Simultaneous Confidence Bounds for Relative Risks in Multiple Comparisons to Control

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Outline

- Introduction
  - Wald interval
  - Score interval
  - Bonferroni correction
  - Correlation matrix of Wald and score test statistics

- Better Intervals?
  - C.I. through inverting minimum test statistic
  - Handling of nuisance parameters in correlation matrix
    - Sidak critical value
    - Dunnett critical value
    - Berger-Boos critical value
  - Performance: Coverage/Power

- Example
  - Phase III clinical trial on efficacy of influenza vaccines
    - Two active treatments and one control
    - Goal: Establish superiority of at least one treatment versus control

Motivating Example

- Study: 11,700 subjects randomized to three groups:

  3900 in each of the two treatment groups (cell and egg-derived influenza vaccines) and the placebo group

- Goal: Establish superiority of the cell- and egg-derived vaccines over placebo

- Superiority defined as at least a 40% reduction in the probability of acquiring influenza relative to placebo.

Notation and Setup

$$Y_i \sim \text{Bin}(n_i, \pi_i), i = 0, 1, 2$$

$$\rho_1 = \pi_1/\pi_0$$

$$\rho_2 = \pi_2/\pi_0$$

Test: $H_{0i} : \rho_i = \rho_i^0$ versus $H_{Ai} : \rho_i < \rho_i^0$ for $i = 1, 2$

For our case: superiority bounds equal to $\rho_1^0 = \rho_2^0 = 0.6$

To judge **size** of effects, i.e.,
the smallest possible reduction:
need simultaneous (upper) confidence bounds

Notation and Setup

Wald Confidence bounds:

Inverting Wald test statistic based on log relative risk

$$T_i^{(1)} = (\log \hat{\rho}_i - \log \rho_i^0) \Big/ \sqrt{(n_i - y_i)/(n_i y_i) + (n_0 - y_0)/(n_0 y_0)}$$

(Katz et al., Biometrics, 1978)

results in upper bounds

$$U_i = \exp\left\{\log \hat{\rho}_i - c\sqrt{(n_i - y_i)/(n_i y_i) + (n_0 - y_0)/(n_0 y_0)}\right\}$$

Notation and Setup

Inverting Score test statistic

$$S_i = (\hat{\pi}_i - \rho_i^0 \hat{\pi}_0) \Big/ \sqrt{\frac{\rho_i^0 \tilde{\pi}_{0(i)}(1 - \rho_i^0 \tilde{\pi}_{0(i)})}{n_i} + (\rho_i^0)^2 \frac{\tilde{\pi}_{0(i)}(1 - \tilde{\pi}_{0(i)})}{n_0}}$$

where $\tilde{\pi}_{0(i)}$ is restricted MLE under H_{0i} (closed form)

(Koopman, Biometrics, 1984 ; Miettinen and Nurminen, Statistics in Medicine, 1985)

results in upper bounds implicitly given by (no closed form)

$$\{\rho_i^0 : S_i(\rho_i^0) > c\}$$

Solved easily by interval halving

- How to select c? For simultaneous upper bounds:

  Bonferroni Correction: $c = z_{\alpha/r}$

Bonferroni Solution

Our data:

$$n_0 = n_1 = n_2 = 3900$$

$$y_0 = 70, y_1 = 26 \text{ and } y_2 = 24$$

Table 1: 97.5% simultaneous upper confidence bounds for the relative risks ρ_1 and ρ_2 comparing cell- and egg-derived vaccines to placebo using the Bonferroni correction.

	Method		
	$\log RR$	score	Exact*
ρ_1	0.620	0.616	0.612
ρ_2	0.581	0.578	0.573

* Using Cytel's StatXact Version 8

Better Intervals?

- Under the null hypotheses $H_{0i} : \rho_i = \rho_i^0, i = 1, \ldots, r,$ (T_1,T_2,…,T_r) and (S_1,S_2,…,S_r) are asympt. multivariate normal.
  Off-diagonal elements of correlation matrix:

$$\lambda_{ij} = \frac{\sigma_{ij}}{\sigma_i \sigma_j} = \left(1 + \frac{n_0}{n_i} \frac{1 - \rho_i^0 \pi_0}{\rho_i^0 - \rho_i^0 \pi_0}\right)^{-1/2} \left(1 + \frac{n_0}{n_j} \frac{1 - \rho_j^0 \pi_0}{\rho_j^0 - \rho_j^0 \pi_0}\right)^{-1/2} := \lambda_i \lambda_j$$

- Bonferroni critical value doesn’t take advantage of correlation
- Goal: Derive test (i.e. critical value) that takes advantage of correlation

Better Intervals?

