

Simultaneous Confidence Bounds for Relative Risks in Multiple Comparisons to Control

**Bernhard Klingenberg
Asst. Prof. of Statistics
Williams College**

Manuscript and R-code available at:
www.williams.edu/~bklingen

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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

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

(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

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

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: $n_0 = n_1 = n_2 = 3900$
 $y_0 = 70, y_1 = 26$ 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 $H_{0i} : \rho_i = \rho_i^0, i = 1, \dots, r,$
 (T_1, T_2, \dots, T_r) and (S_1, S_2, \dots, 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
rejecting H_0 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:

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

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

$$P_{\text{Corr}(\mathbf{T})=\Lambda(\pi_0)}(T_1 \geq c, \dots, T_r \geq c) \geq P_{\text{Corr}(\mathbf{T})=\Gamma}(T_1 \geq c, \dots, T_r \geq c)$$

□ This leads to:

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

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

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

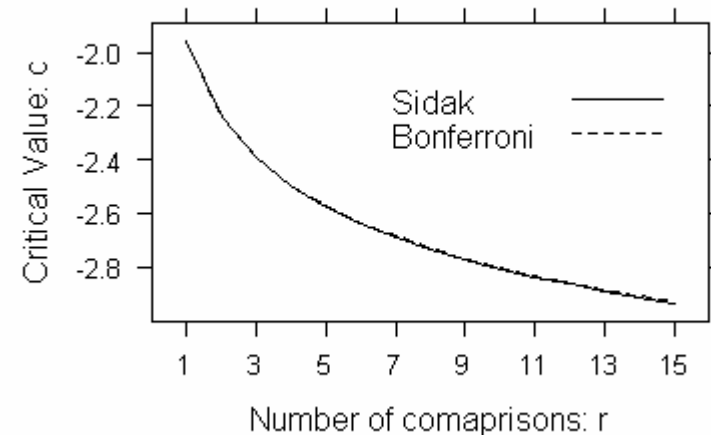
□ Sidak critical value: $c = z_{1-(1-\alpha)^{1/r}}$

Better Intervals?

- In practice, **unnoticeable improvement** over Bonferroni bound

$$C_{\text{Bonf}} = -2.241$$

$$C_{\text{Sid}} = -2.239$$



	Bonferroni		Sidak		
	Wald	Score	Wald	Score	
$\rho_1 :$	0.620	0.616	$\rho_1 :$	0.620	0.616
$\rho_2 :$	0.581	0.578	$\rho_2 :$	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 $\rho_i^0 \in (0, 1)$, $\lambda_i > \left(1 + \frac{n_0}{n_i} \frac{1 - \rho_i^0 \pi_0^{\text{up}}}{\rho_i^0 - \rho_i^0 \pi_0^{\text{up}}}\right)^{-1/2}$

Another Solution

□ Rule to construct Γ :

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

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

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

□ $c = ?$

Remember:

c is chosen as the solution to $P_{\text{Cov}(\mathbf{T})=\Gamma}(T_1 > c, \dots, T_r > c) = 1 - \alpha$
equidistant upper $1 - \alpha$ quantile of the multivariate normal $N(\mathbf{0}, \Gamma)$

Another Solution

□ Improvement?

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

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

λ_{12} ranges from

c_{BB} ranges from

$$\begin{array}{l} \rho_1 = 0.1 \\ \rho_2 = 0.1 \end{array}$$

$$0.08$$

over

$$\begin{array}{l} \rho_1 = 0.5 \\ \rho_2 = 0.6 \end{array}$$

$$0.35$$

to

$$\begin{array}{l} \rho_1 = 1 \\ \rho_2 = 1 \end{array}$$

$$0.5$$

$$-2.237$$

over

$$-2.225$$

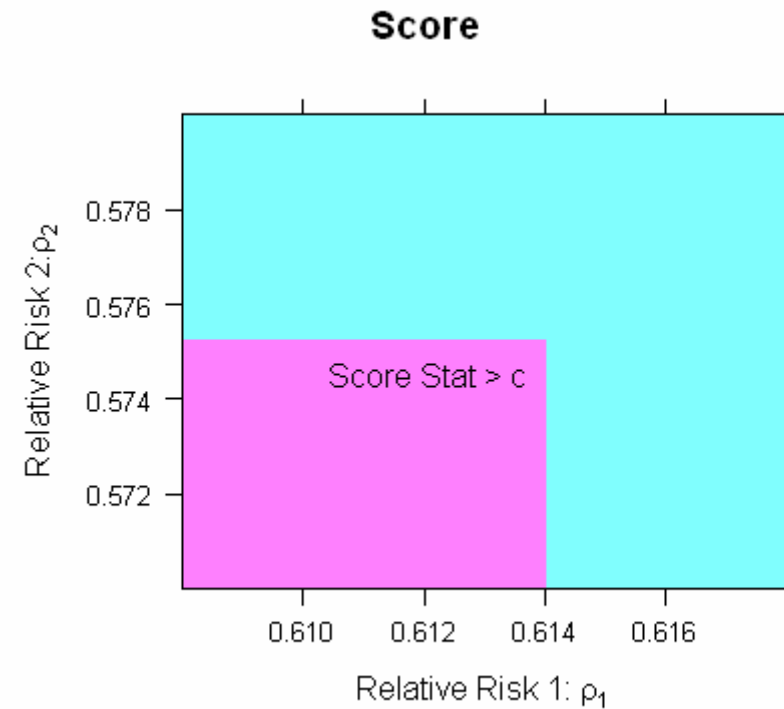
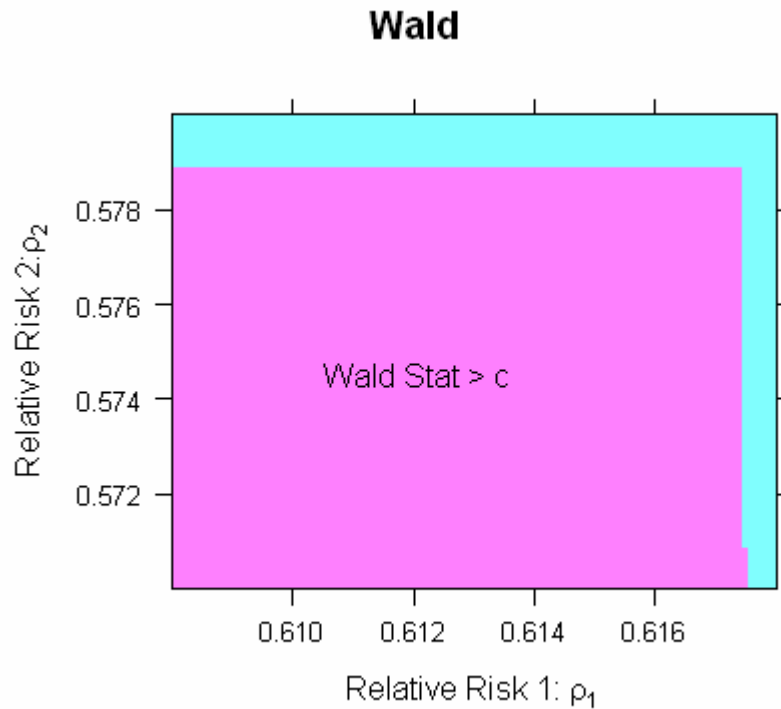
to

$$-2.212$$

- 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



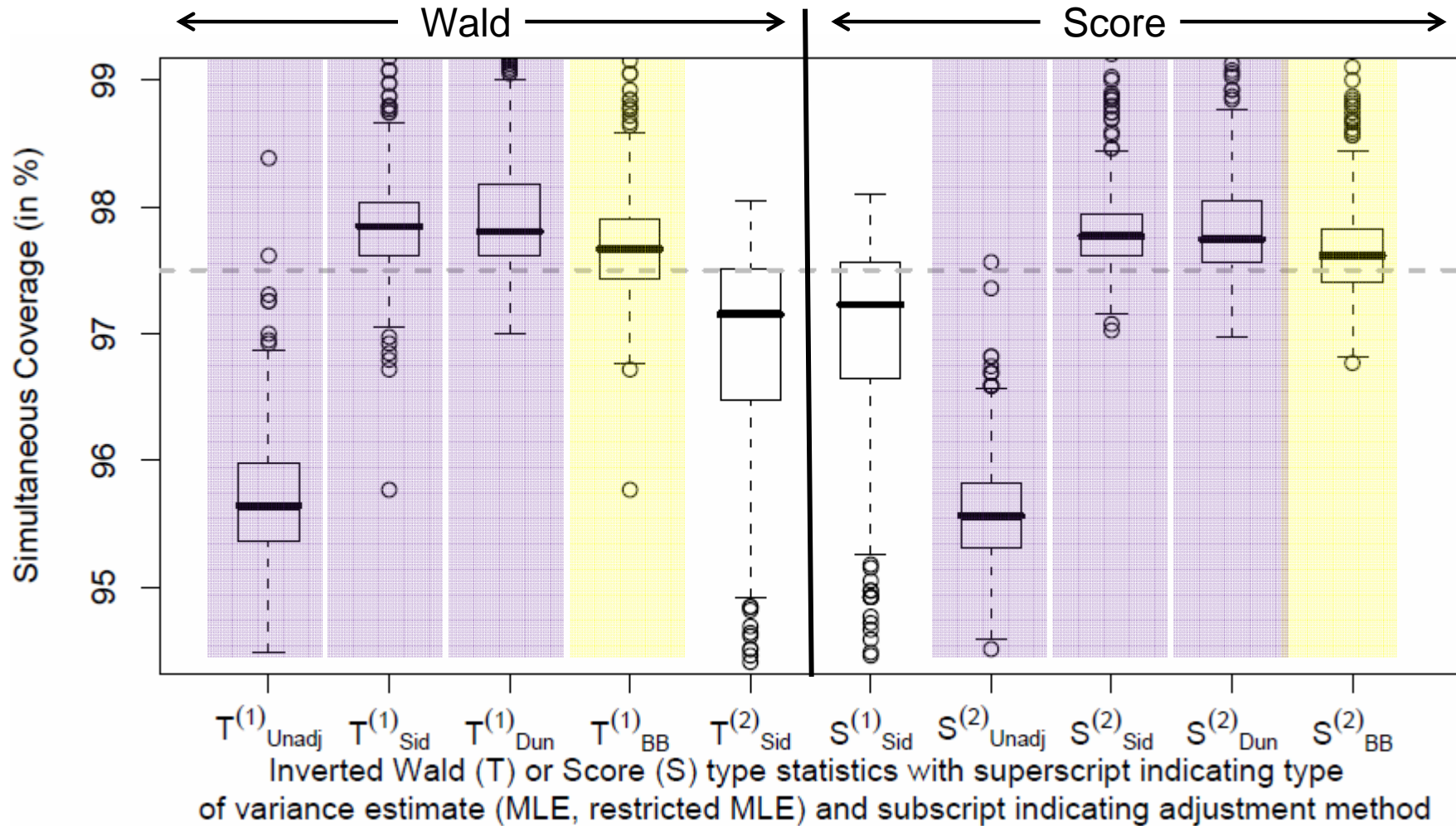
A third Solution

- ❑ 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 (Piegorisch, 1991; Schaarschmidt et al., 2008,2009)
- ❑ Results for all three approaches for our data:

	Sidak			Dunnett			Berger-Boos	
	Wald	Score		Wald	Score		Wald	Score
$\rho_1 :$	0.620	0.616	$\rho_1 :$	0.618	0.615	$\rho_1 :$	0.617	0.614
$\rho_2 :$	0.581	0.577	$\rho_2 :$	0.580	0.576	$\rho_2 :$	0.579	0.575

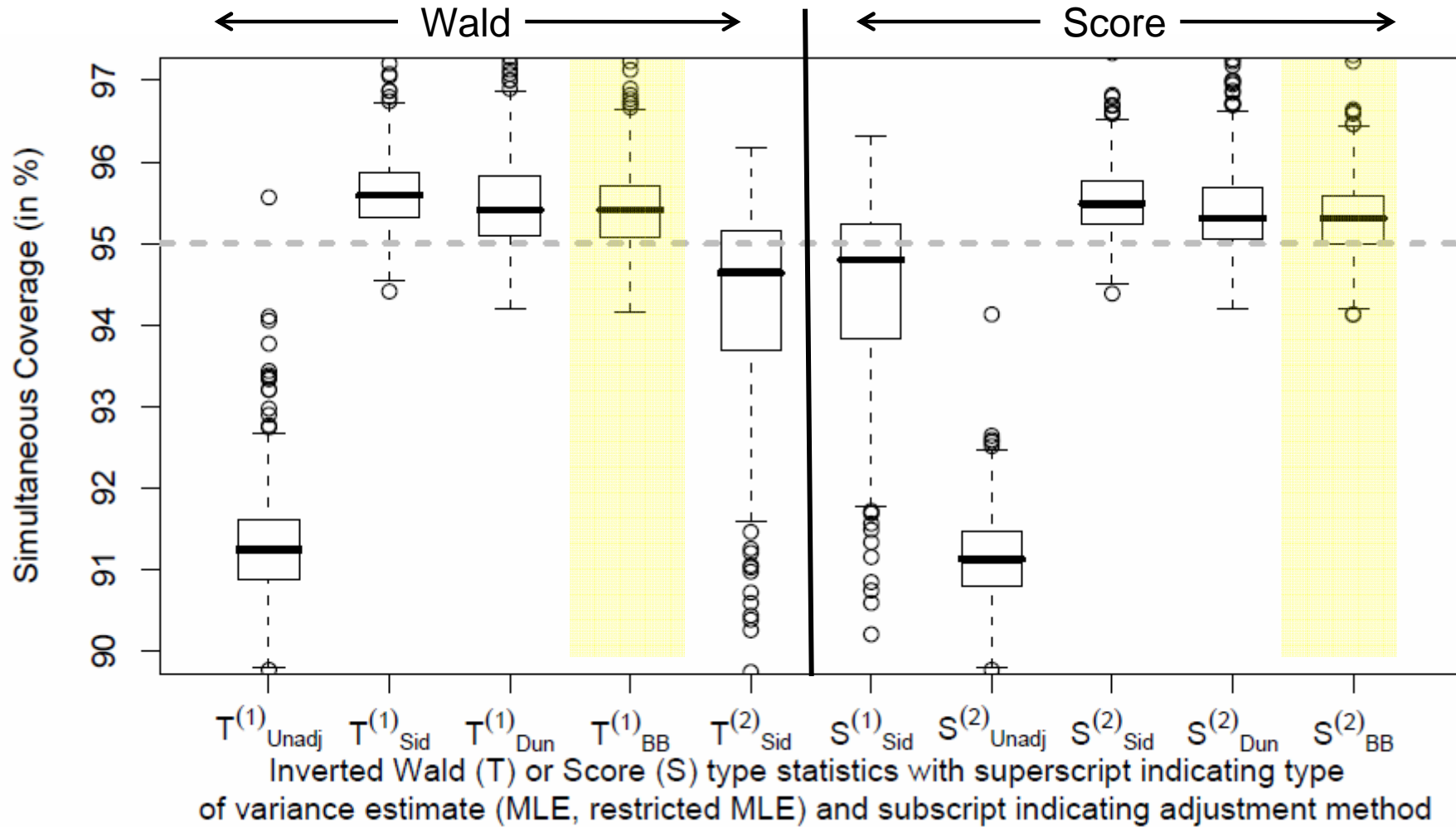
Coverage ($1-\alpha=0.975$)

Simulation Results:



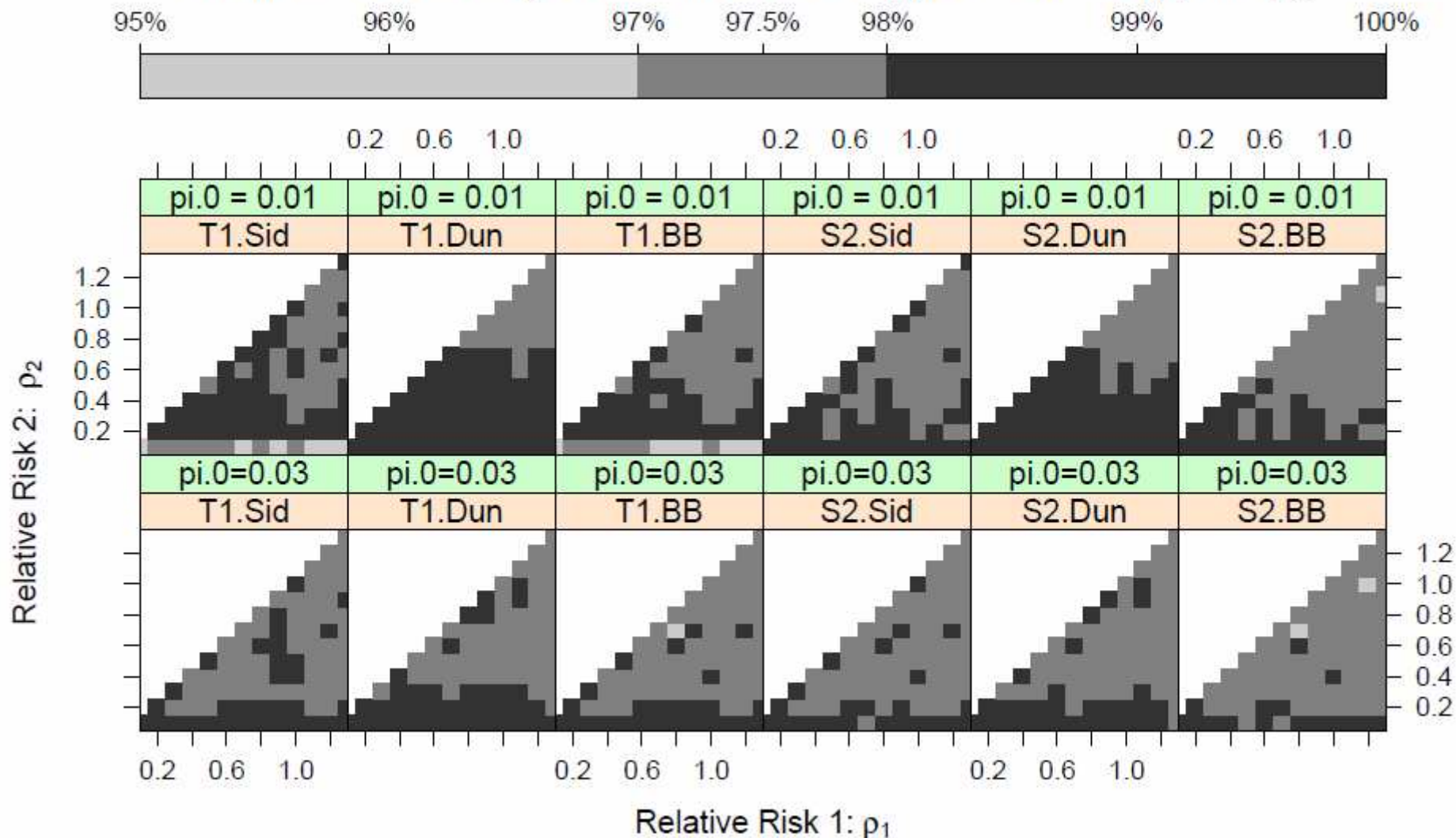
Coverage ($1-\alpha = 0.95$)

Simulation Results:



Coverage ($1-\alpha=0.975$)

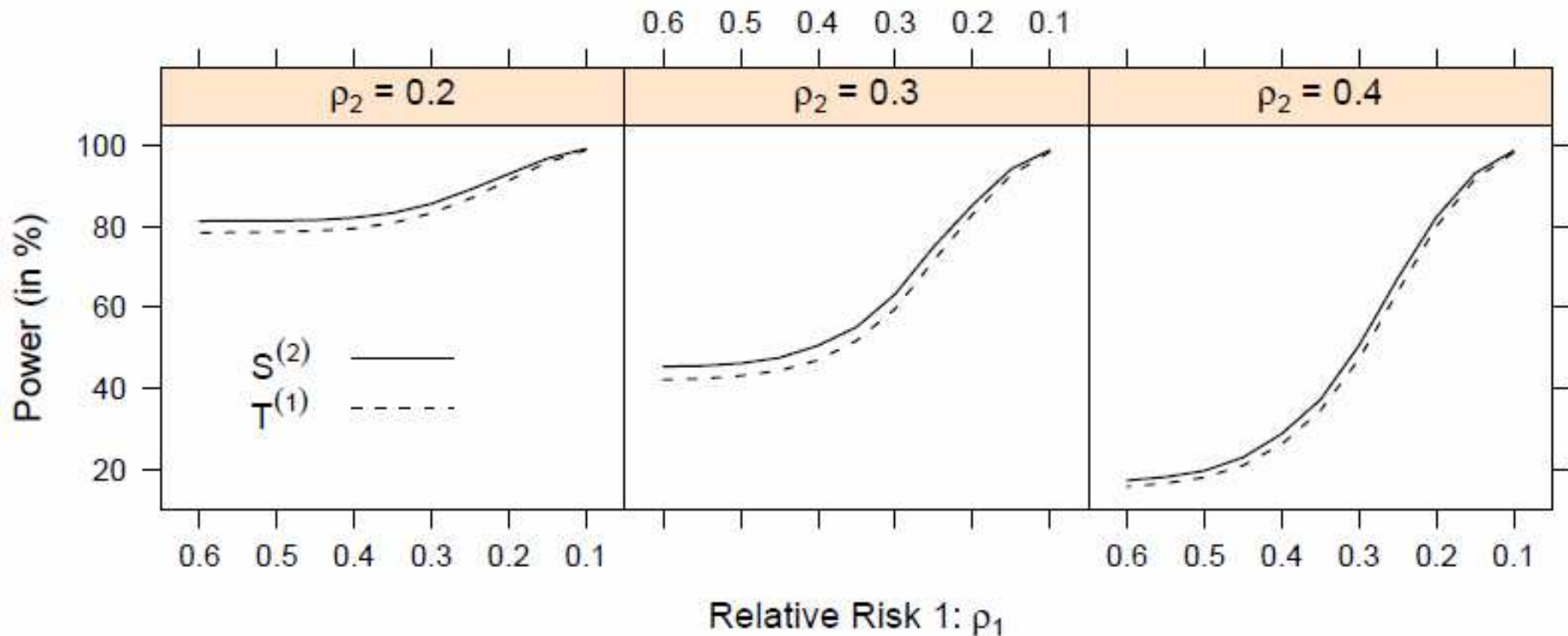
Simultaneous Coverage of nominal 97.5% upper bounds on ρ_1 and ρ_2



Power of declaring superiority

Remember: At least one RR less than 0.6?

$$\alpha=0.025 \quad n_1 = n_2 = n_3 = 3900, \pi_0 = 0.01$$



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	
	<i>T</i>	<i>S</i>	<i>T</i>	<i>S</i>	<i>T</i>	<i>S</i>
$\rho_1:$	0.657	0.652	0.654	0.650	0.653	0.647
$\rho_2:$	0.617	0.612	0.615	0.609	0.613	0.608
$\rho_3:$	0.536	0.531	0.534	0.529	0.532	0.527
$\rho_4:$	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:

