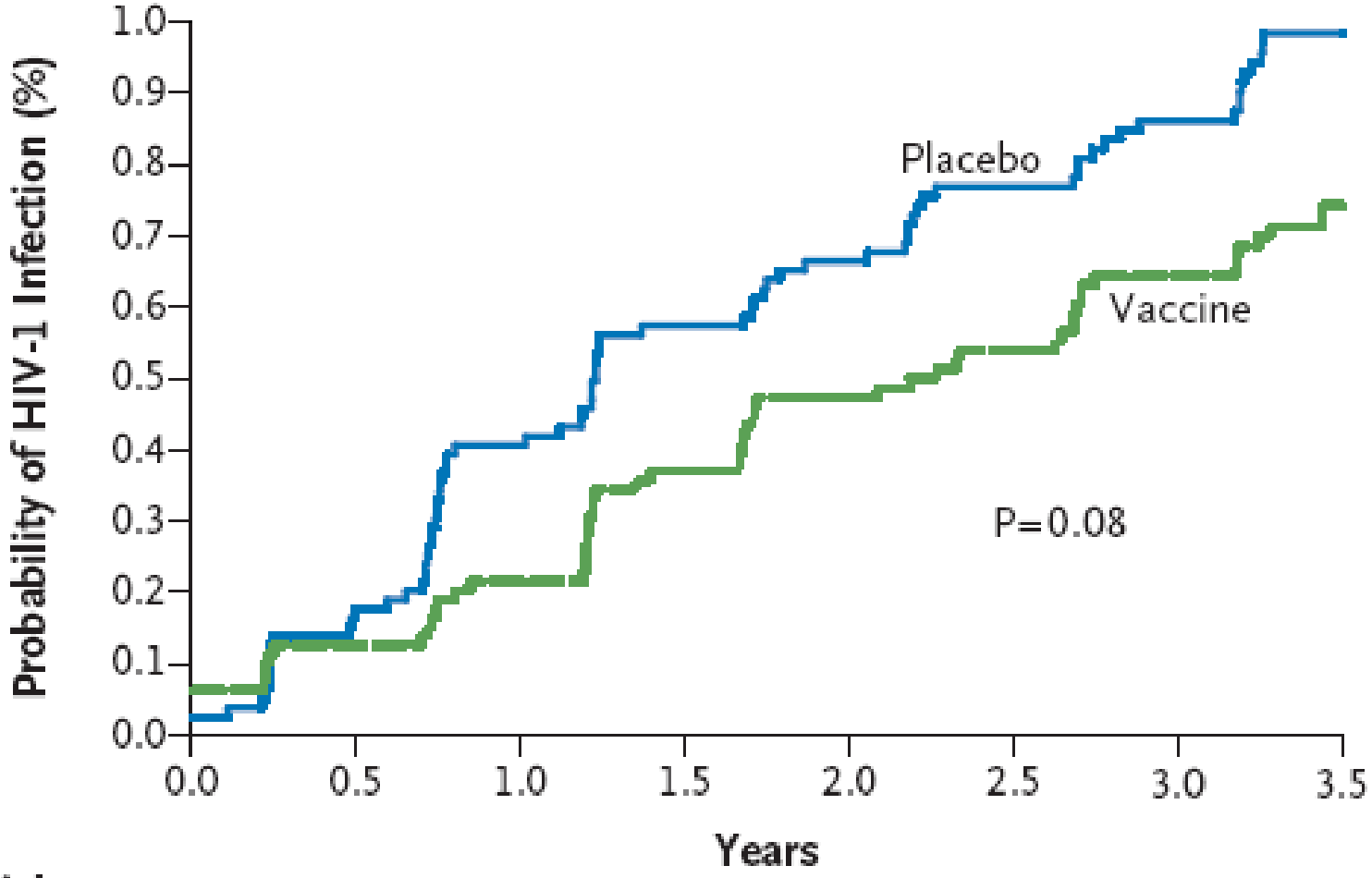

7 Were HIV-positive on PCR
5 Received vaccine
2 Received placebo
16,395 Did not have HIV infection
8197 Received vaccine
8198 Received placebo
2021 Were excluded
1268 Received fewer than 4 doses of vaccine
742 Received vaccine outside time period
6 Had dose error
3 Had HIV infection but were vaccinated per protocol
2 Were ineligible because of age
(12 Had HIV infection but were excluded for one of the reasons above)
1832 Were excluded
1154 Received fewer than 4 doses of vaccine
670 Received vaccine outside time period
1 Had dose error
7 Had HIV infection but were vaccinated per protocol
0 Were ineligible because of age
(17 Had HIV infection but were excluded for one of the reasons above)
6176 Were included in per-protocol analysis
6366 Were included in per-protocol analysis

AIDS Vaccine Trial– Sample Size

- Treatment group:
  - Receive vaccine
- Control group:
  - Receive placebo
- Primary Outcome:
  - HIV Infection Rate
- Expected Outcomes:
  - Vaccine: 1%
  - Placebo: 0.7%
- Error rates:
  - p = 0.05
  - Beta = 0.2
- SD = 0.033