- The smaller T_i or S_i, the more evidence against H_{0i}:
  Test statistic: Minimum of T_i (or S_i)
- Need to find a critical value *c* such that type I error when
  $$\text{rejecting } H_0 \text{ if } \min_i T_i < c$$
  is controlled at level α.
- Problem: The correlation matrix depends on the unknown nuisance parameter π_0, and hence the distribution of the minimum depends on π_0

Better Intervals?

- Need to control worst possible Type I error:

$$\sup_{\pi_0} P_{\mathrm{Corr}(\boldsymbol{T})=\Lambda(\pi_0)}(\min_i T_i < c)$$

- Consider Slepian's Inequality: Let $\Lambda(\pi_0) \geq \Gamma$

$$P_{\mathrm{Corr}(\boldsymbol{T})=\Lambda(\pi_0)}(T_1 \geq c, \ldots, T_r \geq c) \geq P_{\mathrm{Corr}(\boldsymbol{T})=\Gamma}(T_1 \geq c, \ldots, T_r \geq c)$$

- This leads to:

$$\begin{aligned} \sup_{\pi_0} P_{\mathrm{Cov}(\boldsymbol{T})=\Lambda(\pi_0)}(\min_i T_i < c) &= \sup_{\pi_0} \left[1 - P_{\mathrm{Cov}(\boldsymbol{T})=\Lambda(\pi_0)}(T_1 \geq c, \ldots, T_r \geq c)\right] \\ &\leq 1 - P_{\mathrm{Cov}(\boldsymbol{T})=\Gamma}(T_1 \geq c, \ldots, T_r \geq c) = \alpha \end{aligned}$$

c is chosen as the solution to $P_{\mathrm{Cov}(\boldsymbol{T})=\Gamma}(T_1 > c, \ldots, T_r > c) = 1 - \alpha$

Better Intervals?

- Construct matrix Γ:

  For the case $\rho_i^0 \geq 1$, indeed $\lambda_i > \left(1 + \frac{n_0}{n_i}\frac{1}{\rho_i^0}\right)^{-1/2}$

- However, for the more interesting case $0 < \rho_i^0 < 1$

  λ_i is monotonically decreasing in π_0

  trivial lower bound $\lambda_i > \gamma_i \equiv 0$

- So, set Γ equal to the identity matrix

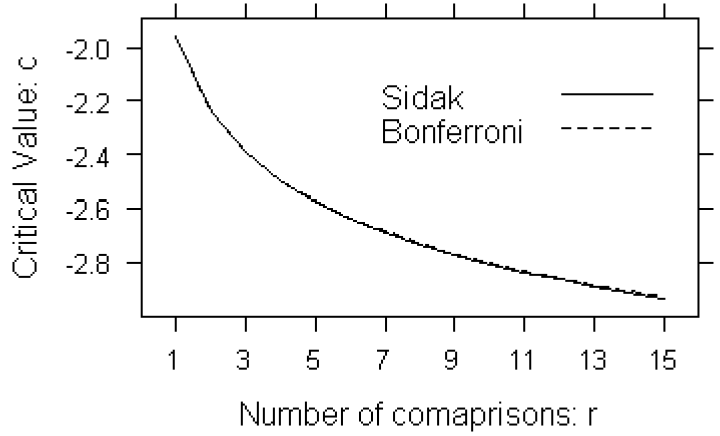
- Sidak critical value: $c = z_{1-(1-\alpha)^{1/r}}$

Better Intervals?

- In practice, unnoticeable improvement over Bonferroni bound

$$c_{Bonf} = -2.241$$

$$c_{Sid} = -2.239$$



	Bonferroni		Sidak	
	Wald	Score	Wald	Score
ρ_1 :	0.620	0.616	0.620	0.616
ρ_2 :	0.581	0.578	0.581	0.577

Another Solution

- Idea: Tighter bounds on correlations λ_{ij} that are almost always "correct".
- Idea: (Berger & Boos, 1992) Take supremum not over entire range of π_0, but over a confidence interval for it. (Say, a 99.99% C.I.)

Let π_0^{up} denote an upper confidence bound for π_0

Then for $\rho_i^0 \in (0,1)$, $\lambda_i > \left(1 + \frac{n_0}{n_i} \frac{1-\rho_i^0 \pi_0^{\mathrm{up}}}{\rho_i^0 - \rho_i^0 \pi_0^{\mathrm{up}}}\right)^{-1/2}$

Another Solution

- Rule to construct Γ:

$$\text{if } \rho_i^0 \geq 1 \qquad \text{set } \gamma_i = \left(1 + \frac{n_0}{n_i}\frac{1}{\rho_i^0}\right)^{-1/2}$$

$$\text{if } 0 < \rho_i^0 < 1 \qquad \text{set } \gamma_i = \left(1 + \frac{n_0}{n_i}\frac{1-\rho_i^0\pi_0^{\text{up}}}{\rho_i^0-\rho_i^0\pi_0^{\text{up}}}\right)^{-1/2}$$

$\Lambda > \Gamma$ for "all plausible values" of the nuisance parameter π_0

- c = ?

Remember:

c is chosen as the solution to $P_{\text{Cov}(\boldsymbol{T})=\Gamma}(T_1 > c, \ldots, T_r > c) = 1 - \alpha$

equidistant upper $1-\alpha$ quantile of the multivariate normal $N(\mathbf{0}, \Gamma)$

Another Solution

- Improvement?

$$\hat{\pi}_0 = 0.0179$$

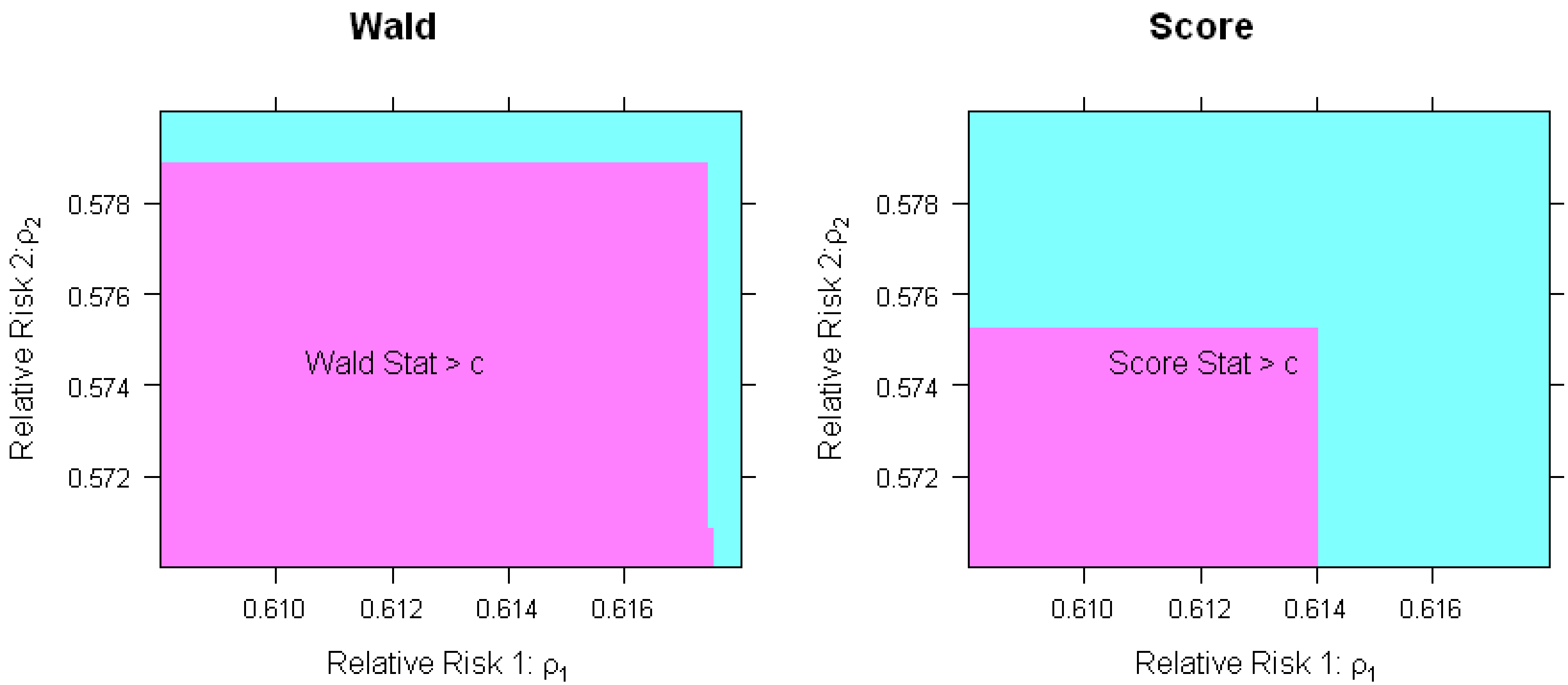
$$\pi_0^{up} = 0.0272$$

	$\rho_1 = 0.1$, $\rho_2 = 0.1$		$\rho_1 = 0.5$, $\rho_2 = 0.6$		$\rho_1 = 1$, $\rho_2 = 1$
λ_{12} ranges from	0.08	over	0.35	to	0.5
c_{BB} ranges from	-2.237	over	-2.225	to	-2.212

- Another Problem: Critical Value c depends on null hypothesis. Computationally more complex to invert test! Need projection to get from simultaneous region to intervals

Another Solution

- Good News: Confidence region nearly rectangular, and Score beats Wald



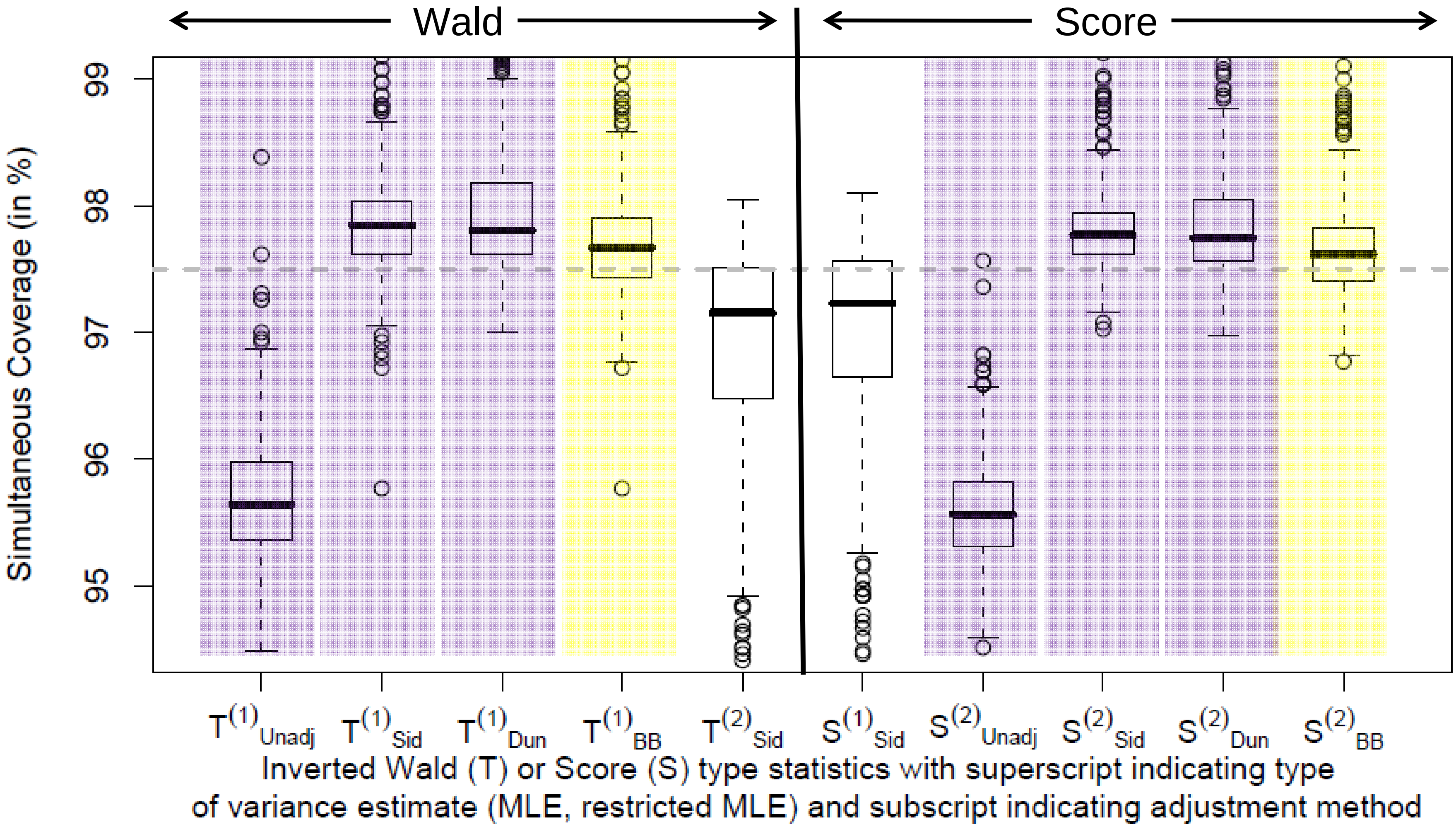
A third Solution

- Yet another solution: Eliminate unknown parameters π_0 and ρ in correlation matrix by plugging in sample estimates (consistent).
- This is called the Dunnett approach (Piegorsch, 1991; Schaarschmidt et al., 2008,2009)
