Pneumonia prevention using topical antibiotics in the Intensive Care Unit (ICU). Another variation on control group variability.

…..or…..

Confidence ellipses: an application of ellip to model the relation between control group rate and intervention effect size within controlled trials.

James C Hurley[1]

[1]Melbourne Medical School,
University of Melbourne

Definition
- the application of statistical techniques
- to the analysis of multiple studies
- to derive summary results
- and to contrast results

i.e. beyond the summary result
- why are the studies so different?
- Control group rate?

This talk

Conflicting results among studies of-

1. Diagnostic test
   - Endotoxin detection
   - 90 studies
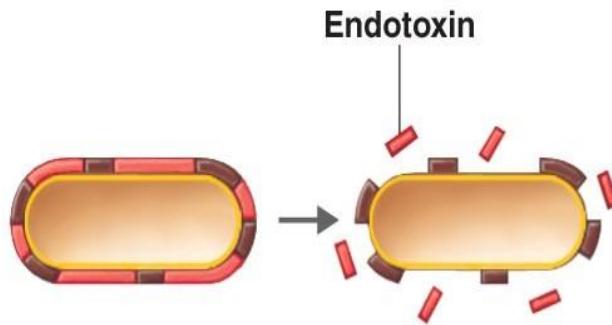
2. Controlled trials
   - Pneumonia prevention in ICU
   - >200 studies
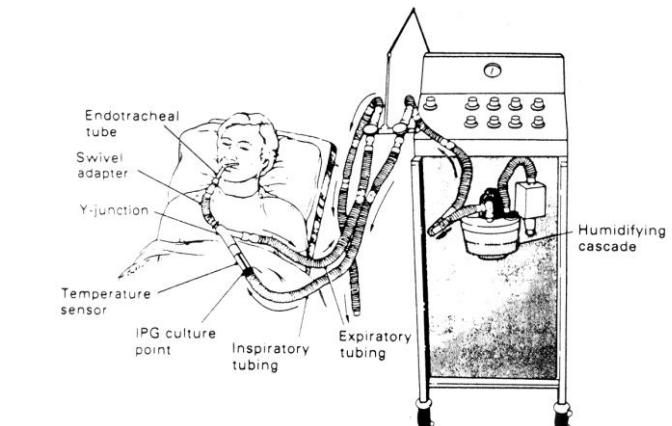
Control group rate…..?

Analytic considerations
- Choice of
  - Effect size
    - RR / OR / RD?
  - Scale
    - Linear / other
- Effect size versus control group rate (confounded relationship)
- Low or zero event rate issues
- Linear regression?
- Ecological fallacy
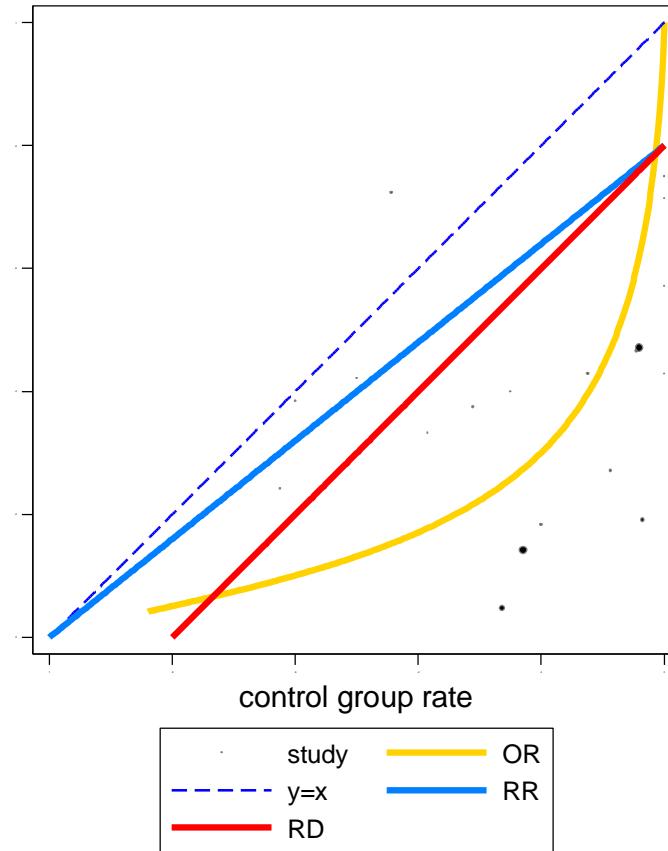
Interest
- Higher risk = Greater benefit?
- Lower risk = adverse effects ("J curve")?
- Contextual effects?

control group rate

·· study		OR
y=x		RR
RD		

Galton (1886) – height of children versus parents

DIAGRAM BASED ON TABLE I.
(all female heights are multiplied by 1'08)

5
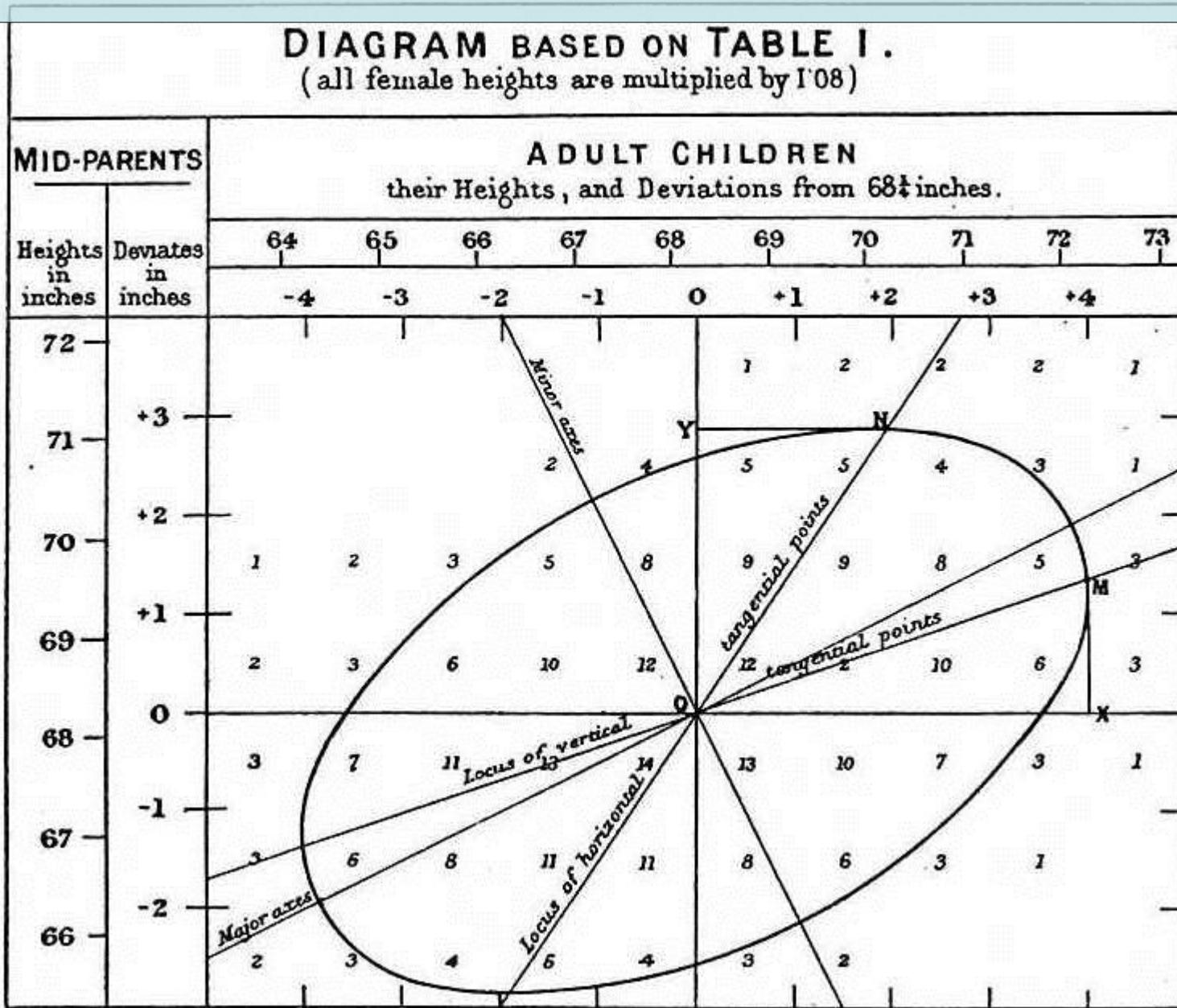
Meta-analysis in Stata

- `meta` – 1997

- `metan` – 1998
  - `labbe`
  - `funnel`

- `metacum`

- `metareg`

- `metandi`
  - `metandiplot`

- `mvmeta`

Meta-Analysis in Stata:
An Updated Collection from
the Stata Journal

EDITED BY JONATHAN A. C. STERNE
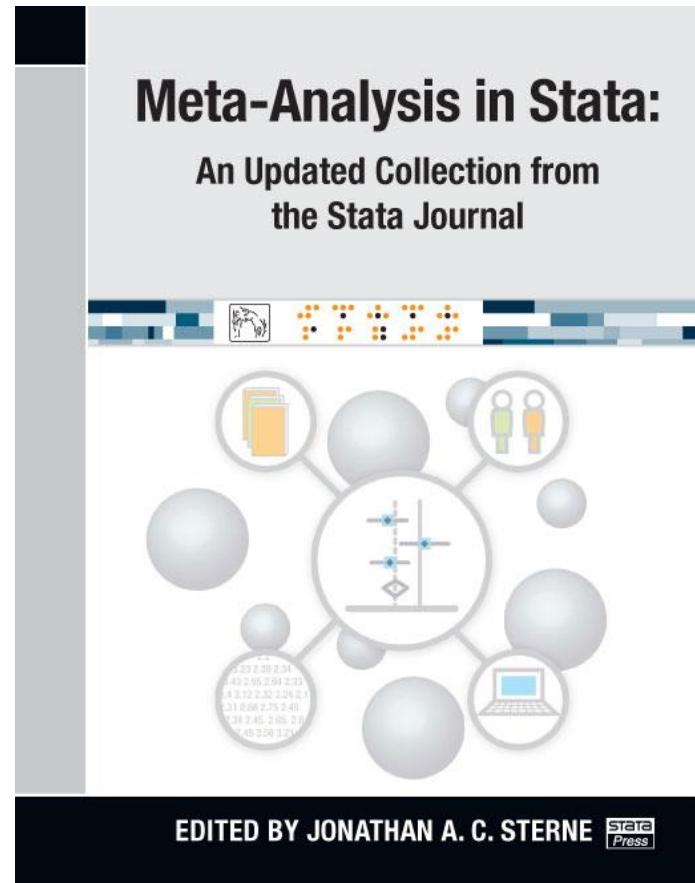
All come with graphical presentation to enable contrasting of results in addition to statistical summary.

Endotoxemia detection
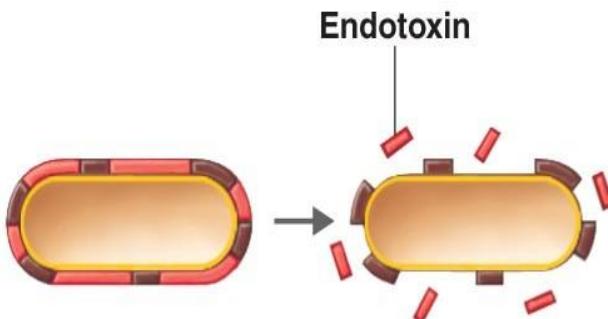
Endotoxin

|		Gram negative bacteremia	
		+ (no.)	**-** (no.)
Endotoxemia	**+**	TP	FP
	-	FN	TN

$$DOR = ((TP/FN)/(FP/TN))$$

How the ROC works
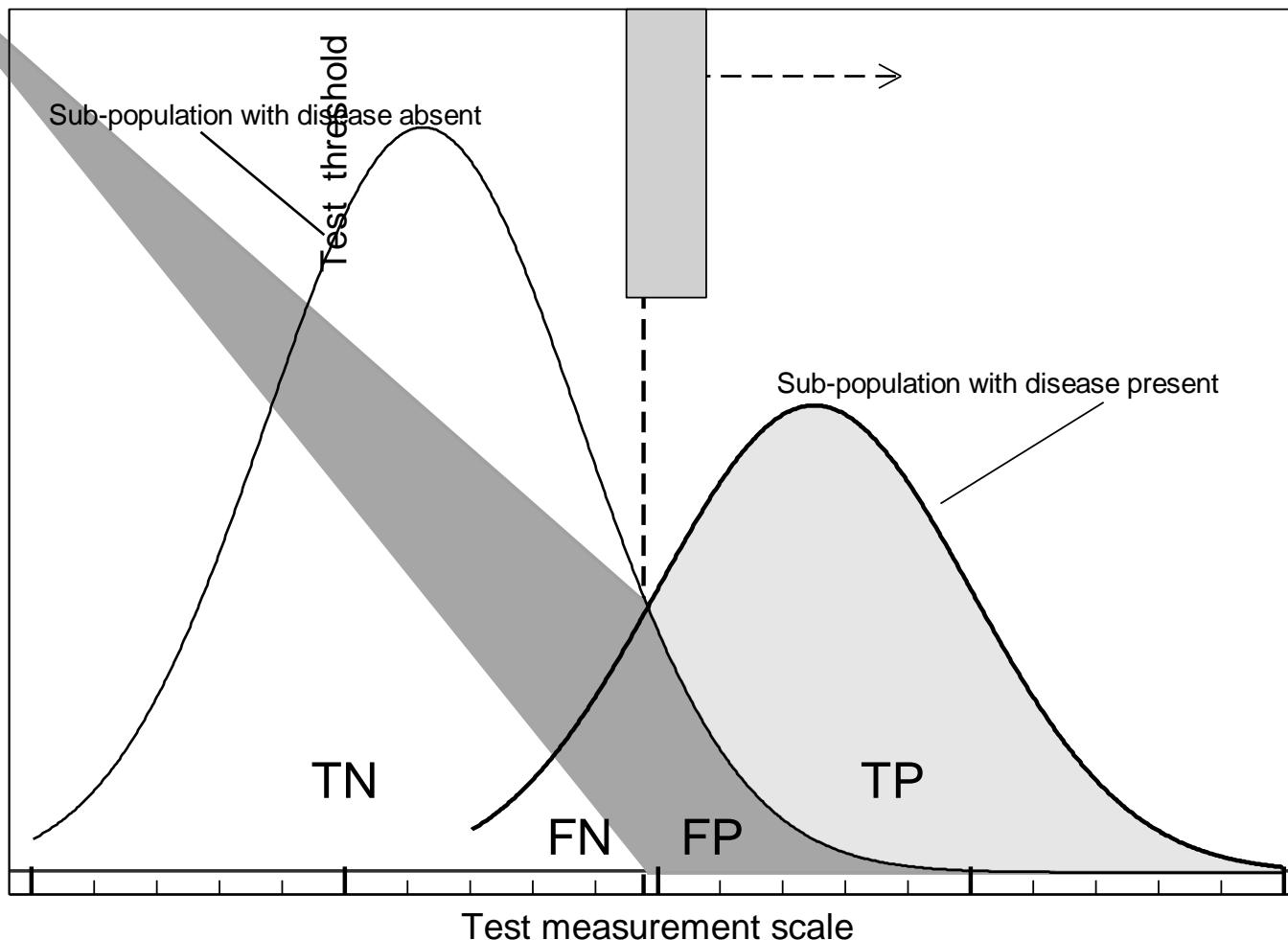
From - **Hurley JC.** (2011). Meta-analysis of Clinical Studies of Diagnostic Tests: Developments in How the Receiver Operating Characteristic "Works". Arch Pathol Lab Med. 135: 1585-1590
http://www.archivesofpathology.org/doi/abs/10.5858/arpa.2011-0016-SO

8

Endotoxemia detection
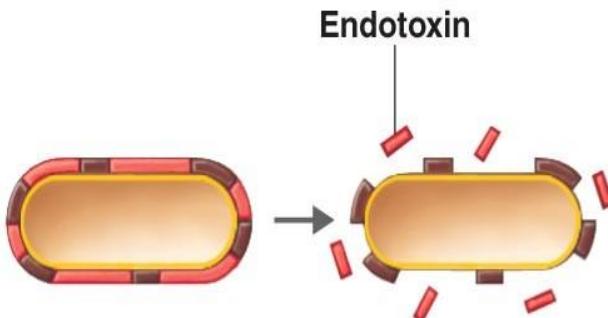
Endotoxin

		Gram negative bacteremia	
		+ (no.)	**-** (no.)
Endotoxemia	+	TP	FP
	-	FN	TN

Sensitivity = (TP/(FN+TP))

Specificity = (TN/(TN+FP))

All studies (n=90)
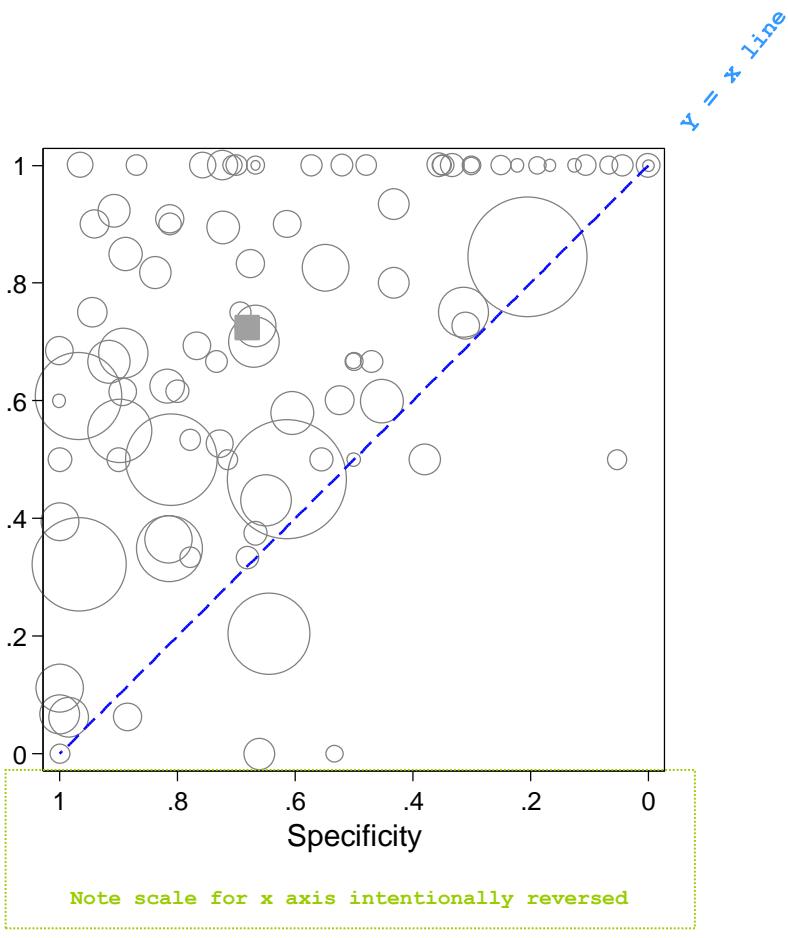

```
metandiplot tp fp fn tn, predopts(off) confopts(off) curveopts(off) addplot(function
        y=1-x, lp(dash) lc(blue)) legend(off) ylab( , ang(h))
```

Data available at - **Hurley JC.** 2013. Endotoxemia. concordance with Gram-negative bacteremia and association with outcome.
Doctor of Medical Science thesis. University of Melbourne. Melbourne, Australia. Available online: URL http://repository.unimelb.edu.au/10187/17991 (accessed on 25 July 2015).
Hurley JC. (2009). Does gram-negative bacteremia occur without endotoxemia? A meta-analysis using hierarchical summary ROC curves. Eur. J. Clin. Microbiol. Infect Dis. 29: 207-215.
http://rd.springer.com/article/10.1007/s10096-009-0841-2#page-1
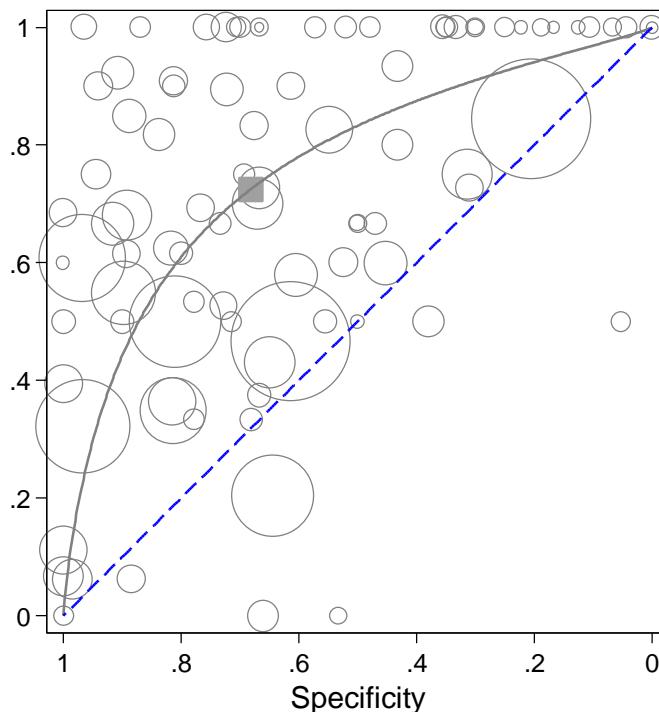
```
metandiplot tp fp fn tn, predopts(off) confopts(off) addplot(function y=1-x, lp(dash)
     lc(blue)) legend(off) ylab( , ang(h))
```

Data available at - **Hurley JC.** 2013. Endotoxemia. concordance with Gram-negative bacteremia and association with outcome.
Doctor of Medical Science thesis. University of Melbourne. Melbourne, Australia. Available online: URL http://repository.unimelb.edu.au/10187/17991 (accessed on 25 July 2015).
Hurley JC. (2009). Does gram-negative bacteremia occur without endotoxemia? A meta-analysis using hierarchical summary ROC curves. Eur. J. Clin. Microbiol. Infect Dis. 29: 207-215.
http://rd.springer.com/article/10.1007/s10096-009-0841-2#page-1
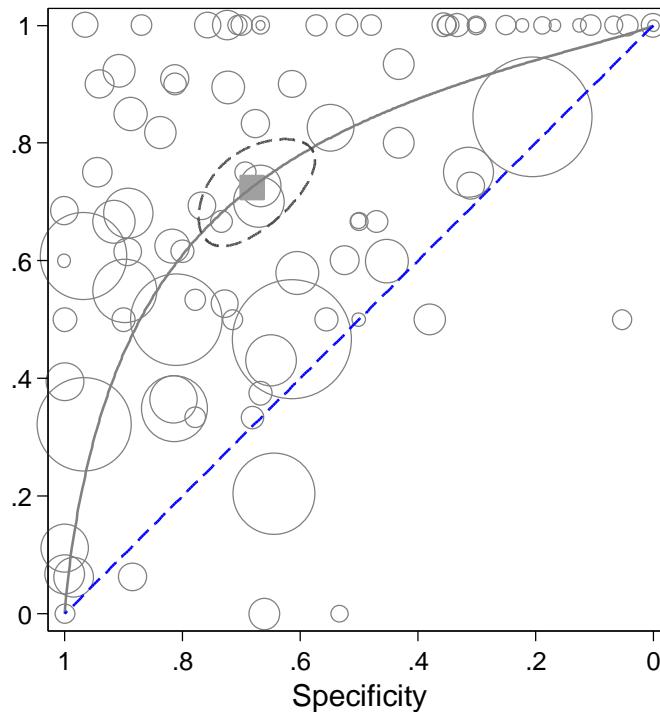
```
metandiplot tp fp fn tn, predopts(off) addplot(function y=1-x, lp(dash) lc(blue))
      legend(off) ylab( , ang(h))
```

Data available at - **Hurley JC.** 2013. Endotoxemia. concordance with Gram-negative bacteremia and association with outcome.
Doctor of Medical Science thesis. University of Melbourne. Melbourne, Australia. Available online: URL http://repository.unimelb.edu.au/10187/17991 (accessed on 25 July 2015).
Hurley JC. (2009). Does gram-negative bacteremia occur without endotoxemia? A meta-analysis using hierarchical summary ROC curves. Eur. J. Clin. Microbiol. Infect Dis. 29: 207-215.
http://rd.springer.com/article/10.1007/s10096-009-0841-2#page-1

All studies (n=90)

2x2 with a zero cell
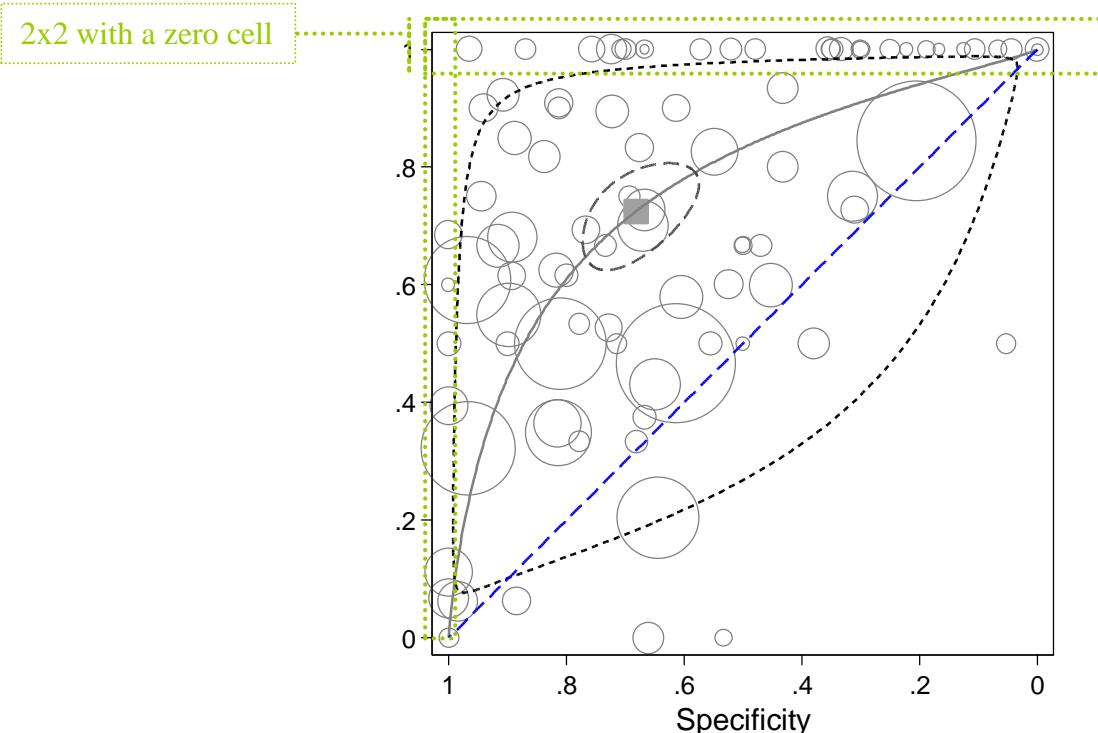
```
metandiplot tp fp fn tn, addplot(function y=1-x, lp(dash) lc(blue))
    legend(off) ylab( , ang(h))
```

Data available at - **Hurley JC.** 2013. Endotoxemia. concordance with Gram-negative bacteremia and association with outcome.
Doctor of Medical Science thesis. University of Melbourne. Melbourne, Australia. Available online: URL http://repository.unimelb.edu.au/10187/17991 (accessed on 25 July 2015).
Hurley JC. (2009). Does gram-negative bacteremia occur without endotoxemia? A meta-analysis using hierarchical summary ROC curves. Eur. J. Clin. Microbiol. Infect Dis. 29: 207-215.
http://rd.springer.com/article/10.1007/s10096-009-0841-2#page-1
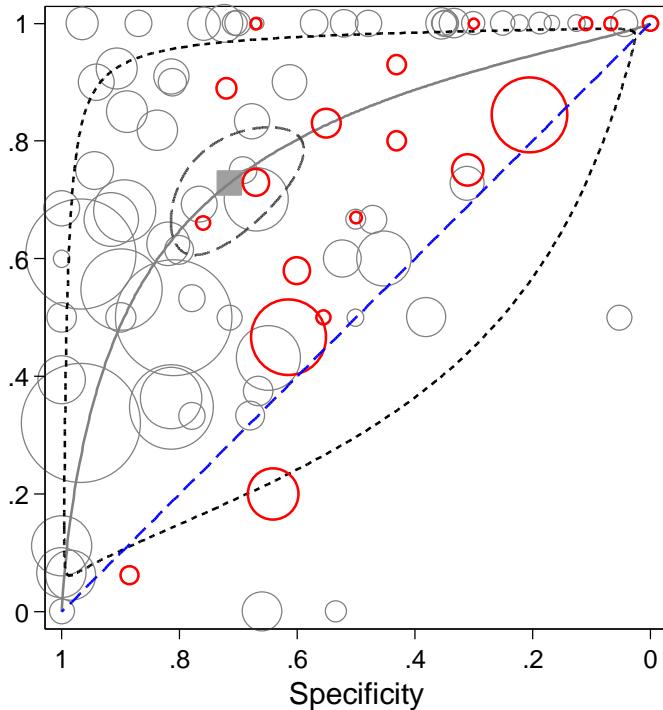
```
metandiplot tp fp fn tn if pop!="i", addplot(scatter TPpct spc if pop=="i" [aweight =
    t], msize(small) mcolor(red) msymbol(circle_hollow)|| function y=1-x, lp(dash)
    lc(blue)) legend(off) ylab( , ang(h))
```

Endotoxin detection

- `metandiplot` reveals the broad literature experience
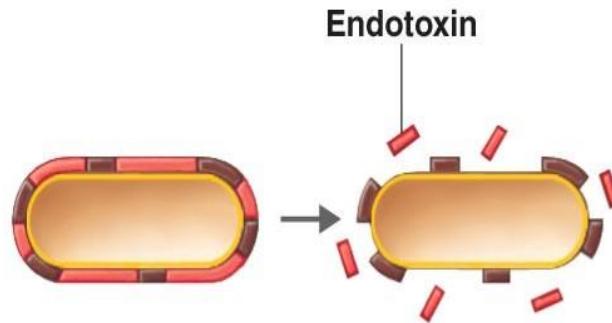
and now to ….

- Pneumonia prevention in ICU (>200 studies)

Ventilator

Humidifier

Hand with suction catheter

Sinus

Nasal gastric tube

Endotrachial tube

Tubing

Nebulize

Vocal cord

Thyroid cartilage

Condensate

Pooled secretions

Subglottic space

Biofilm

Cuff

Artery and vein

Airway management

Topical antibiotic prophylaxis (SDD)

Esophagus

Studies of non-antibiotic methods

Stomach

Gastric pH

Studies of antibiotic methods

Gastric fluid

Tube feed
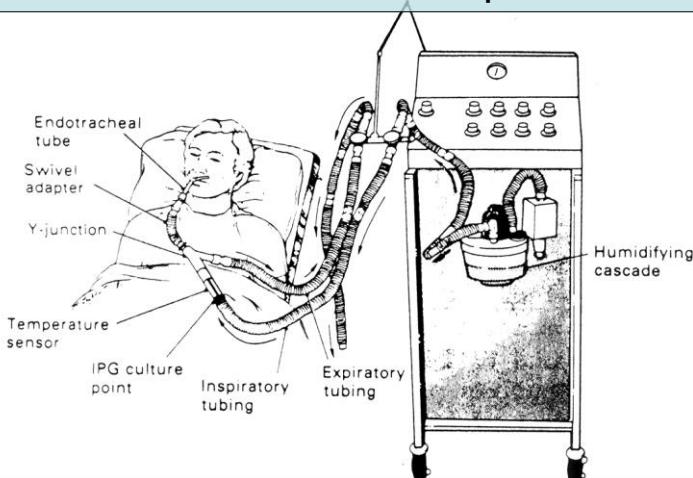
Interventions under study;

- Non-antibiotic methods
- Methods using topical antibiotics
  - Concurrent design
  - Non-concurrent design.

		Study group	
		Intervention (no.)	Control (no.)
Pneumonia / Bacteremia	+	ivap_n	vap_n
	-	ivap_m	vap_m

$$OR = ((ivap\_n/\ ivap\_m)/(vap\_n/\ vap\_m))$$

17

BACT-ES: topical antibiotic methods

author

nonconcurrent control-SDD
Stoutenbeek'87 SDD [S62]
Cerda [S]
Tissot van Patot [S]
de Smet SDD [S58]
de Smet SOD [S58]
Ledingham [S]
Silvestri'04 V [S]
McClelland [S]
Sydow [S]
Godard [S59]
Hartenauer [S60]
Fox [S]
Brun-Buisson [S56]
Viviani [S]
Nardi [S64]
Hammond-SDD [S]
Hammond-SDD [S]
Hartenauer [S60]
Subtotal (I-squared = 68.5%, p = 0.000)
.
concurrent control-SDD
Rolando [S92]
Aerdts [S68]
Rodriguez_Roldan [S91]
Blair [S72]
Korinek [S84]
Rolando [S93]
Zobel [S101]
Rocha [S90]
Finch [S]
Cerra [S73]
Gaussorgues [S78]
Cockerill [S74]
Flaherty [S77]
Krueger [S]
Langlois-Karaga [S]
Kerver [S83]
Ulrich [S97]
Verwaest OA [S99]
Sanchez-Garcia [S]
Stoutenbeek '96 [S]
Georges [S79]
Jacobs [S82]
Hammond [S]
Camus PT [S]
Quinio [S88]
Ferrer [S76]
Stoutenbeek '07 [S95]
Wiener [S100]
Tetteroo [S96]
Ruza [S]
Garbino_Fl [S102]
de le Cal [S75]
Verwaest PTA [S99]
Arnow [S69]
Brun-Buisson [S56]
Palomar_PTA [S86]
Barret [S70]
Hellinger [S80]
Bion [S71]
Laggner [S85]
Palomar Ctx' [S]
Subtotal (I-squared = 32.4%, p = 0.027)
.
Overall (I-squared = 49.4%, p = 0.000)

.01   .03   .1   .3   1   3   10

favours intervention   favours control

VAP-ES: non-antibiotic methods

8

Infection prevention in ICU
Summary odds ratios

	Non-antimicrobial studies	Topical- antimicrobial studies
Bacteremia	0.87; 0.72 – 1.06	0.69; 0.59 – 0.81
Pneumonia (VAP)	0.74; 0.69 – 0.79	0.48; 0.43 – 0.54
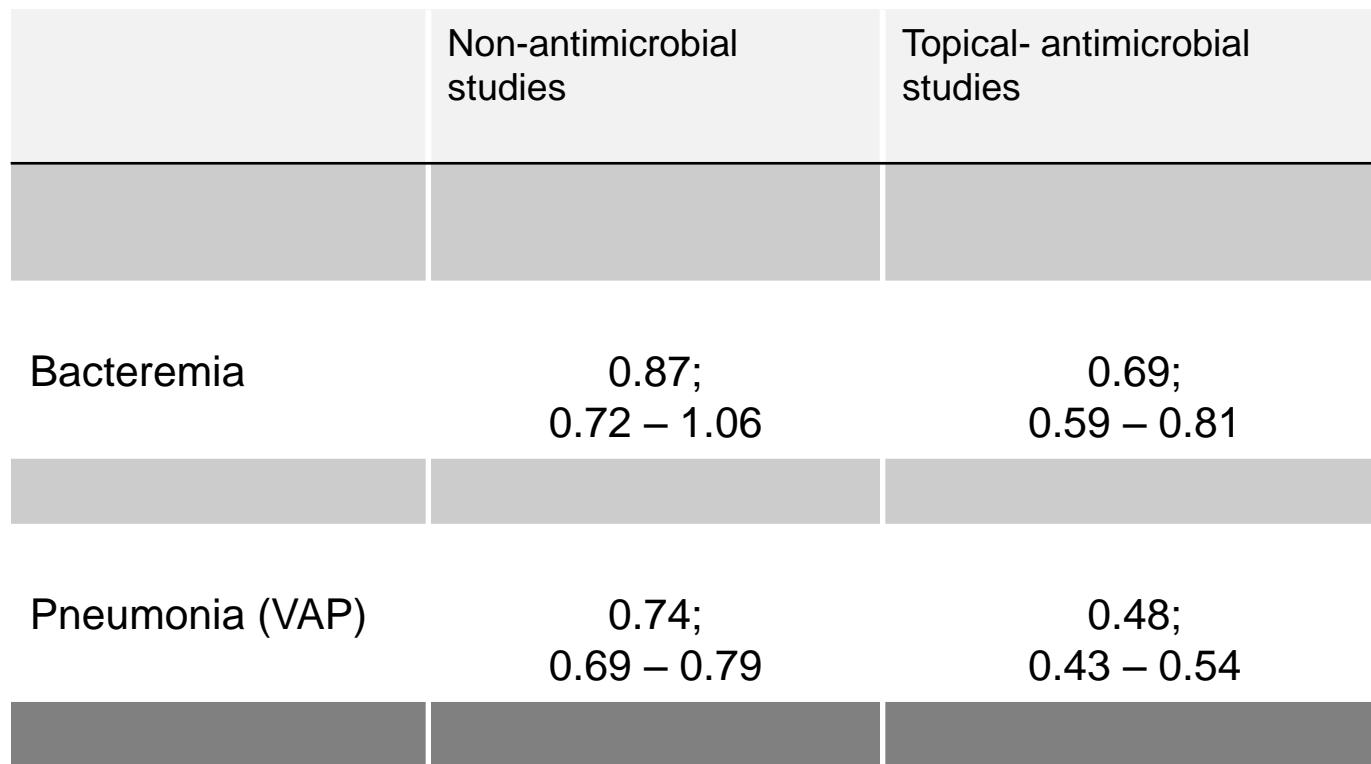
How the RCT works
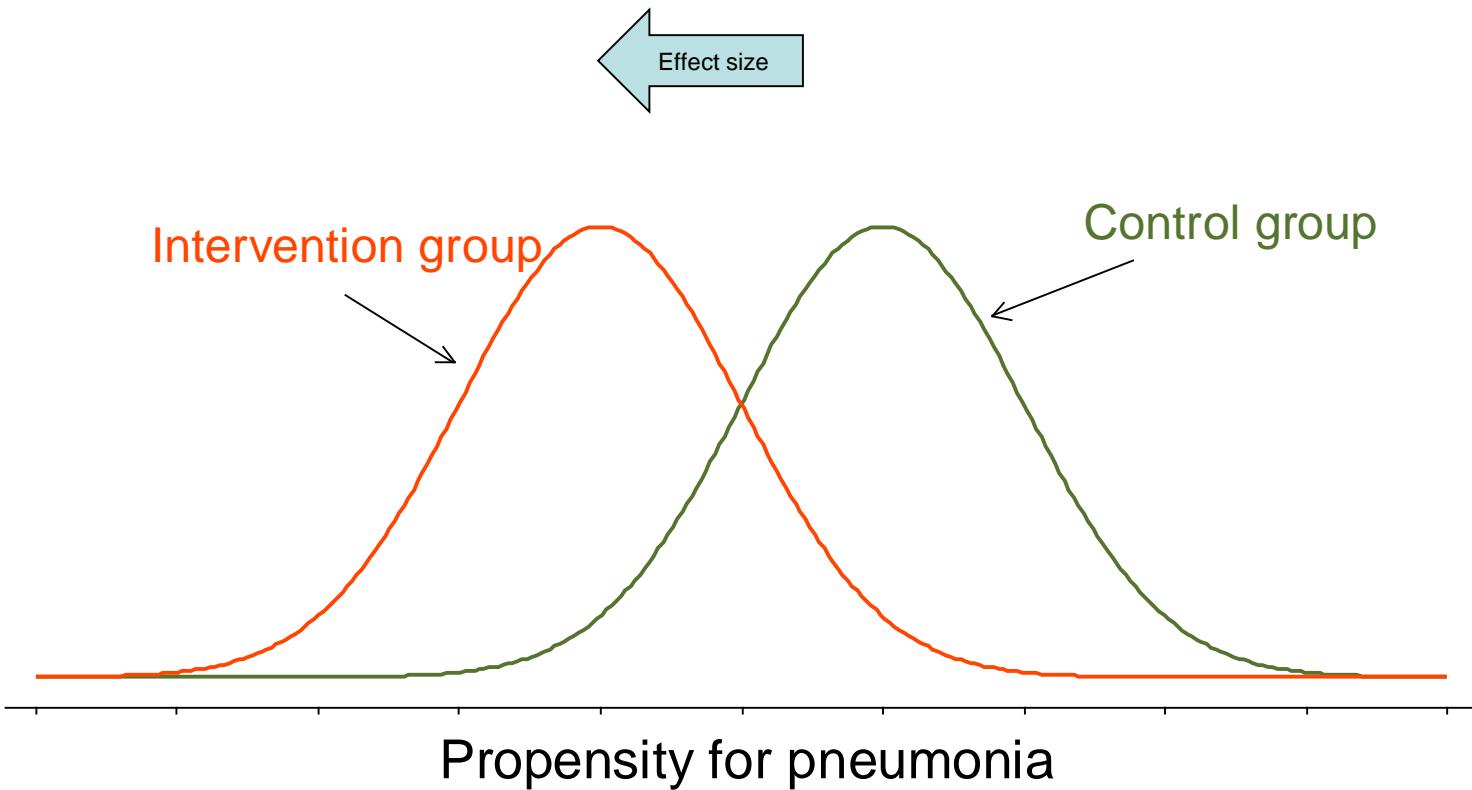
Infection prevention in ICU

vap = ventilator associated pneumonia
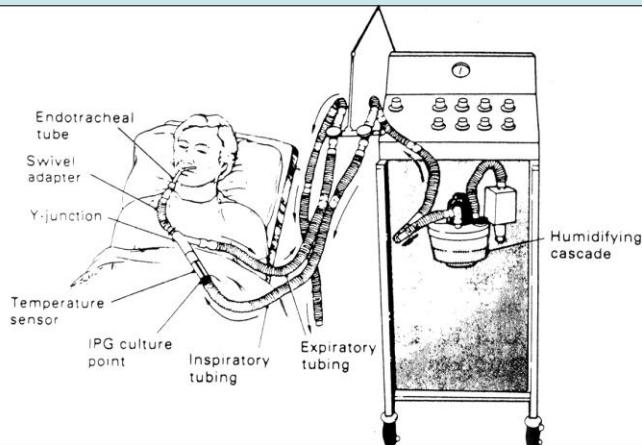
		Study group	
		Intervention (no.)	Control (no.)
Pneumonia / Bacteremia	**+**	ivap_n	vap_n
	-	ivap_m	vap_m

Logit IGR = log(ivap_n/ ivap_m)

Logit CGR = log(vap_n/ vap_m)

n = 177

n = 52

non-antibiotic groups

C_group VAP incidence (%)

topical antibiotic_concurrent groups

C_group VAP incidence (%)

Linear scale
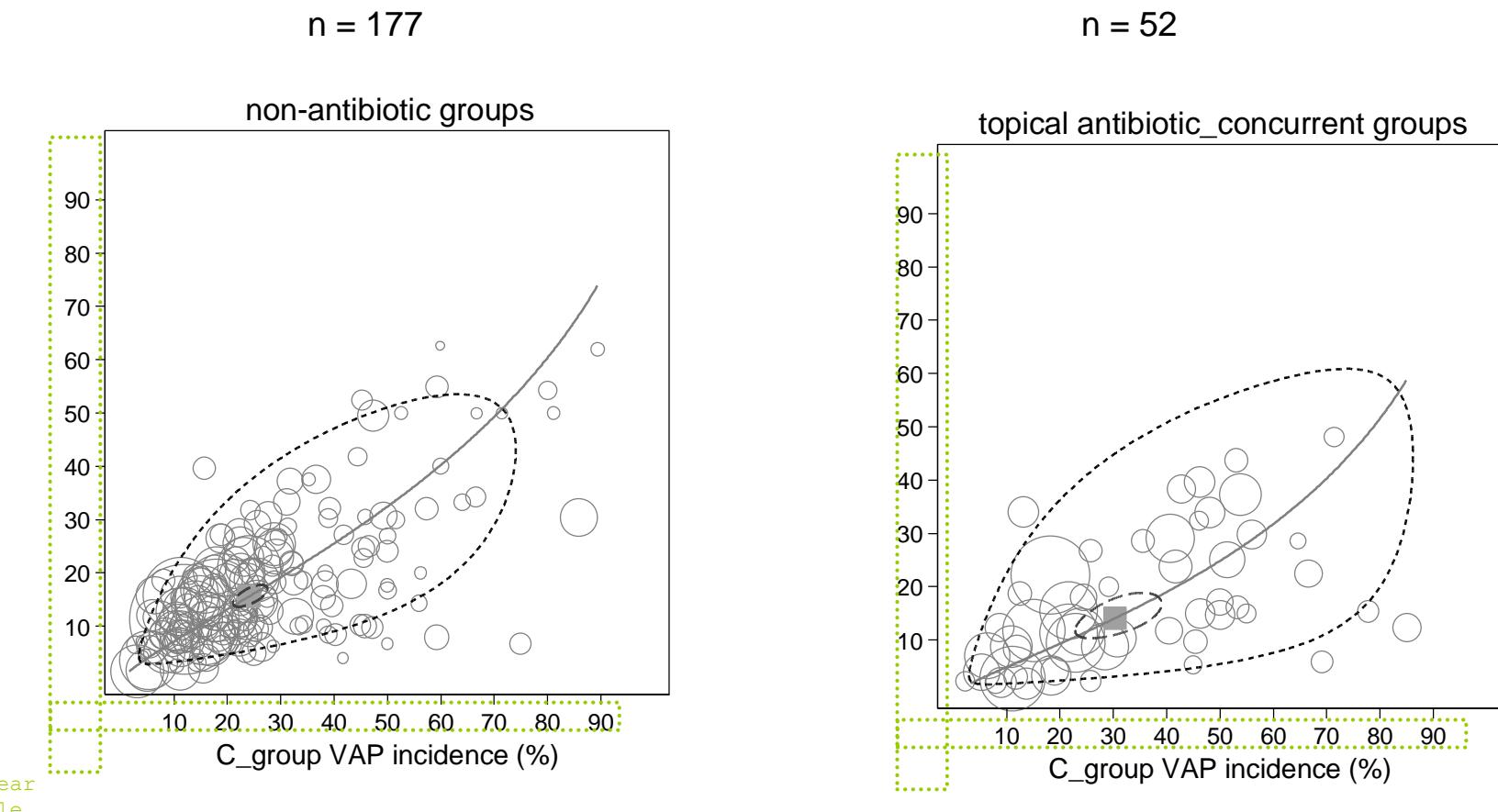
```
metandiplot    vap_n ivap_n vap_m ivap_m , legend(off) ylab( , ang(h)) title(Pneumonia)
metandiplot    vap_n ivap_n vap_m ivap_m, yla(`lay', ang(h)) xla(`lax') yti("`yttl'") xti("`xttl'") legend(off)
```

Studies of infection prevention in ICU
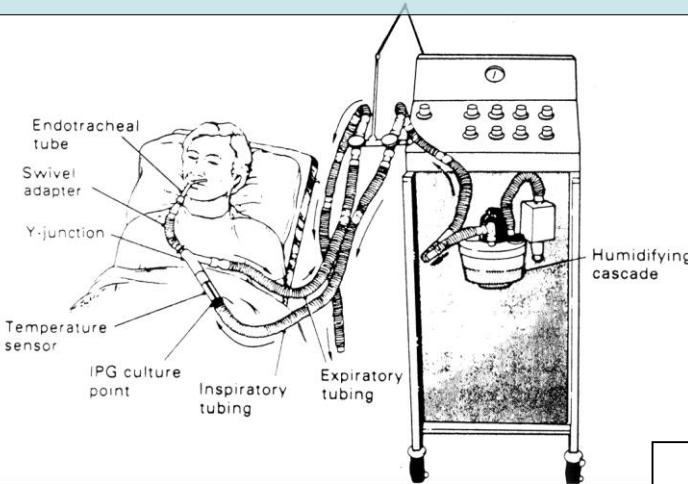
Electronic search terms
Ventilator associated pneumonia OR bacteremia
AND Mechanical ventilation OR Intensive care unit
AND Systematic review OR meta-analysis

8 systematic reviews or meta-analyses

None | **Non-antibiotic** | **Topical antibiotic**

47 | 98 | 34

1 | 10 | 17

48 studies | **108 studies** | **51 studies**

Observational groups

N= 48 groups

Non-antibiotic:

N=217 groups

Topical antibiotic: Non-concurrent

N= 26 groups

Topical antibiotic: Concurrent

N= 78 groups

control

108 | 14 | 38

1 48 | **2** | **3** | **4** | **5**

intervention

108 | 12 | 40
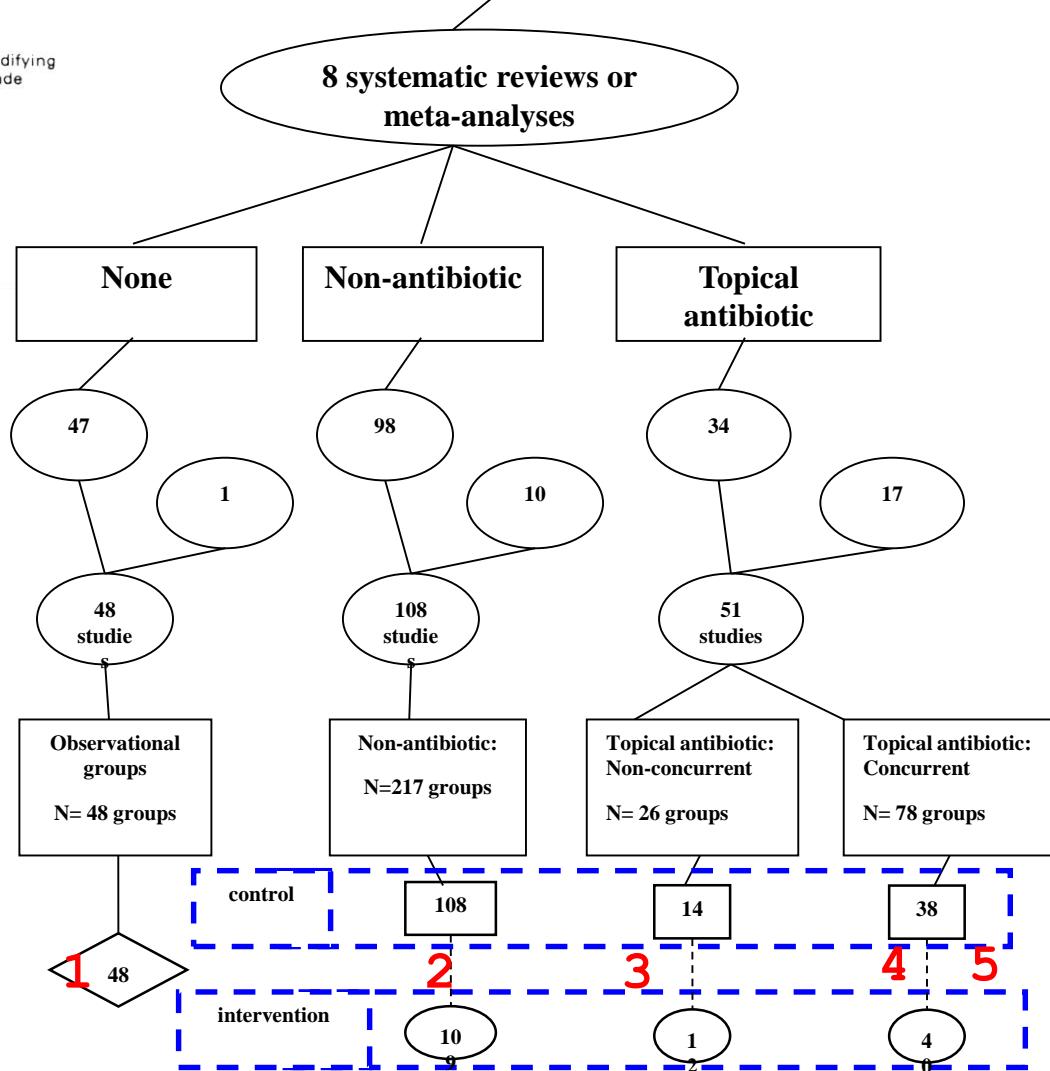
Note, the numbers do not tally as some systematic reviews and studies each provided studies and groups in more than one category, respectively.

23

Observation study design
(no intervention under study; C = I)

Bacteremia

Pneumonia

24
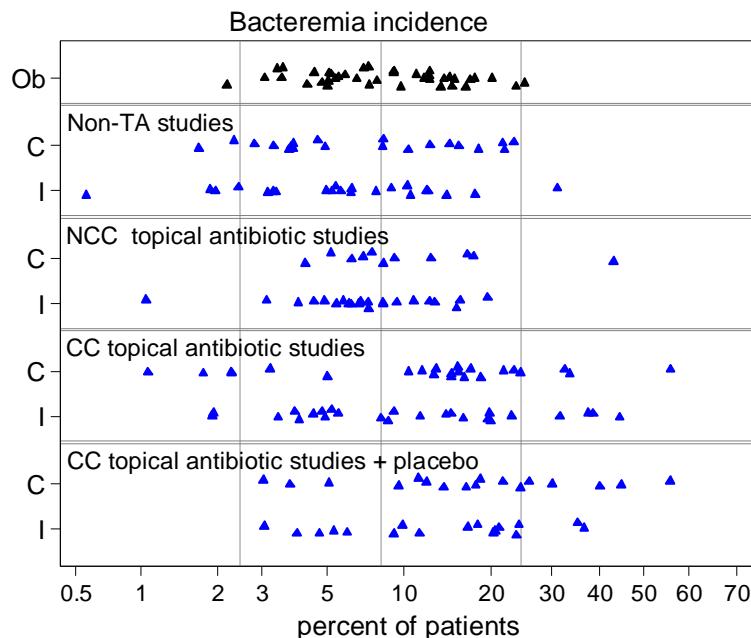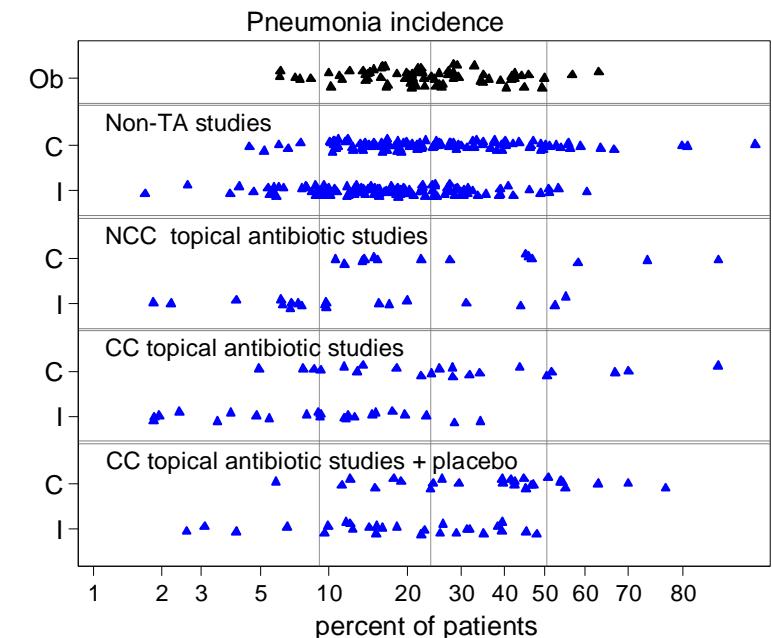
Observation study design
(no intervention under study; C = I)

Bacteremia
n = 39
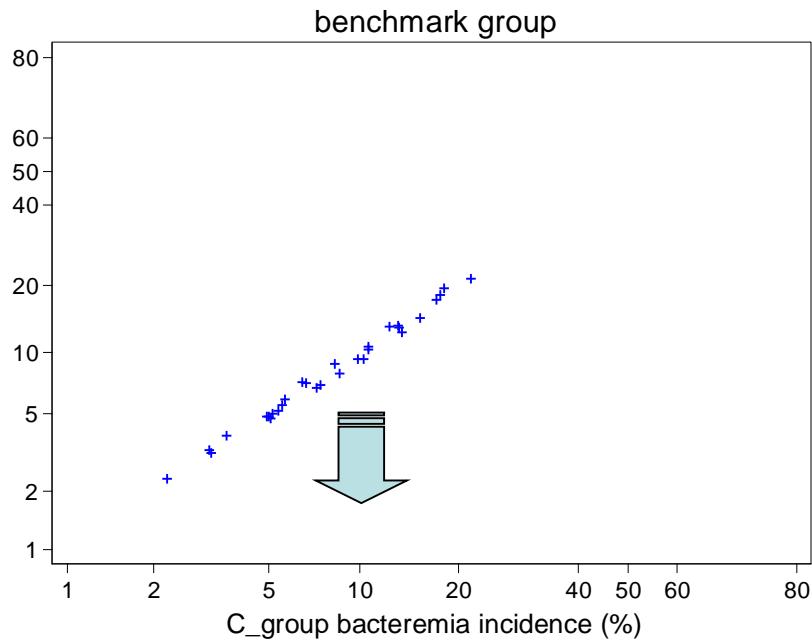
Pneumonia
n = 48
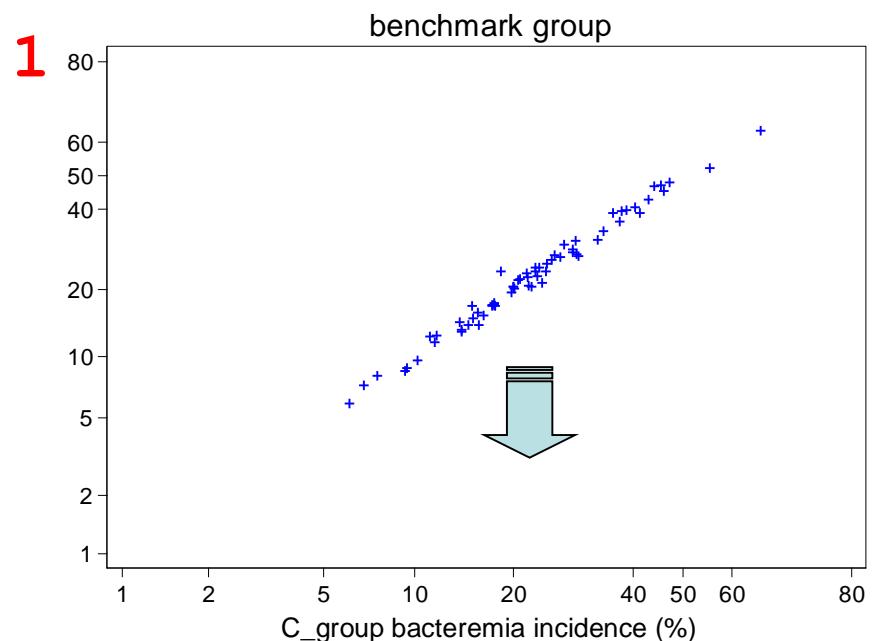

```
twoway (scatter vlogodds ivlogodds if figure ==1, ms(+) msize(small) mcolor(blue) jitter (3)), yla(`la', ang(h))
xla(`la') yti("`yttl'") xti("`xttl'") legend(off) ti(benchmark group)

twoway (scatter blogodds iblogodds if figure ==1, ms(+) msize(small) mcolor(blue) jitter (3)), yla(`la', ang(h))
xla(`la') yti("`yttl'") xti("`xttl'") legend(off) ti(benchmark group)
```

Non-antibiotic methods for infection prevention

Bacteremia
n = 20
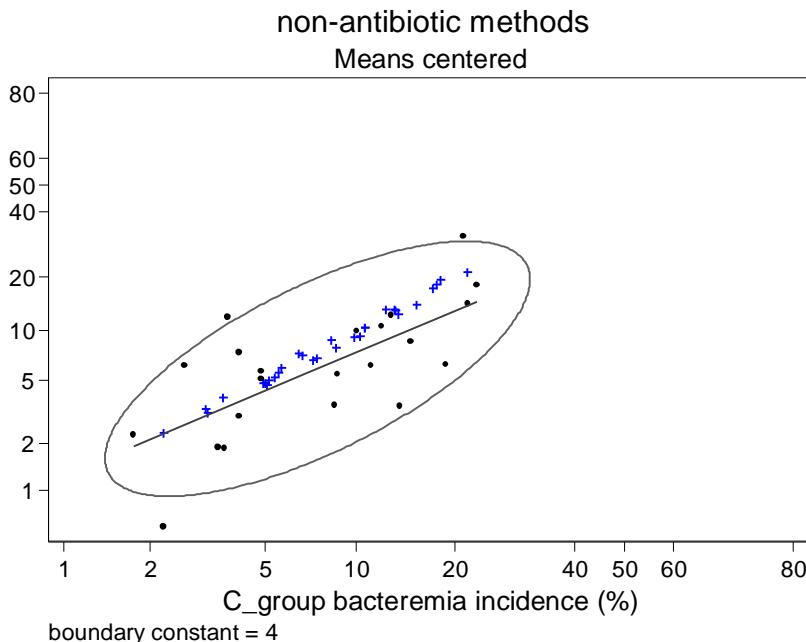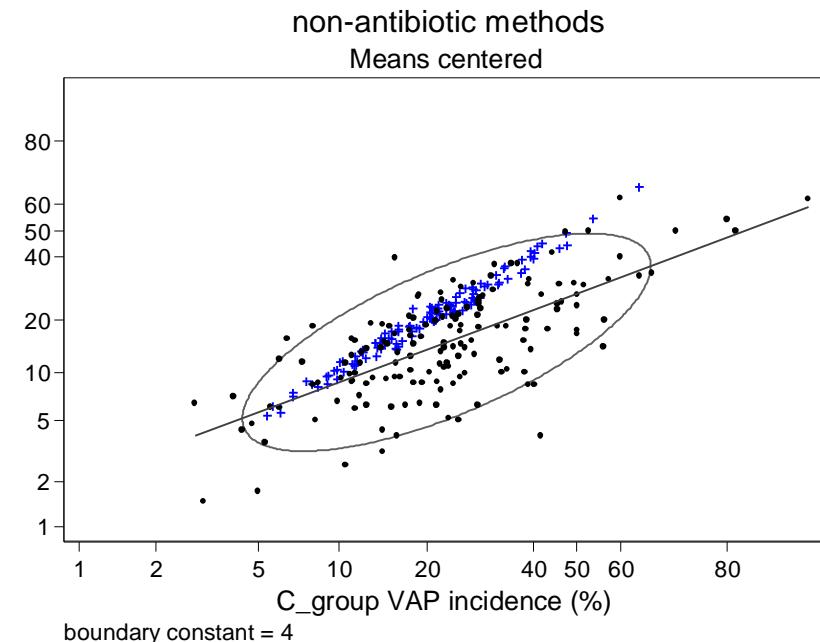
non-antibiotic methods
Means centered

Pneumonia
n = 105

non-antibiotic methods
Means centered

2

C_group bacteremia incidence (%)

boundary constant = 4

C_group VAP incidence (%)

boundary constant = 4

```
ellip blogodds iblogodds if figure ==3, yla(`la', ang(h)) xla(`la') yti("`yttl'") xti("`xttl'") legend(off) plot(scatter
blogodds iblogodds if figure ==1, ms(+) msize(small) mcolor(blue) jitter (3)|| scatter blogodds iblogodds if figure ==3, ms(o)
msize(small) mcolor(black) || lfit blogodds iblogodds if figure ==3) legend(off) ti(non-antibiotic methods)
```

```
ellip vlogodds ivlogodds if figure ==3, yla(`la', ang(h)) xla(`la') yti("`yttl'") xti("`xttl'") legend(off) plot(scatter vlogodds
ivlogodds if figure ==1, ms(+) msize(small) mcolor(blue) jitter (3)|| scatter vlogodds ivlogodds if figure ==3, ms(o) msize(small)
mcolor(black) || lfit vlogodds ivlogodds if figure ==3) legend(off) ti(non-antibiotic methods)
```

# Topical antibiotic methods for infection prevention
(Non Concurrent Control)

Bacteremia
n = 16

Pneumonia
n = 24

NCC antibiotic methods
Means centered

NCC antibiotic methods
Means centered

3

boundary constant = 4

boundary constant = 4
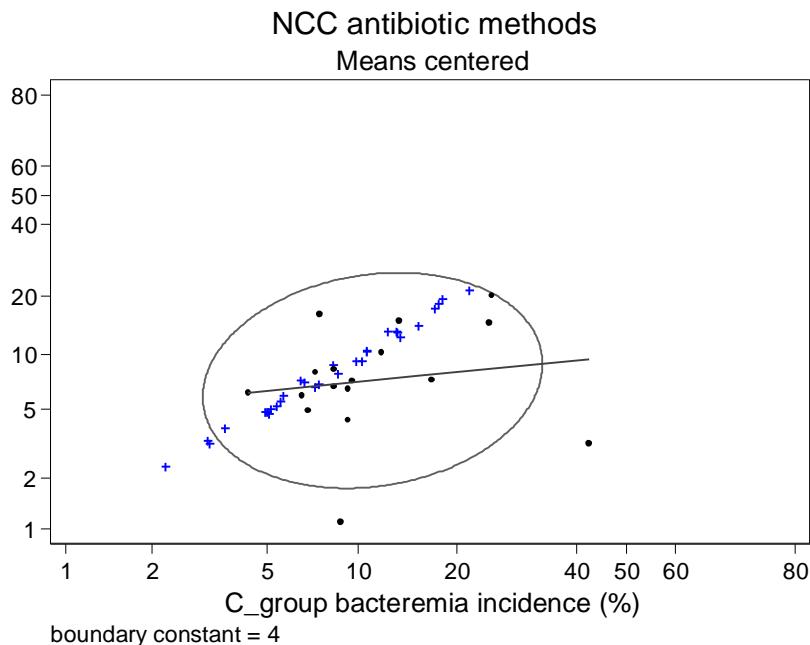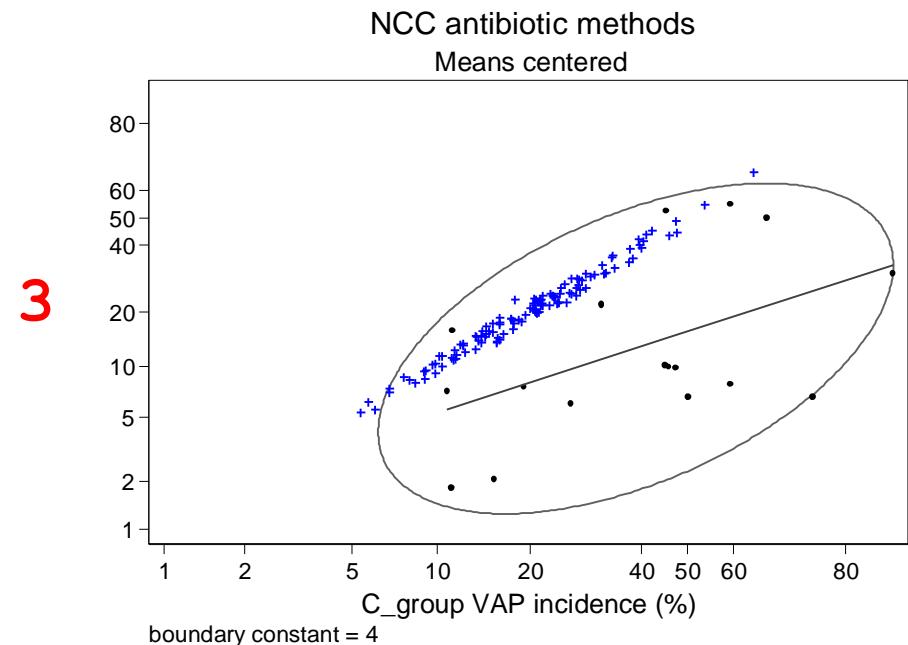
```
ellip blogodds iblogodds if figure ==5, yla(`la', ang(h)) xla(`la') yti("`yttl'") xti("`xttl'") legend(off)
plot(scatter blogodds iblogodds if figure ==1, ms(+) msize(small) mcolor(blue) jitter (3)|| scatter blogodds
iblogodds if figure ==5, ms(o) msize(small) mcolor(black) || lfit blogodds iblogodds if figure ==5) legend(off)
ti(NCC antibiotic methods)
```

Topical antibiotic methods for infection prevention (Concurrent Control)

Bacteremia
n = 40

Pneumonia
n = 42

CC antibiotic methods
Means centered

C_group bacteremia incidence (%)
boundary constant = 4

CC antibiotic methods
Means centered

C_group VAP incidence (%)
boundary constant = 4

4
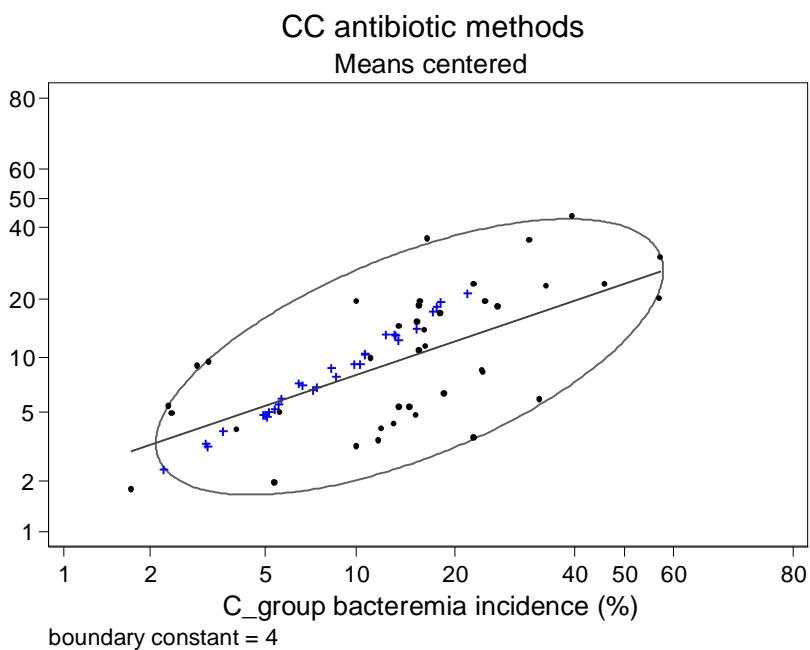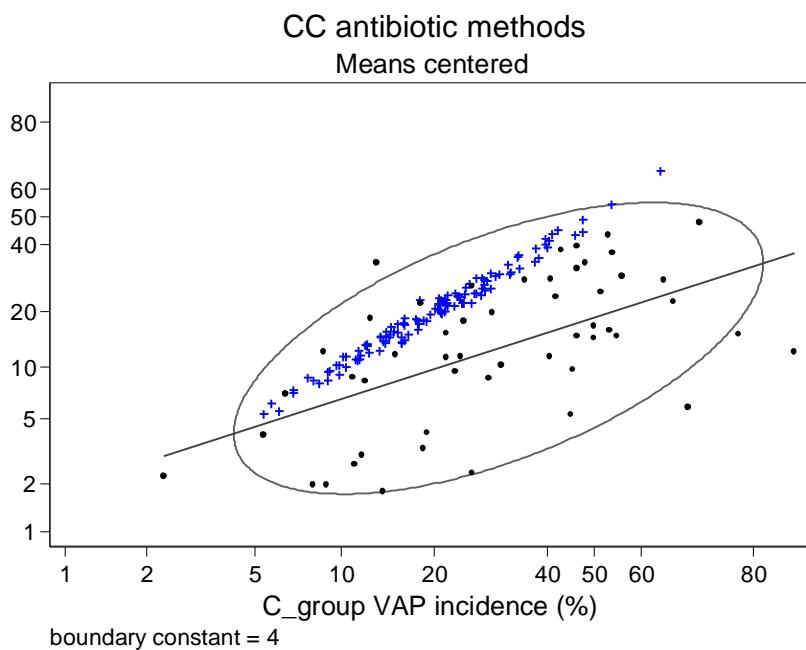
```
ellip blogodds iblogodds if figure ==7, yla(`la', ang(h)) xla(`la') yti("`yttl'") xti("`xttl'") legend(off) plot(scatter
blogodds iblogodds if figure ==1, ms(+) msize(small) mcolor(blue) jitter (3)|| scatter blogodds iblogodds if figure ==7 &
plac==1, ms(o) msize(small) mcolor(black) || lfit blogodds iblogodds if figure ==7) legend(off) ti(CC antibiotic & topical
placebo)
```

Topical antibiotic methods for infection prevention
## (Concurrent Control
Topical placebo)

Bacteremia
n = 40
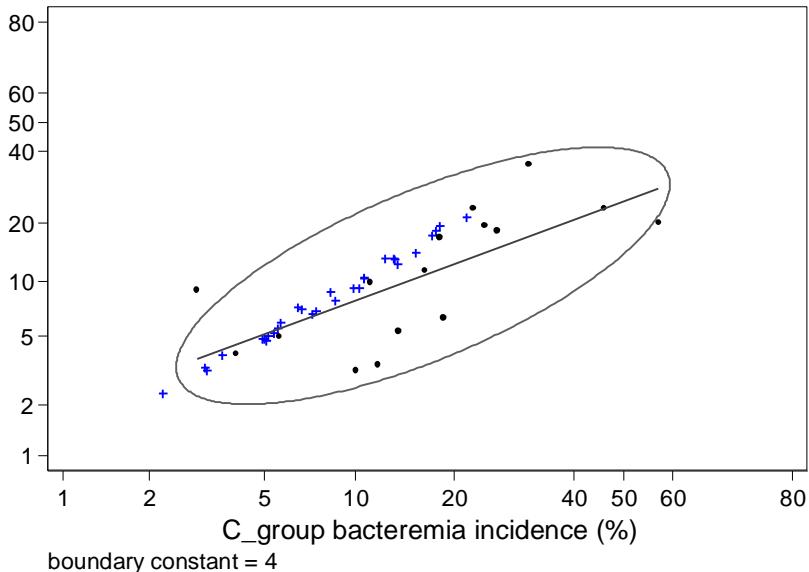
Pneumonia
n = 42

CC antibiotic & topical placebo
Means centered
C_group bacteremia incidence (%)
boundary constant = 4

5

CC antibiotic & topical placebo
Means centered
C_group VAP incidence (%)
boundary constant = 4
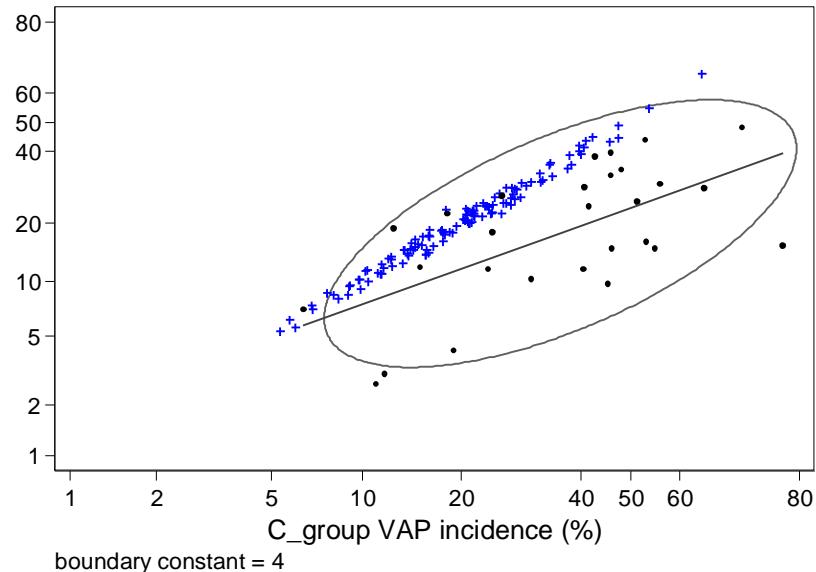
```
ellip blogodds iblogodds if figure ==7 & plac==1, yla(`la', ang(h)) xla(`la') yti("`yttl'") xti("`xttl'") legend(off)
plot(scatter blogodds iblogodds if figure ==1, ms(+) msize(small) mcolor(blue) jitter (3)|| scatter blogodds iblogodds if
figure ==7 & plac==1, ms(o) msize(small) mcolor(black) || lfit blogodds iblogodds if figure ==7 & plac==1) legend(off)
ti(CC antibiotic & topical placebo)
```

**a.   Observation study design**
- **no study intervention**
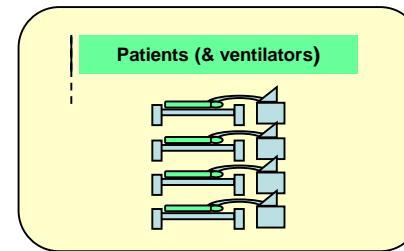
b. Non-antibiotic intervention
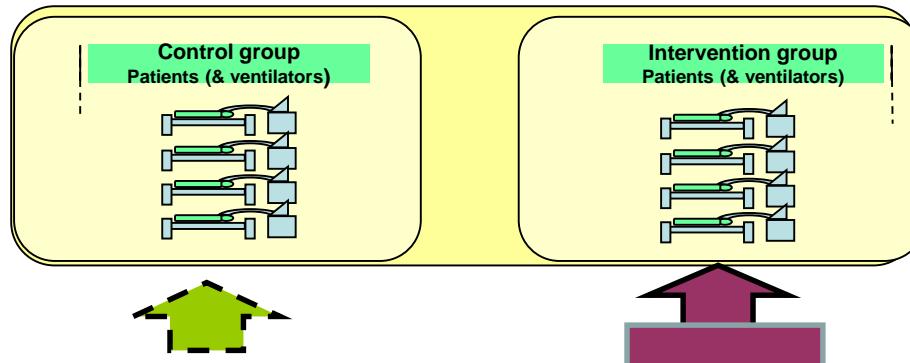
c. Topical antibiotics
- **Non-concurrent study design**
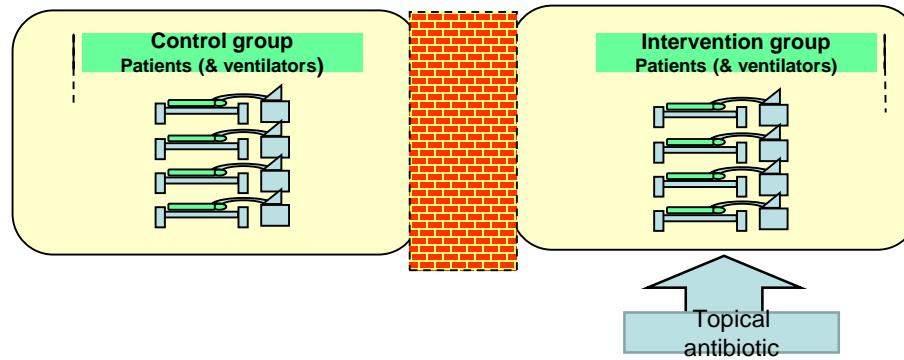
d. Topical antibiotics
- **Concurrent study design**

1

2

3

4
5
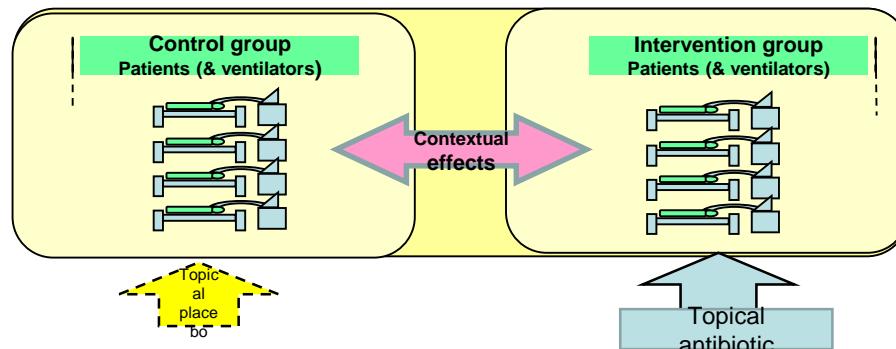
30

Summary

- Meta-analysis capabilities in Stata
  - derivation of summary effect sizes
  - a 'visual' of the relationships of
    - component studies (as individual or sub-groups) to overall effect sizes.
    - component groups within studies to overall effect sizes.

- Relationship of effect size to control group variability
  - A range of approaches (pro & con for each).
  - Graphics within `metan` & `metandi` offer novel insights
  - Ellipse versus linear regression
  - "Tea leaf reading" or enabling the data to speak for themselves?