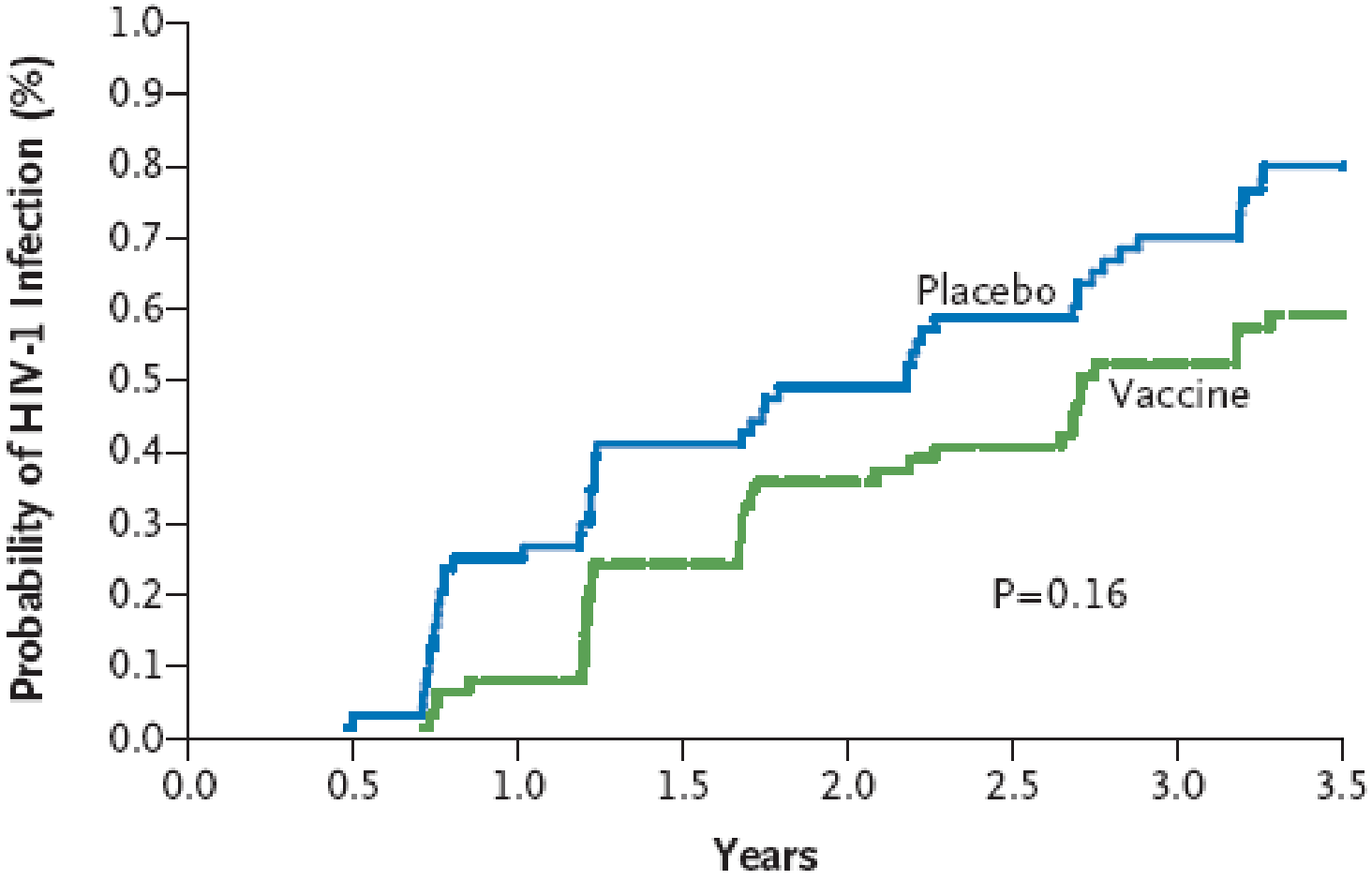


A Intention-to-Treat Analysis



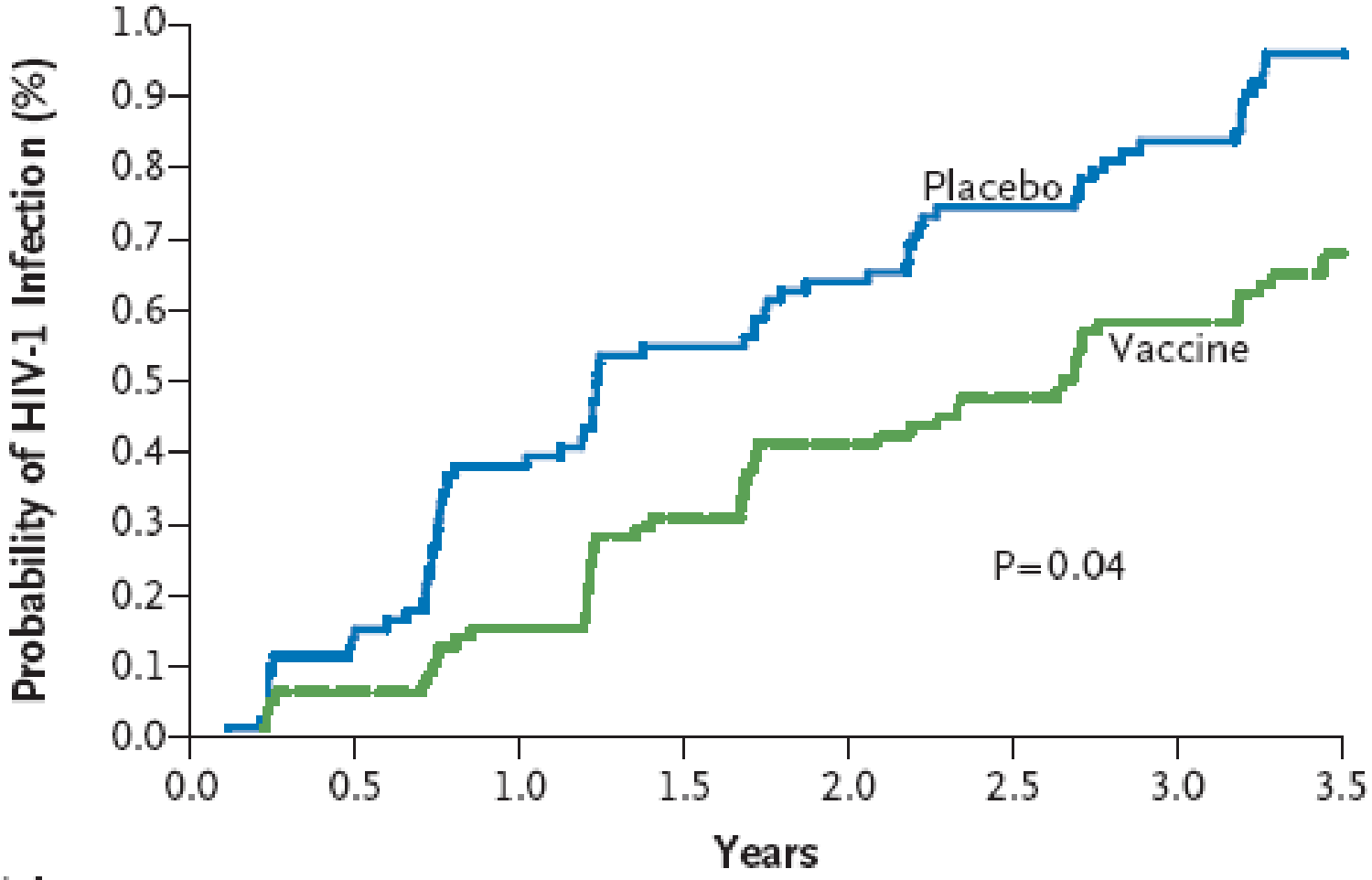
No. at Risk					
Placebo	8200	7775	7643	7441	7325
Vaccine	8202	7797	7665	7471	7347
Cumulative No. of Infections					
Placebo		32	52	67	76
Vaccine		17	37	50	56

B Per-Protocol Analysis



No. at Risk					
Placebo	6366	6283	6220	6089	6002
Vaccine	6176	6140	6068	5958	5874
Cumulative No. of Infections					
Placebo		16	31	44	50
Vaccine		5	22	32	36

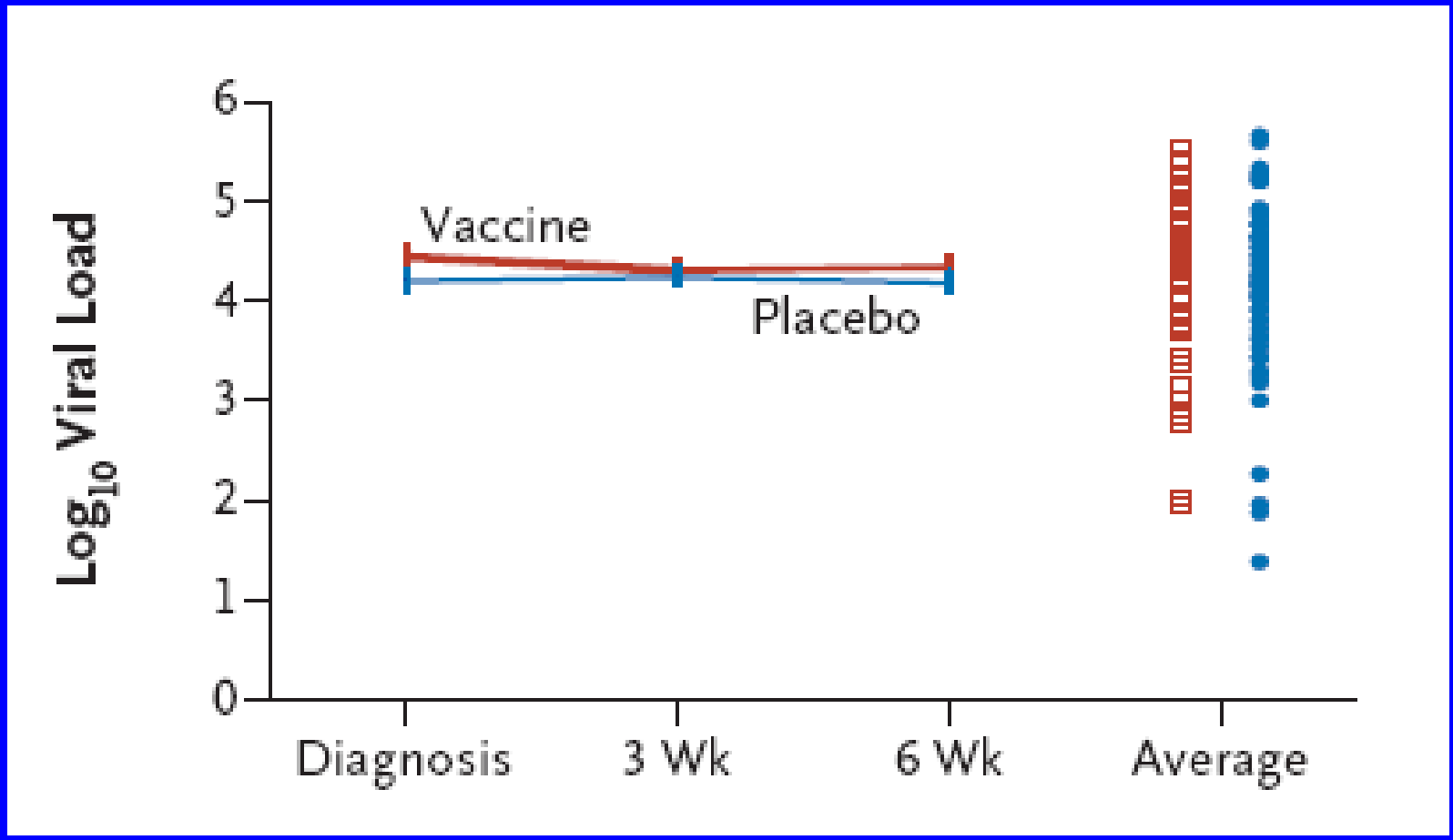
C Modified Intention-to-Treat Analysis



No. at Risk					
Placebo	8198	7775	7643	7441	7325
Vaccine	8197	7797	7665	7471	7347
Cumulative No. of Infections					
Placebo		30	50	65	74
Vaccine		12	32	45	51

Table 2. Rate of HIV Infection and Vaccine Efficacy, According to Selected Baseline Variables (Modified Intention-to-Treat Population).

Variable	Vaccine (N=8197)				Placebo (N=8198)				Vaccine Efficacy
	No. Evaluated	No. with Infection	No. of Person-Years	Rate	No. Evaluated	No. with Infection	No. of Person-Years	Rate	
				no./person-yr				*no./person-yr*	*% (95% CI)*
All subjects	7960	51	26,507	0.192	7988	74	26,478	0.279	31.2 (1.7 to 51.8)
Sex									
Male	4875	32	16,221	0.197	4885	43	16,179	0.266	25.8 (–17.3 to 53.0)
Female	3085	19	10,286	0.185	3103	31	10,300	0.301	38.6 (–8.6 to 65.3)
Age group									
≤20 yr	2228	12	7,358	0.163	2185	11	7,216	0.152	7.1 (–143.0 to 52.7)
21–25 yr	3517	20	11,713	0.171	3610	40	11,946	0.335	49 (12.8 to 70.2)
≥26 yr	2215	19	7,437	0.255	2193	23	7,316	0.314	18.7 (–49.3 to 55.7)
Living with partner									
Yes	4017	19	13,466	0.141	4083	34	13,612	0.25	43.5 (1.0 to 67.8)
No	3943	32	13,041	0.245	3905	40	12,866	0.311	21 (–25.7 to 50.4)
Risk group									
Low	3767	17	12,565	0.135	3837	29	12,798	0.227	40.4 (–8.5 to 67.2)
Medium	2297	12	7,642	0.157	2222	22	7,353	0.299	47.6 (–6.0 to 74.0)
High	1896	22	6,300	0.349	1929	23	6,327	0.364	3.7 (–72.7 to 46.3)


Log10 Viral Load
6
5
4
3
2
1
0
Vaccine
Placebo
Diagnosis
3 Wk
6 Wk
Average