- Results for all three approaches for our data:

	Sidak			Dunnett			Berger-Boos	
	Wald	Score		Wald	Score		Wald	Score
ρ_1 :	0.620	0.616	ρ_1 :	0.618	0.615	ρ_1 :	0.617	0.614
ρ_2 :	0.581	0.577	ρ_2 :	0.580	0.576	ρ_2 :	0.579	0.575

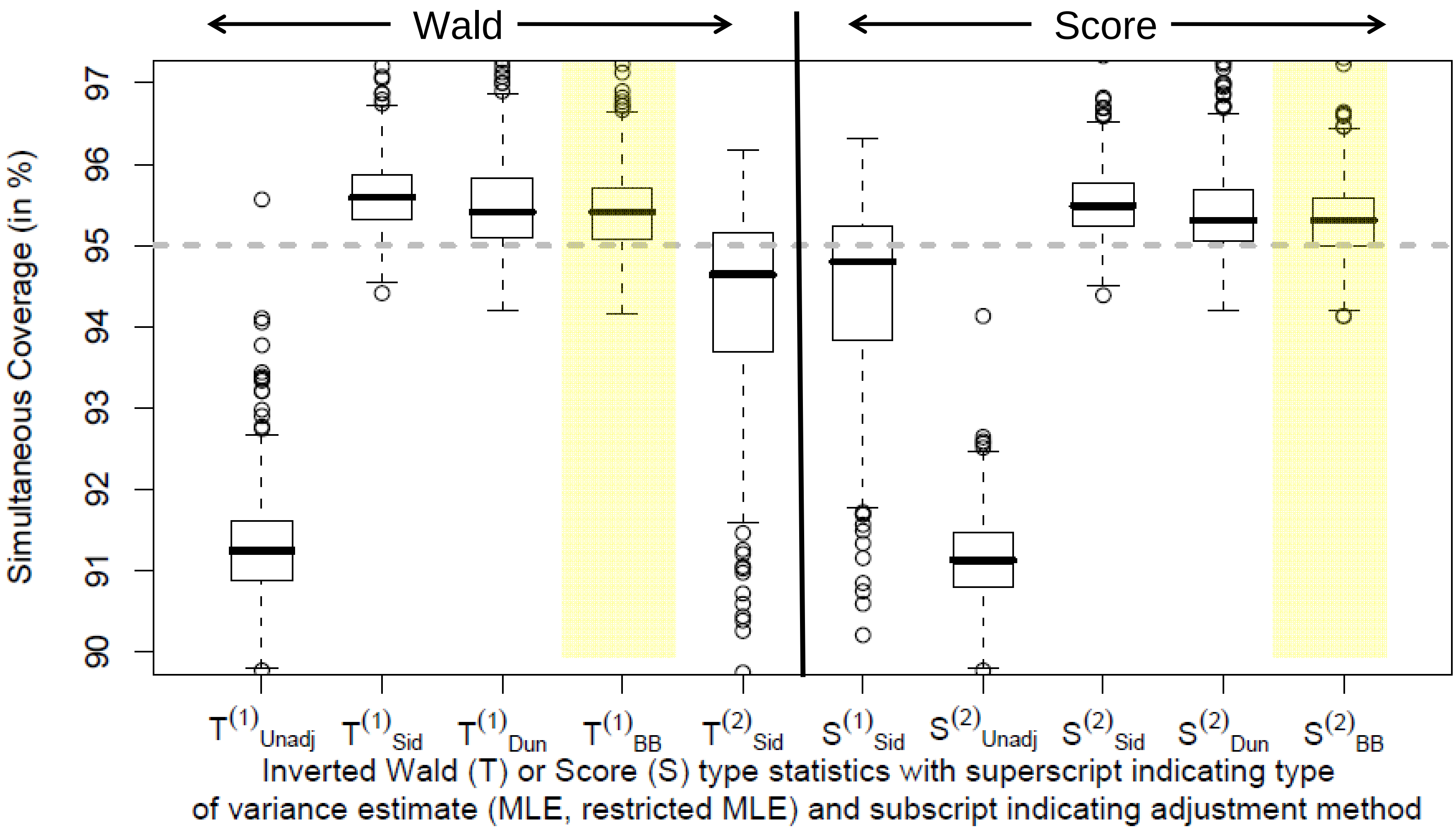
Coverage (1-α=0.975)

Simulation Results:

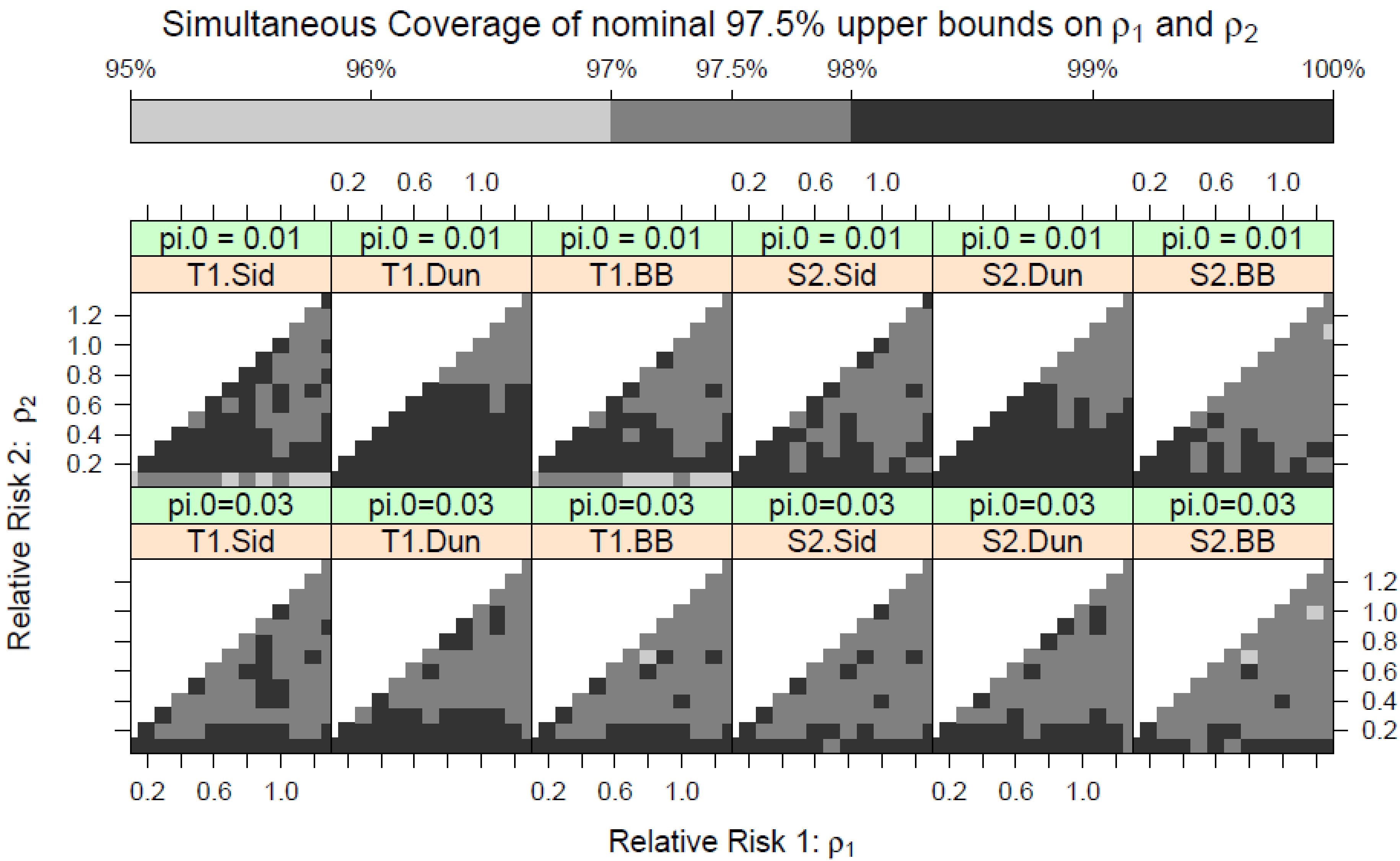


Coverage (1-α = 0.95)

Simulation Results:



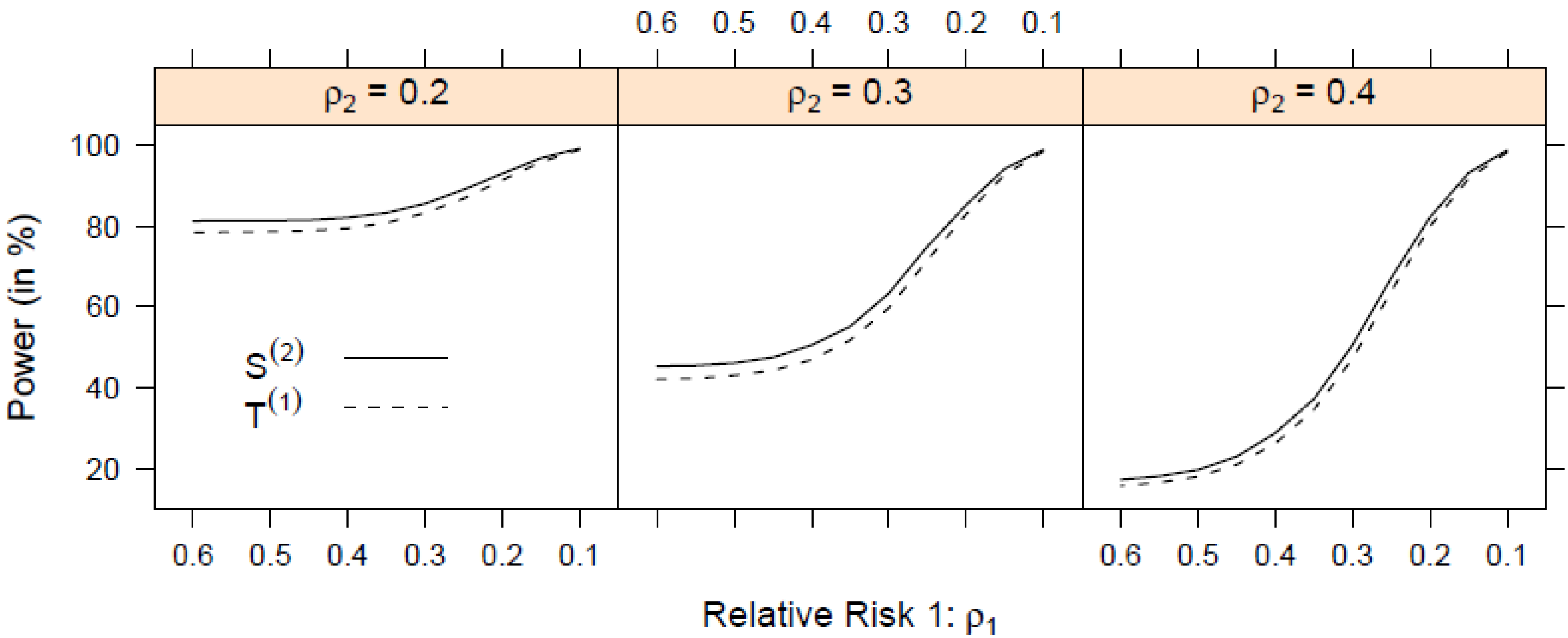
Coverage (1-α=0.975)



Power of declaring superiority

Remember: At least one RR less than 0.6?

α=0.025 $n_1 = n_2 = n_3 = 3900, \pi_0 = 0.01$



More than 2 comparisons

Suppose **r = 4 comparisons to control**:

y_0=70, y_1=26, y_2=24, y_3=20, y_4=32

Simultaneous confidence intervals:

	Sidak		Dunnett		Berger-Boos	
	T	S	T	S	T	S
ρ_1:	0.657	0.652	0.654	0.650	0.653	0.647
ρ_2:	0.617	0.612	0.615	0.609	0.613	0.608
ρ_3:	0.536	0.531	0.534	0.529	0.532	0.527
ρ_4:	0.776	0.771	0.773	0.769	0.771	0.766

Summary and Recommendations

- Score bounds slightly better than Wald bounds, but Wald has closed form (better here means smaller upper bounds while still holding nominal coverage)

- Score bounds with Berger-Boos correction work best

- Score bounds with Dunnett correction work nearly almost as good and are computationally simpler, especially for large *r* (relevant for simulation)

- In general, no dramatic improvement (for both Score and Wald bounds) over Sidak correction, which is yet simpler

R implementation

```
> source("http://lanfiles.williams.edu/»bklingen/simRR/simRR.R")
> y <- c(70,26,24)
> n <- c(3900,3900,3900)
> RRci.S2.Sid(y,n,conflev=0.975) # Sidak adj. simult. score bounds
      UB1       UB2
0.6160457 0.5772260
> RRci.S2.Dun(y,n,conflev=0.975) # Dunnett adj. simult. score bounds
Loading required package: mvtnorm
      UB1       UB2
0.6149397 0.5761532
> RRci.S2.BB(y,n,conflev=0.975) # Berger-Boos adj. simult. score bounds
      UB1       UB2
0.6138859 0.5751453
```

R implementation

```
> sim.result <- sim.cov.pow(
          p0 = 0.4,
          RR = c(0.9,0.8,0.7),
          n = c(50,100,100,100),
          conflev = 0.975,
          RR.null = c(1, 1, 1),
          which.stat = c("S2.Sid","S2.Dun","S2.BB","T1.Sid","T1.Dun"),
          sims = 3900 )

> sim.result$coverage
S2.Sid   S2.Dun   S2.BB   T1.Sid   T1.Dun
0.978    0.976    0.976   0.978    0.974
> sim.result$pow.least
S2.Sid   S2.Dun   S2.BB   T1.Sid   T1.Dun
0.23     0.24     0.24    0.23     0.25
```

Additional Material: Lower bounds?

- Suppose you want to show that at least one of five treatments is better (in terms of success probability) than control (maybe for a given superiority margin, i.e., at least three times better)

- Find simultaneous lower bounds for the improvement with each treatment over control

- There exists a procedure that is universally better than Sidak (or Bonferroni) adjusted bounds:

Remember: For the case $\rho_i^0 \geq 1$, indeed $\lambda_i > \left(1 + \frac{n_0}{n_i}\frac{1}{\rho_i^0}\right)^{-1/2}$

Lower bounds?

- Rule to construct Γ:

$$\gamma_i = \left(1 + \frac{n_0}{n_i}\right)^{-1/2}$$

$$\gamma_{ij} = \gamma_i \gamma_j \text{ if } \rho_i^0, \rho_j^0 \geq 1$$

$$\gamma_{ij} = 0 \text{ otherwise}$$

- Then, $\Lambda > \Gamma$ for all values of the nuisance parameter
- Resulting critical value *c* always smaller than Sidak or Bonferroni adjusted

Lower bounds?

- Bounds on Correlation: