Visualizing and diagnosing spillover within randomized controlled trials using diagnostic test assessment methods in STATA

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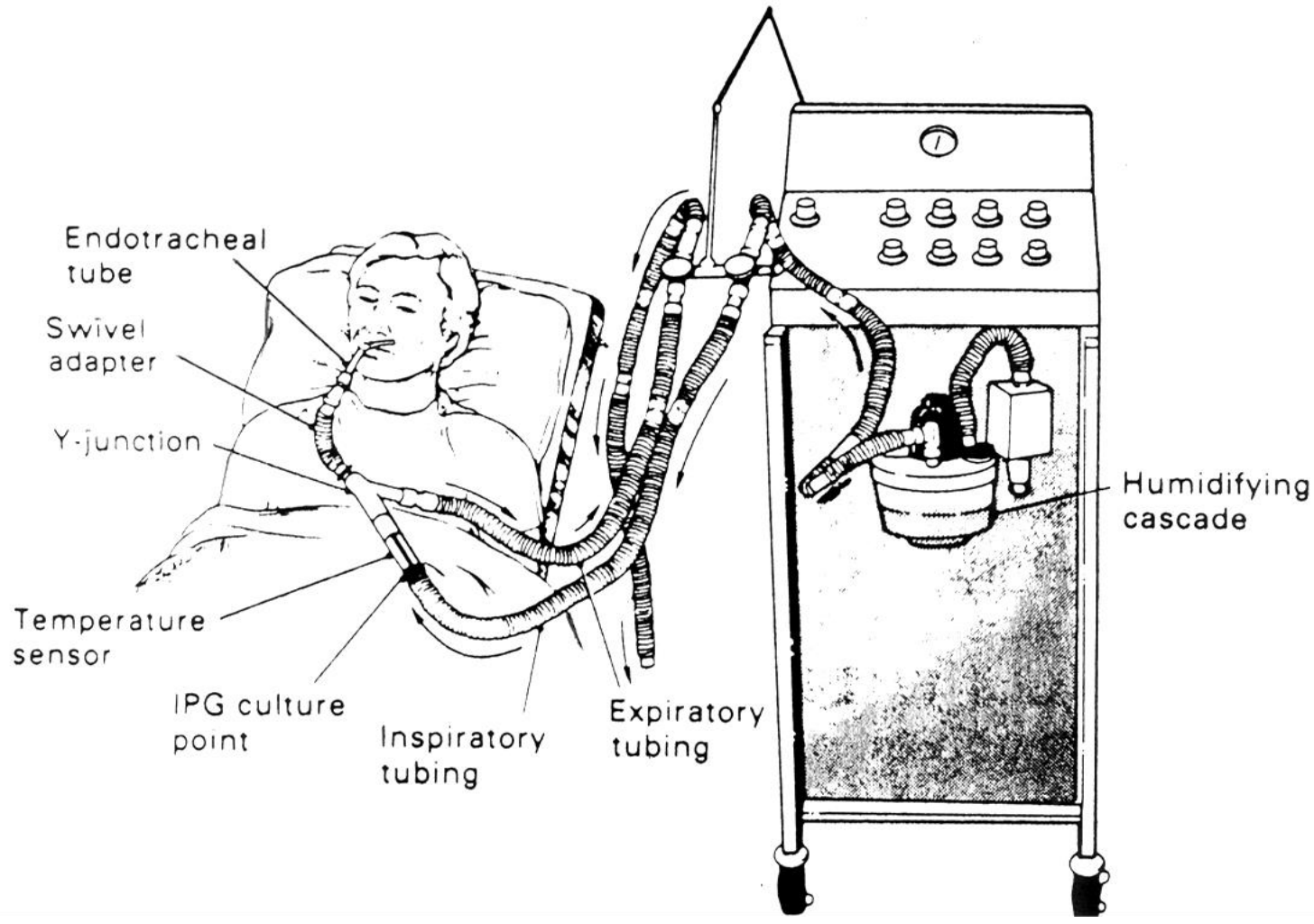
Hurley JC. Visualizing and diagnosing spillover within randomized concurrent controlled trials through the application of diagnostic test assessment methods.
BMC Medical Research Methodology. 2024 Aug 16;24(1):182.

Disclosures

James Hurley has no conflicts of interest to declare



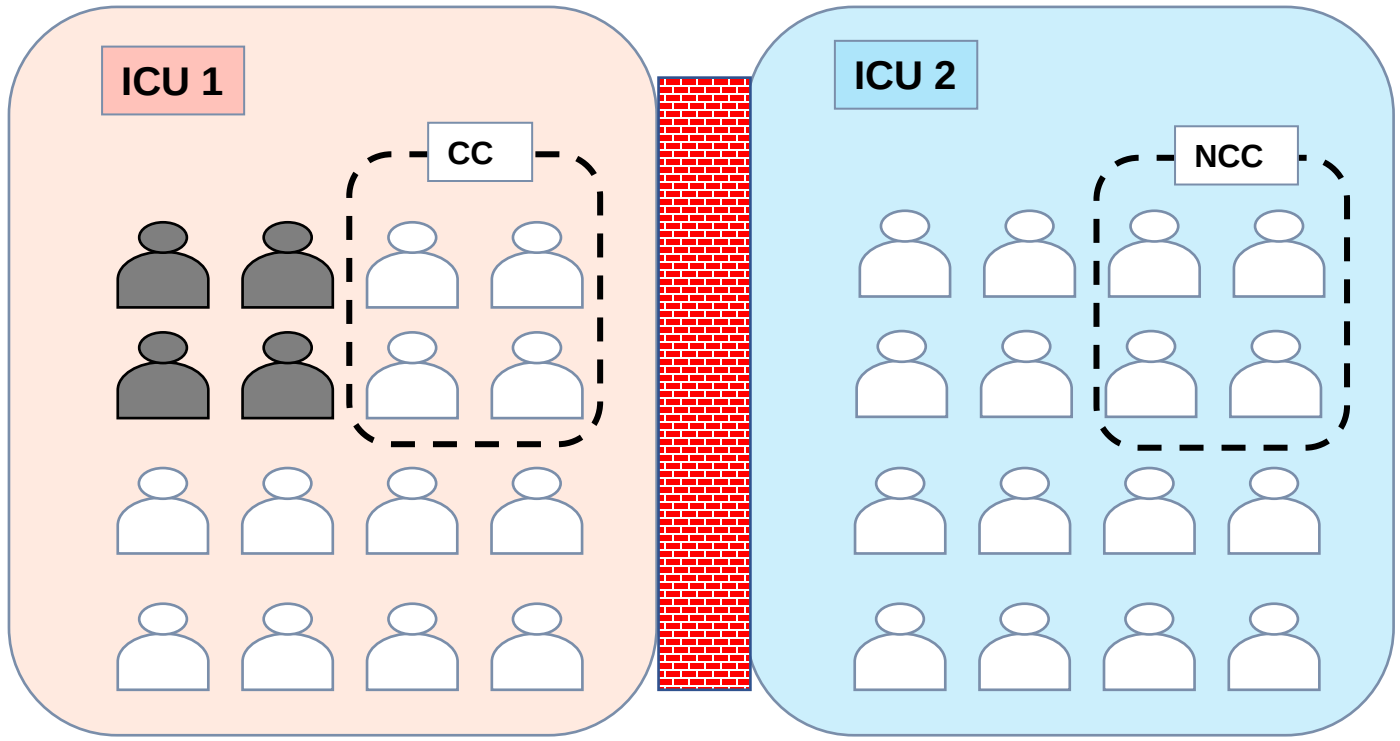
Pneumonia

- 5 to 40% of ICU patients receiving MV - [Expert range]
- Cross infection in the ICU is a driver

- Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Resp Crit Care Med. 2002;165(7):867–903.

Research question:

Does spillover from intervention groups influence the event rate in concurrent control groups of antimicrobial interventions used to prevent pneumonia?



Pneumonia prevention interventions

- Non-antimicrobial based – ineffective
- Antimicrobial – effective

Inference from RCT's assume SUTVA

- SUTVA = Stable Unit treatment value assumption

Non-antimicrobial

Study	Treatment Yes	Treatment No	Control Yes	Control No	Odds ratio with 95% CI	Weight (%)
Wu, 103	11	45	48	8	0.04 [0.02, 0.11]	.94
Rabitsch, 77	0	12	5	7	0.05 [0.00, 1.13]	.18
Martin, 7	0	56	4	57	0.11 [0.01, 2.15]	.19
Drakulovic, 97	3	36	16	31	0.16 [0.04, 0.61]	.67
Montecalvo_G, 67	0	19	2	17	0.18 [0.01, 4.00]	.17
Cai, 96	4	23	13	14	0.19 [0.05, 0.69]	.69
Hang, 98	3	17	9	10	0.20 [0.04, 0.90]	.55
Tryba, 44	3	26	11	21	0.22 [0.05, 0.89]	.62
Eddleston '91, 18	3	27	10	20	0.22 [0.05, 0.91]	.61
Yu, 105	5	28	14	18	0.23 [0.07, 0.75]	.78
Hu, 99	8	35	21	22	0.24 [0.09, 0.63]	.96
Klarin, 108	1	22	3	18	0.27 [0.03, 2.85]	.28
Xue, 104	4	44	12	36	0.27 [0.08, 0.92]	.75
Welte, 79	9	18	16	9	0.28 [0.09, 0.88]	.8
Spindler-Vesel, 112	4	22	34	53	0.28 [0.09, 0.89]	.8
Khorvash, 25	10	61	24	42	0.29 [0.12, 0.66]	1.1
Hsu, 64	5	54	15	47	0.29 [0.10, 0.86]	.85
Martin, 92	2	29	8	34	0.29 [0.06, 1.49]	.5
Kudsk, 52	6	45	14	31	0.30 [0.10, 0.85]	.88
Behrens, 10	0	22	1	20	0.30 [0.01, 7.88]	.16
Day, 61	1	13	2	9	0.35 [0.03, 4.42]	.24
Acosta-escribano, 60	16	34	31	23	0.35 [0.16, 0.78]	1.1
Chourdakis, 55	20	14	20	5	0.36 [0.11, 1.18]	.76
Keeley, 101	5	12	7	6	0.36 [0.08, 1.62]	.56
Tan, 113	7	9	13	6	0.36 [0.09, 1.43]	.63
Nguyen, 59	3	11	6	8	0.36 [0.07, 1.91]	.49
Combes, 71	4	50	9	41	0.36 [0.10, 1.27]	.72
Eyer, 56	4	15	8	11	0.37 [0.09, 1.53]	.6
Morrow, 111	17	56	33	40	0.37 [0.18, 0.75]	1.3
Hill, 57	4	18	9	15	0.37 [0.09, 1.45]	.65
Prod'hom, 37	10	73	21	59	0.38 [0.17, 0.88]	1.1
Kirton , 88	10	130	22	118	0.41 [0.19, 0.91]	1.2
Cioffi, 13	9	41	17	33	0.43 [0.17, 1.08]	1
White, 69	5	45	11	43	0.43 [0.14, 1.35]	.81
Kortbeek , 66	10	27	18	25	0.51 [0.20, 1.32]	.99
Zeitoun, 80	7	16	11	13	0.52 [0.16, 1.71]	.76
Altintas, 48	5	25	11	30	0.55 [0.17, 1.78]	.77
Roustan, 94	5	50	9	52	0.58 [0.18, 1.84]	.79
Kollef'08_silverETT, 95	37	729	56	687	0.62 [0.41, 0.96]	1.6
Solouki, 41	6	62	8	53	0.64 [0.21, 1.97]	.82
Hurni, 87	5	54	7	49	0.65 [0.19, 2.18]	.75
Knight, 109	12	118	17	112	0.67 [0.31, 1.47]	1.2
Memish, 93	14	109	19	101	0.68 [0.33, 1.43]	1.2
Ephgrave, 19	11	59	15	55	0.68 [0.29, 1.62]	1.1
Pickworth , 35	5	39	6	33	0.71 [0.20, 2.52]	.71
Metz , 8	12	72	15	64	0.71 [0.31, 1.63]	1.1
Montejo, 68	16	34	20	31	0.73 [0.32, 1.65]	1.1
Fabian, 20	15	50	52	127	0.73 [0.38, 1.42]	1.3
Hanisch, 4	10	47	6	22	0.78 [0.25, 2.42]	.81
JustoMeirelles, 51	2	10	2	8	0.80 [0.09, 7.00]	.32
Prod'hom, 37	18	63	21	59	0.80 [0.39, 1.65]	1.2
Boots, 82	6	36	7	34	0.81 [0.25, 2.65]	.77
Conrad, 14	17	164	20	158	0.82 [0.41, 1.62]	1.3
Lacherade '05, 90	47	138	53	131	0.84 [0.53, 1.33]	1.6
Dreyfuss, 86	6	55	8	62	0.85 [0.28, 2.59]	.83
Deppe, 73	12	34	11	27	0.87 [0.33, 2.27]	.97
Somberg, 42	3	32	16	151	0.88 [0.24, 3.22]	.69
Kollef '98, 89	15	148	15	132	0.89 [0.42, 1.89]	1.2
Kotzampassi, 110	15	21	16	20	0.89 [0.35, 2.27]	1
Ryan_C, 38	7	49	8	50	0.89 [0.30, 2.65]	.85
Johnson, 74	8	8	10	9	0.90 [0.24, 3.41]	.67
Thomason, 43	42	94	49	99	0.90 [0.55, 1.49]	1.5
Davies, 63	18	73	19	70	0.91 [0.44, 1.87]	1.2
Simms_S , 39	8	22	9	23	0.93 [0.30, 2.84]	.83
Bonten '95, 12	16	58	15	52	0.96 [0.43, 2.12]	1.2
Fogas, 21	9	29	10	31	0.96 [0.34, 2.70]	.9
Yildizdas, 9	16	22	6	8	0.97 [0.28, 3.35]	.73
Lorente'06a, 76	33	203	31	190	1.00 [0.59, 1.69]	1.5
Lee, 27	1	29	1	29	1.00 [0.06, 16.76]	.2
Adams, 70	0	10	0	10	1.00 [0.02, 55.27]	.11
Thomason, 43	42	94	43	97	1.01 [0.60, 1.68]	1.5
Forestier, 107	24	78	24	82	1.05 [0.55, 2.00]	1.3
Hanisch, 4	10	34	6	22	1.08 [0.34, 3.39]	.8
Yildizdas, 9	17	21	6	8	1.08 [0.31, 3.72]	.73
Wischmeyer, 54	18	55	12	40	1.09 [0.47, 2.52]	1.1
Ben-Menachem, 11	13	87	12	88	1.10 [0.47, 2.53]	1.1
Conrad, 72	6	10	6	11	1.10 [0.27, 4.55]	.61
Branson, 84	3	46	3	51	1.11 [0.21, 5.77]	.49
Yildizdas, 46	20	22	17	21	1.12 [0.47, 2.71]	1.1
Kantorova, 24	7	64	6	63	1.15 [0.37, 3.61]	.8
Lorente'05, 75	43	167	42	191	1.17 [0.73, 1.88]	1.6
Yildizdas, 9	20	22	6	8	1.21 [0.36, 4.10]	.74
Leng, 102	5	23	5	28	1.22 [0.31, 4.73]	.65
Cook, 15	114	482	98	506	1.22 [0.91, 1.64]	1.8
Boots, 83	32	158	27	164	1.23 [0.70, 2.15]	1.5
Alcoforado, 81	5	3	4	3	1.25 [0.16, 9.92]	.34
[illegible]	[illegible]	33	4	34	1.29 [0.32, 5.22]	.62
[illegible]	[illegible]	63	5	70	1.33 [0.39, 4.58]	.73
[illegible]	[illegible]	19	6	17	1.34 [0.40, 4.56]	.74
[illegible]	[illegible]	34	10	47	1.38 [0.52, 3.69]	.95
[illegible]	[illegible]	37	10	37	1.40 [0.55, 3.55]	1
[illegible]	[illegible]	17	10	20	1.41 [0.49, 4.07]	.88
[illegible]	[illegible]	55	13	60	1.43 [0.63, 3.21]	1.1
[illegible]	[illegible]	28	9	28	1.44 [0.53, 3.92]	.93
[illegible]	[illegible]	33	3	29	1.46 [0.32, 6.67]	.56
[illegible]	[illegible]	14	9	17	1.48 [0.48, 4.59]	.82
[illegible]	[illegible]	64	5	70	1.53 [0.46, 5.07]	.76
[illegible]	[illegible]	13	9	12	1.54 [0.49, 4.81]	.81
[illegible]	[illegible]	54	4	56	1.56 [0.42, 5.82]	.67
[illegible]	[illegible]	64	15	65	1.56 [0.75, 3.25]	1.2
[illegible]	[illegible]	17	3	20	1.57 [0.31, 8.01]	.5
[illegible]	[illegible]	15	5	15	1.60 [0.42, 6.03]	.67
[illegible]	[illegible]	99	8	101	1.66 [0.66, 4.17]	1
[illegible]	[illegible]	12	8	15	1.72 [0.53, 5.62]	.77
Kantorova, 5	8	64	5	70	1.75 [0.54, 5.63]	.79
Martin, 32	12	28	7	30	1.84 [0.63, 5.33]	.87
Karlstadt, 6	1	53	0	33	1.88 [0.07, 47.47]	.16
Tryba, 45	6	194	3	197	2.03 [0.50, 8.24]	.62
Ben-Menachem, 2	12	88	3	47	2.14 [0.57, 7.95]	.68
Laggner, 26	2	14	1	15	2.14 [0.17, 26.33]	.25
Prakash, 36	15	10	10	15	2.25 [0.73, 6.98]	.81
Driks, 17	16	53	7	54	2.33 [0.89, 6.12]	.97
Ben-Menachem, 2	13	87	3	47	2.34 [0.64, 8.63]	.68
Davies, 62	2	29	1	34	2.34 [0.20, 27.20]	.26
Kappstein, 23	25	30	12	37	2.57 [1.11, 5.95]	1.1
Eddleston '94, 3	1	13	0	12	2.78 [0.10, 74.70]	.15
Lorente'06b, 91	21	32	8	43	3.53 [1.39, 8.98]	1
Fan, 50	20	20	8	32	4.00 [1.48, 10.79]	.94
Apte , 1	13	3	9	9	4.33 [0.91, 20.60]	.54
Mustafa, 33	9	7	3	12	5.14 [1.03, 25.60]	.51
Levy, 28	5	30	1	31	5.17 [0.57, 46.86]	.31
Phillips, 34	4	21	0	33	14.02 [0.72, 273.76]	.18
Overall					0.82 [0.71, 0.93]	

Test of $\theta_i = \theta_j$: Q(121) = 229.85, p = 0.00
Test of θ = 0: z = -2.99, p = 0.00

1/256 1/16 1 16 256
odds ratio

Non-antimicrobial;
ES 0.82 (0.71-0.93)
N = 122
I^2 = 50.4

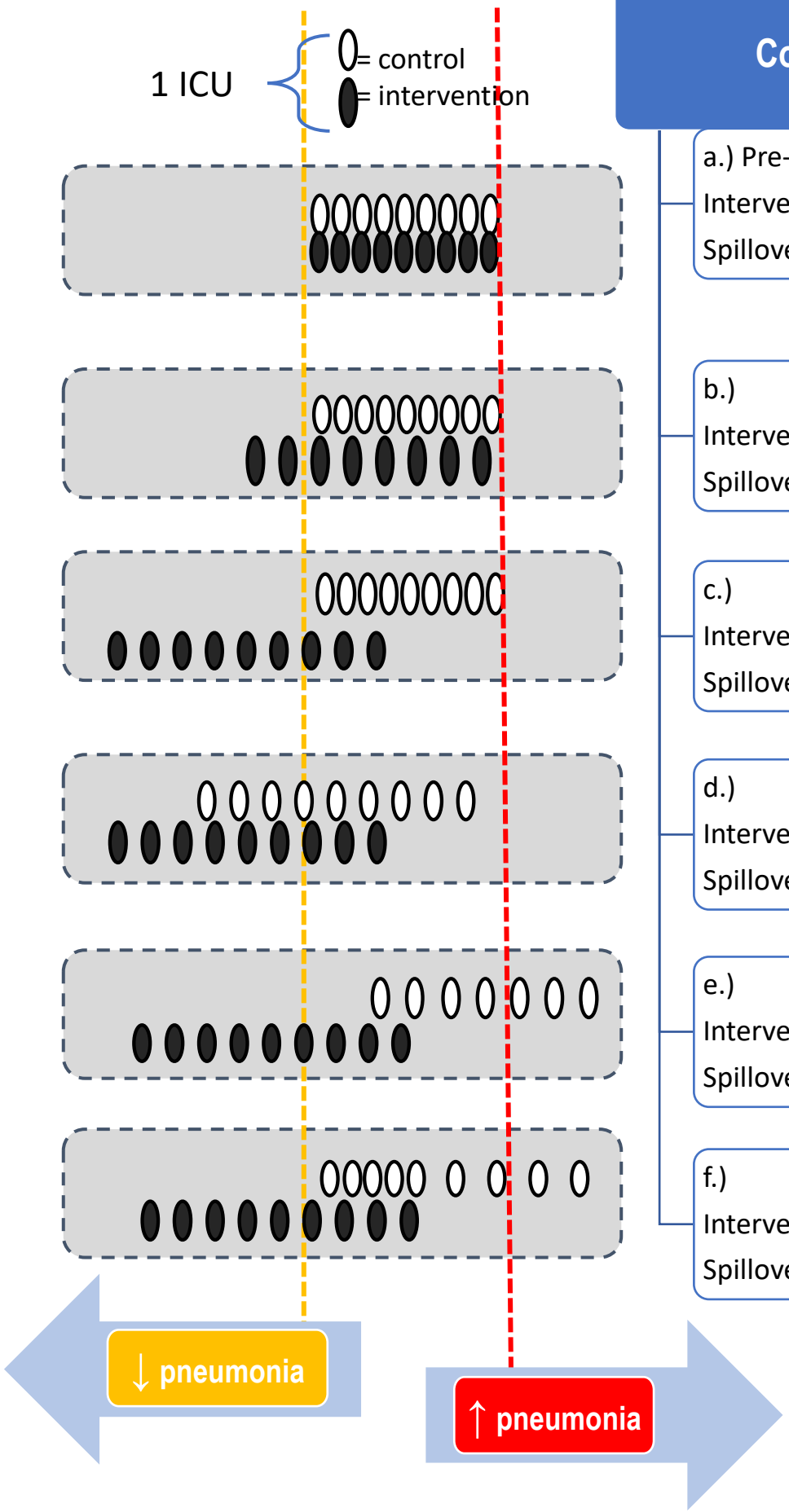
Antimicrobial

Study	Treatment Yes	Treatment No	Control Yes	Control No	Odds ratio with 95% CI	Weight (%)
Fu , 121	7	33	37	3	0.02 [0.00, 0.07]	1.1
Aerdts, 167	1	17	29	10	0.02 [0.00, 0.17]	.67
Rodríguez-Roldán, 193	0	13	11	6	0.02 [0.00, 0.41]	.4
Pugin, 191	4	21	24	3	0.02 [0.00, 0.12]	.98
Tang, 145	5	25	25	5	0.04 [0.01, 0.16]	1.2
Kerver, 174	5	44	31	16	0.06 [0.02, 0.18]	1.4
Unertl, 194	1	18	9	11	0.07 [0.01, 0.61]	.65
Jacobs, 173	0	36	4	39	0.12 [0.01, 2.31]	.41
Georges , 187	3	28	15	18	0.13 [0.03, 0.51]	1.2
Yao, 148	4	24	14	11	0.13 [0.03, 0.49]	1.2
Seguin, 142	3	33	12	19	0.14 [0.04, 0.58]	1.1
Abele-Horn, 166	13	45	20	10	0.14 [0.05, 0.38]	1.5
Winter, 182	3	88	17	75	0.15 [0.04, 0.53]	1.3
Pneumatikos , 190	5	26	16	14	0.17 [0.05, 0.56]	1.3
Ulrich, 180	7	41	26	26	0.17 [0.06, 0.45]	1.6
Cabov, 116	1	16	6	17	0.18 [0.02, 1.64]	.64
Feng, 136	8	57	29	39	0.19 [0.08, 0.46]	1.6
Fourrier'00, 119	5	25	14	14	0.20 [0.06, 0.67]	1.3
Rocha, 177	7	40	25	29	0.20 [0.08, 0.53]	1.6
Mo, 138	15	90	47	58	0.21 [0.11, 0.40]	1.9
Palomar, 176	10	31	25	17	0.22 [0.09, 0.56]	1.6
Hu, 137	4	21	10	12	0.23 [0.06, 0.89]	1.2
Blair, 168	11	115	37	93	0.24 [0.12, 0.50]	1.8
Nobahar, 139	5	29	13	21	0.28 [0.09, 0.90]	1.3
De Riso, 118	5	168	17	163	0.29 [0.10, 0.79]	1.5
Boland, 169	3	12	7	8	0.29 [0.06, 1.45]	.97
Korinek, 189	20	43	37	23	0.29 [0.14, 0.61]	1.8
Cockerill, 170	4	71	12	63	0.30 [0.09, 0.96]	1.3
Quinio, 192	19	57	38	34	0.30 [0.15, 0.60]	1.8
Bergmans, 183	9	78	38	101	0.31 [0.14, 0.67]	1.8
Özçaka, 129	12	17	22	10	0.32 [0.11, 0.92]	1.5
Xu, 146	10	52	16	28	0.34 [0.13, 0.84]	1.6
Caruso, 135	14	116	31	101	0.39 [0.20, 0.78]	1.9
Tantipong, 132	5	53	10	42	0.40 [0.13, 1.25]	1.4
Krueger, 175	91	174	149	113	0.40 [0.28, 0.56]	2.2
Grap, 122	7	14	10	8	0.40 [0.11, 1.47]	1.2
Xu, 146	11	47	16	28	0.41 [0.17, 1.01]	1.6
Chen, 117	16	44	28	32	0.42 [0.19, 0.89]	1.8
Sanchez-Garcia, 178	32	99	60	80	0.43 [0.26, 0.73]	2
Stoutenbeek, 179	62	139	100	100	0.45 [0.30, 0.67]	2.1
Feng, 136	18	53	29	39	0.46 [0.22, 0.94]	1.8
Stefanescu, 144	6	14	10	11	0.47 [0.13, 1.70]	1.2
Scannapieco, 130	14	83	12	37	0.52 [0.22, 1.23]	1.7
Koeman-Ch, 124	13	114	23	107	0.53 [0.26, 1.10]	1.8
de la Cal, 171	18	35	26	28	0.55 [0.25, 1.21]	1.8
Munro, 128	38	54	55	45	0.58 [0.32, 1.02]	2
Finch, 172	4	16	7	17	0.61 [0.15, 2.48]	1.1
Koeman, 188	16	112	23	107	0.66 [0.33, 1.33]	1.9
Verwaest PTA, 181	31	169	40	145	0.66 [0.40, 1.12]	2
Brun-Buisson, 184	3	33	6	44	0.67 [0.16, 2.86]	1.1
Gastinne, 186	26	194	34	191	[illegible]	[illegible]
Pobo, 140	15	59	18	55	[illegible]	[illegible]
Prendergast, 141	8	30	10	30	[illegible]	[illegible]
Zhao, 149	73	89	82	80	[illegible]	[illegible]
Xu, 147	30	34	26	26	[illegible]	[illegible]
Sebastian, 131	12	29	14	31	[illegible]	[illegible]
Camus, 185	53	77	53	73	[illegible]	[illegible]
Bellissimo-Rodrigues, 114	16	48	17	52	[illegible]	[illegible]
Kusahara, 125	15	31	16	34	[illegible]	[illegible]
Berry, 134	6	127	6	132	[illegible]	[illegible]
Wiener, 195	8	22	8	23	1.05 [0.33, 3.27]	1.4
Fourrier'05, 120	13	101	12	102	1.09 [0.48, 2.51]	1.7
Seguin, 143	24	54	20	52	1.16 [0.57, 2.34]	1.8
Meidani , 126	7	43	6	44	1.19 [0.37, 3.84]	1.3
Jacomo, 123	16	71	11	62	1.27 [0.55, 2.94]	1.7
Meinberg, 127	18	10	11	13	2.13 [0.70, 6.48]	1.4
Tuon, 133	4	4	2	6	3.00 [0.36, 24.92]	.69
Berry, 115	4	67	1	77	4.60 [0.50, 42.14]	.64
Overall					0.39 [0.31, 0.48]	

Test of $\theta_i = \theta_j$: Q(67) = 203.73, p = 0.00
Test of θ = 0: z = -8.91, p = 0.00

1/512 1/64 1/8 1 8
odds ratio

Antimicrobial;
ES 0.39 (0.31-0.48)
N = 68
I^2 = 72.7



Conditions	Heterogeneity	Pneumonia incidence changes & apparent effect size (ES)
a.) Pre-intervention Intervention = n/a Spillover = n/a	Control = + Intervention = +	Control = 0 Intervention = 0 ES [apparent] = 0
b.) Intervention ineffective Spillover = 0	Control = + Intervention = ++	Control = 0 Intervention = ± ES [apparent] = ±
c.) Intervention effective Spillover = 0	Control = + Intervention = ++	Control = 0 Intervention = - - ES [apparent] = - -
d.) Intervention effective Spillover [beneficial] = -	Control = ++ Intervention = ++	Control = - Intervention = - - ES [apparent] = -
e.) Intervention effective Spillover [harmful] = +	Control = ++ Intervention = ++	Control = + Intervention = - - ES [apparent] = - - -
f.) Intervention effective Spillover [partially harmful] = +/0	Control = ++ Intervention = ++	Control = +/0 Intervention = - - ES [apparent] = - / - -

Heterogeneity

Q statistic

- Assesses whether observed differences in results are compatible with chance alone
- Null hypothesis: No between-studies heterogeneity (Homogeneity)
- Statistically significant when p-value<0.10

• Attention required!
• Low power, when studies have small sample size or are few in number
• High power to detect small amount of heterogeneity in presence of many studies

I^2 Statistic

The proportion (%) of total variability in effect estimates due to between study heterogeneity (rather than chance)

- Rough guide:
    - 0%-40%: might not important
    - 30%-60%: moderate heterogeneity
    - 50%-90%: substantial heterogeneity
    - 75%-100%: considerable heterogeneity

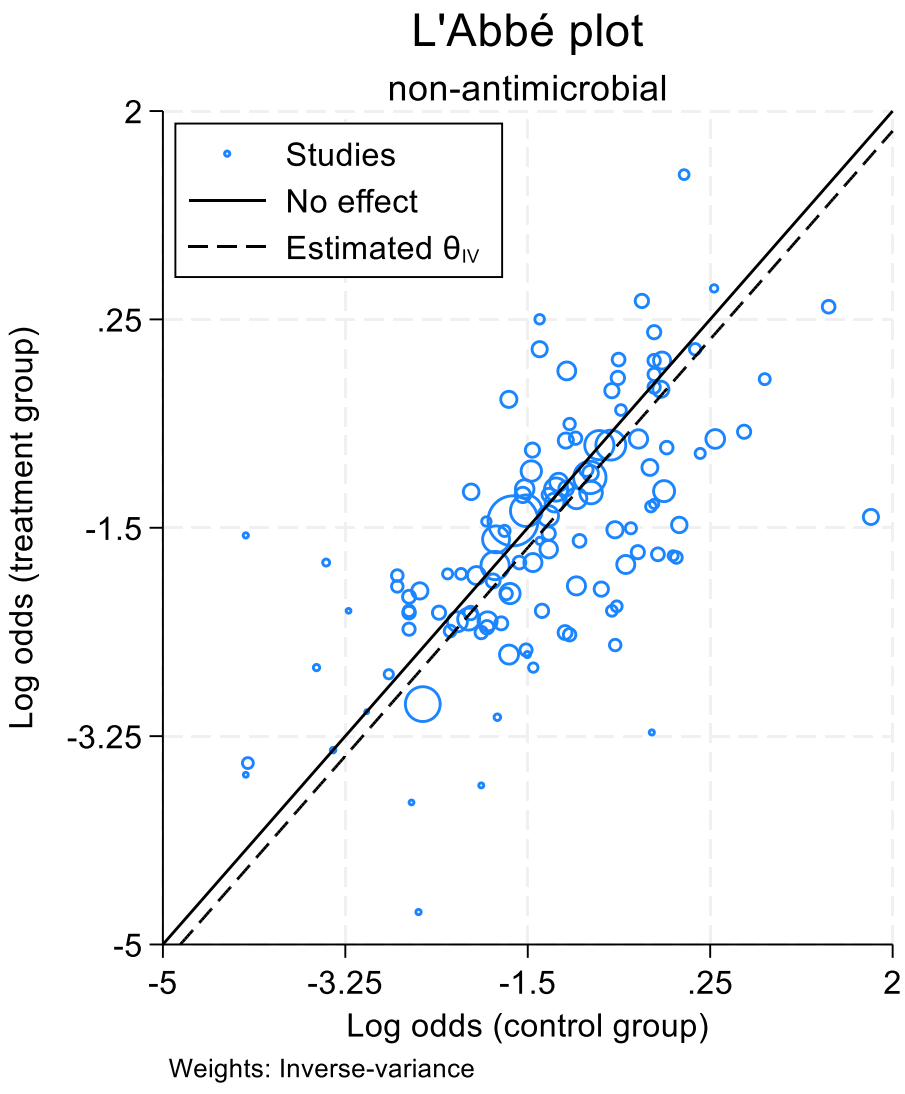
Interpretation and importance depend on

1. magnitude and direction of effects,
2. strength of evidence for heterogeneity

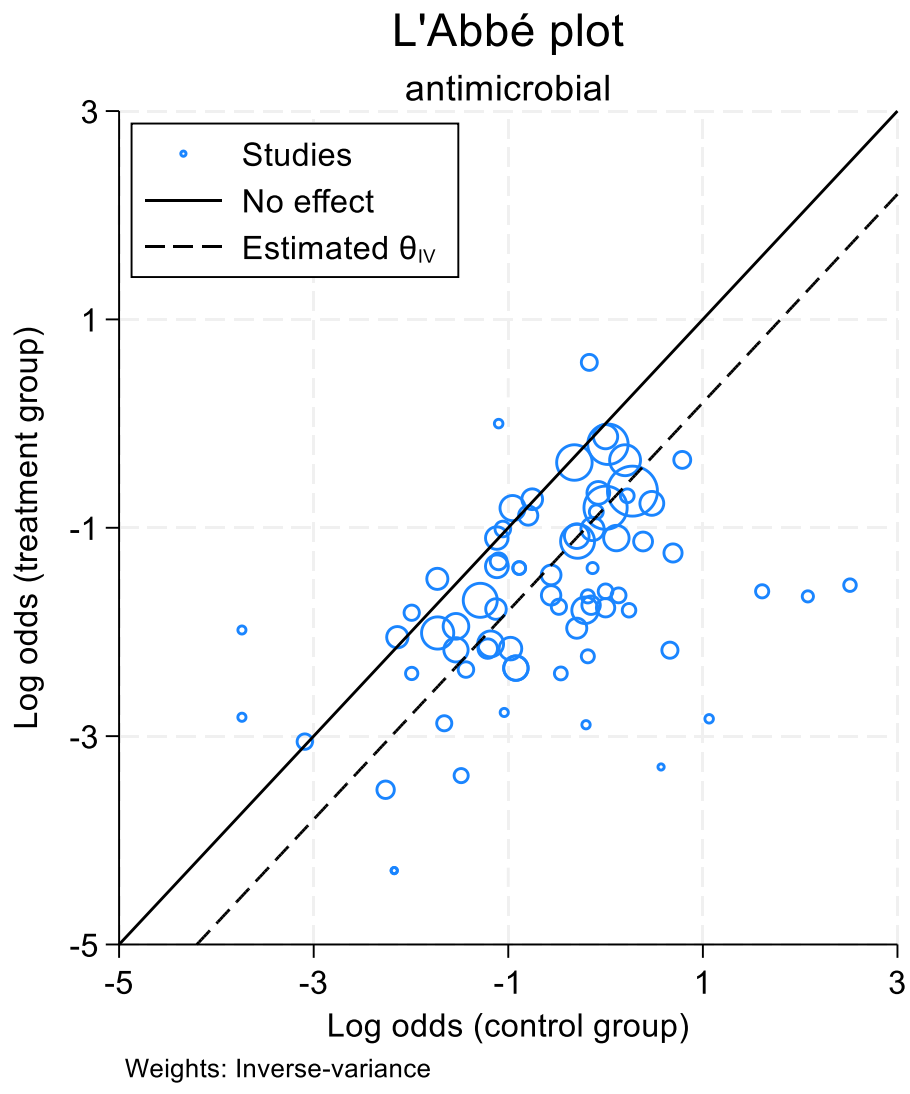
(e.g., p-value from the Chi^2 test, or a confidence interval for I^2: uncertainty in the value of I^2 is substantial when the number of studies is small)

Visual

Non-antimicrobial



Antimicrobial



(Note default logit scales)

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ysize(6)
```

```
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(6)
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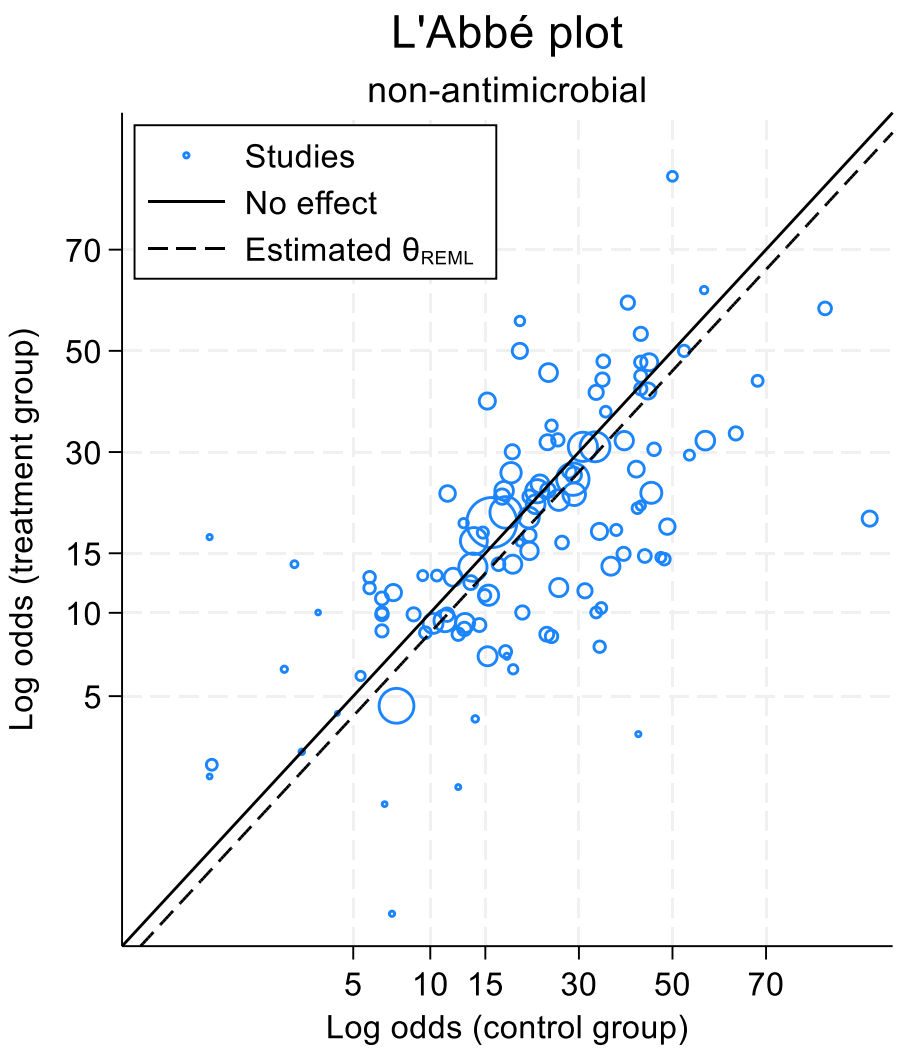
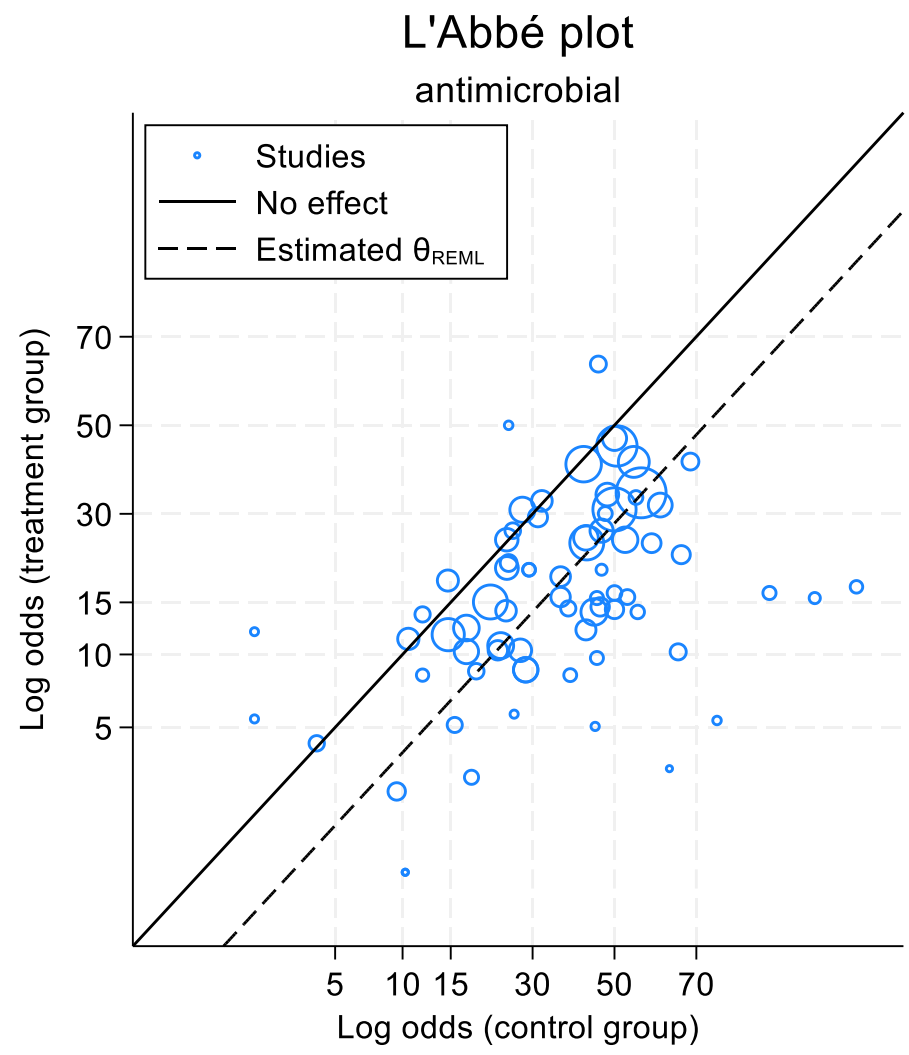
Non-antimicrobial



Antimicrobial



(Note user modified linear labels to logit scales)

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meta labbeplot if Cochrane0==100, random ylabel(-2.9 "5" -2.2
"10" -1.7 "15" -.85 "30" 0 "50" .85 "70", angle(horizontal))
xlabel(-2.9 "5" -2.2 "10" -1.7 "15" -.85 "30" 0 "50" .85 "70")
sub(non-antimicrobial) legend(pos(10) ring(0)
region(lcolor(black))) xsize(5) ysize(6)
```

```
meta labbeplot if Cochrane0==700, random ylabel(-2.9 "5" -2.2
"10" -1.7 "15" -.85 "30" 0 "50" .85 "70", angle(horizontal))
xlabel(-2.9 "5" -2.2 "10" -1.7 "15" -.85 "30" 0 "50" .85 "70")
sub(antimicrobial) legend(pos(10) ring(0)
region(lcolor(black))) xsize(5) ysize (6)
```

L’abbe plot

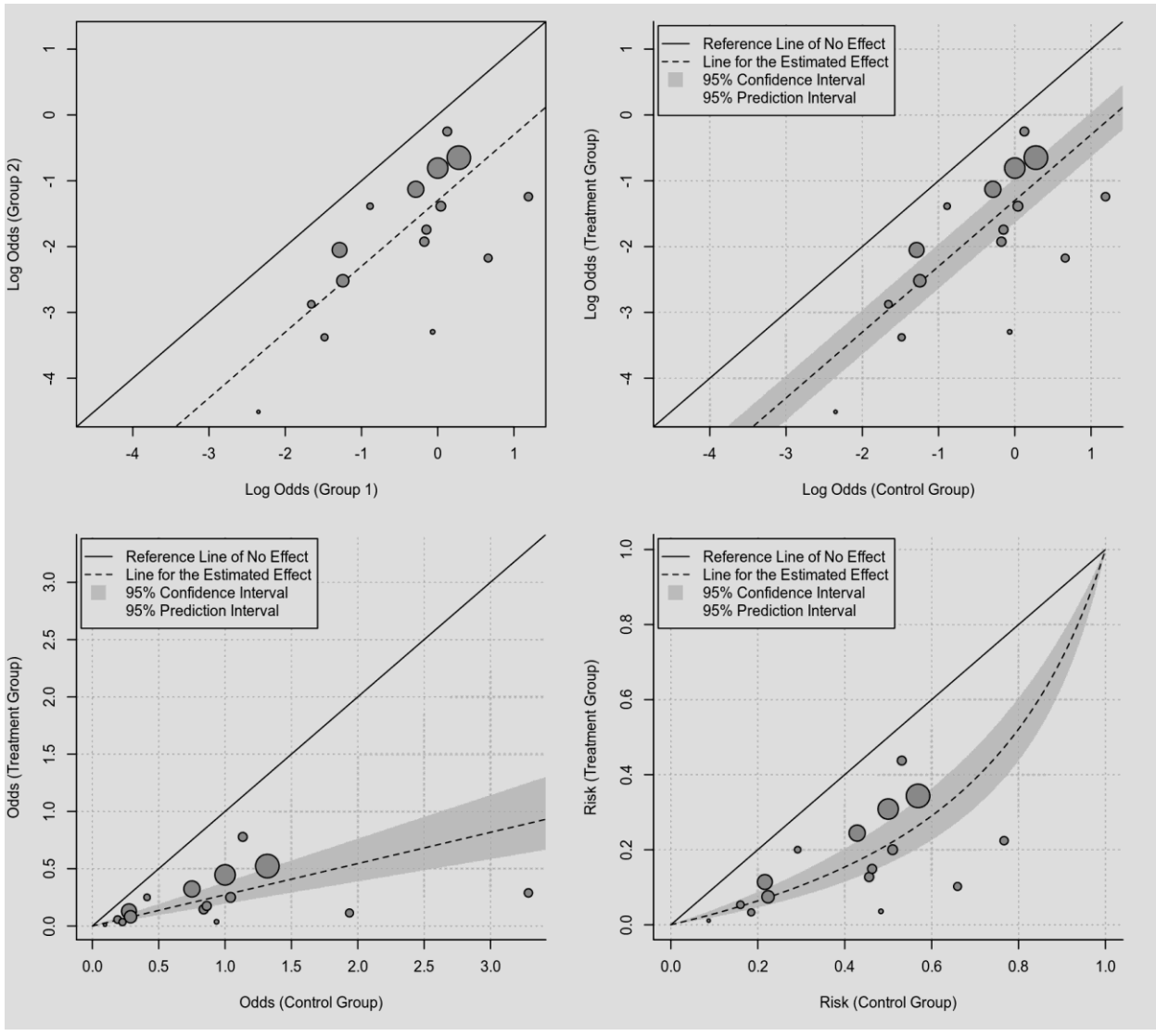


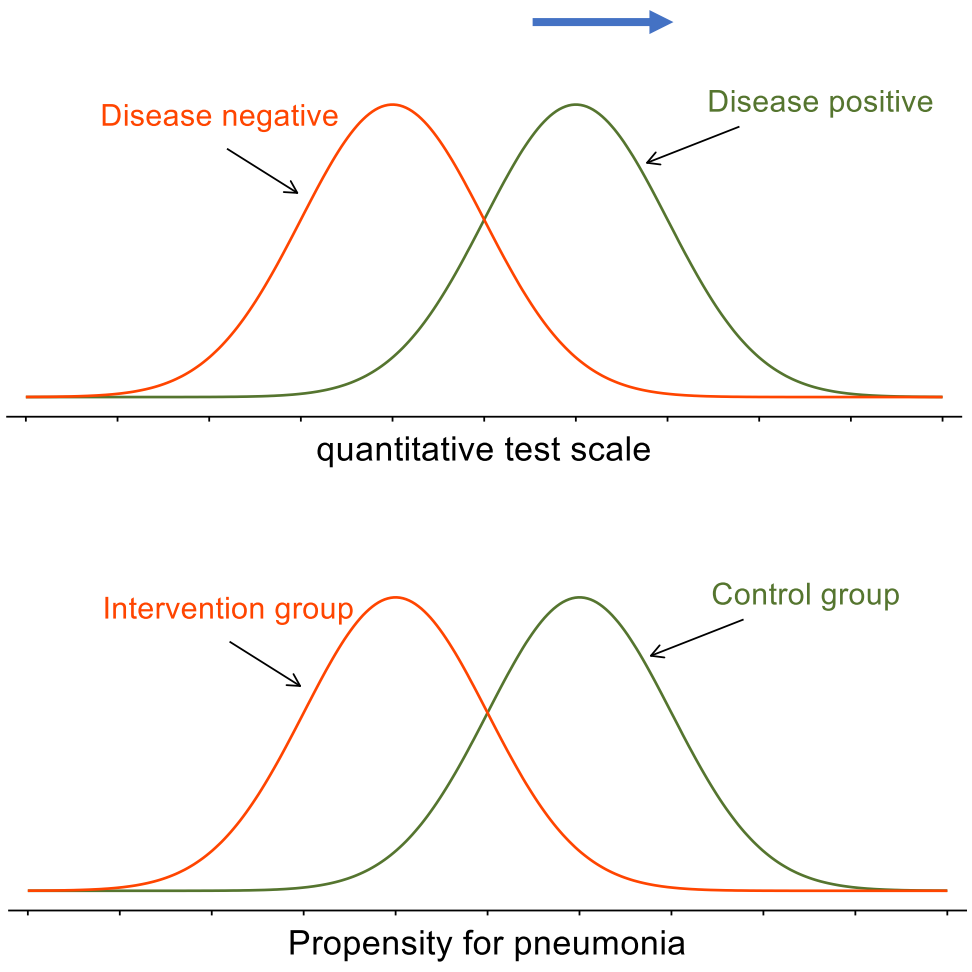
Image from www.metafor-project.org/doku.php:labbe_plot

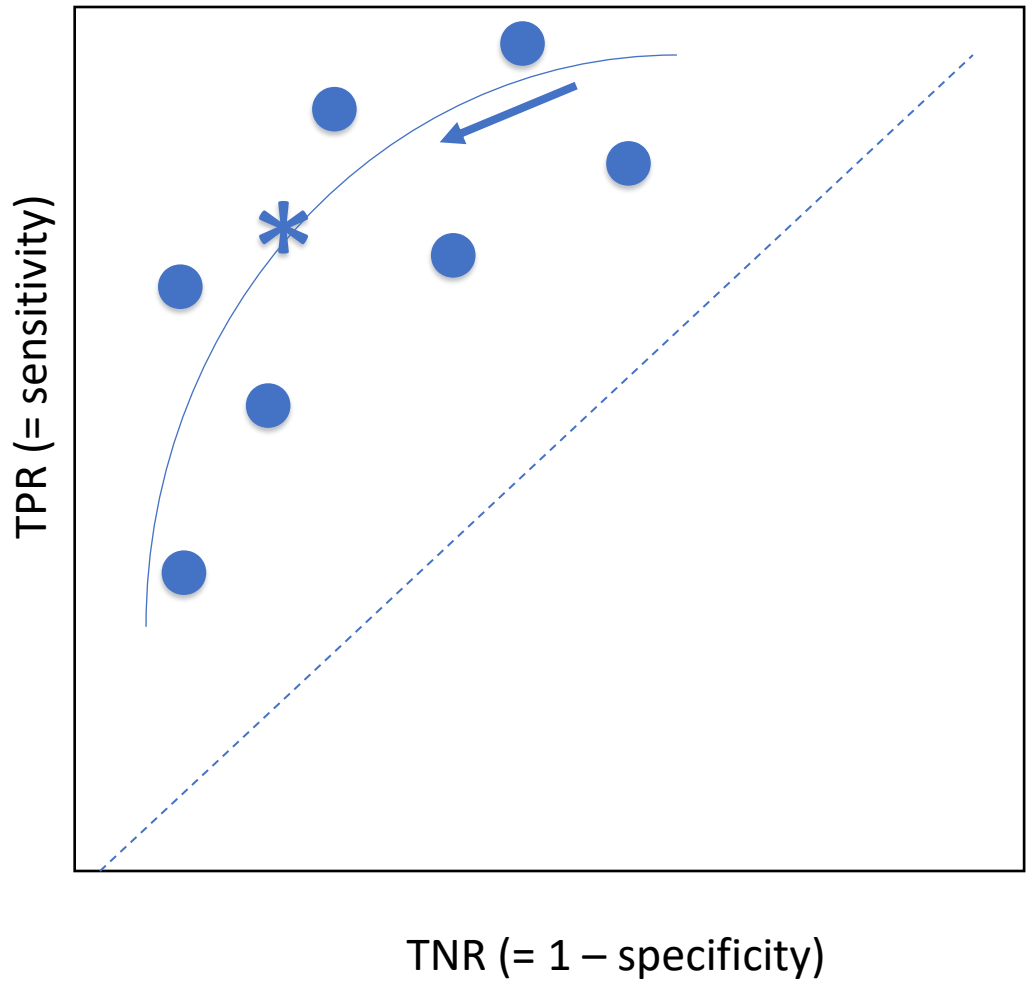
- Data exploration
  - RR vs OR vs RD
  - ‘J’ curve effects
- 20th century tool i.e
  - contrast meta-analysis
  - Ideal for RCCT’s
- Limitations
  - Visual impression
  - Axis scales

SROC

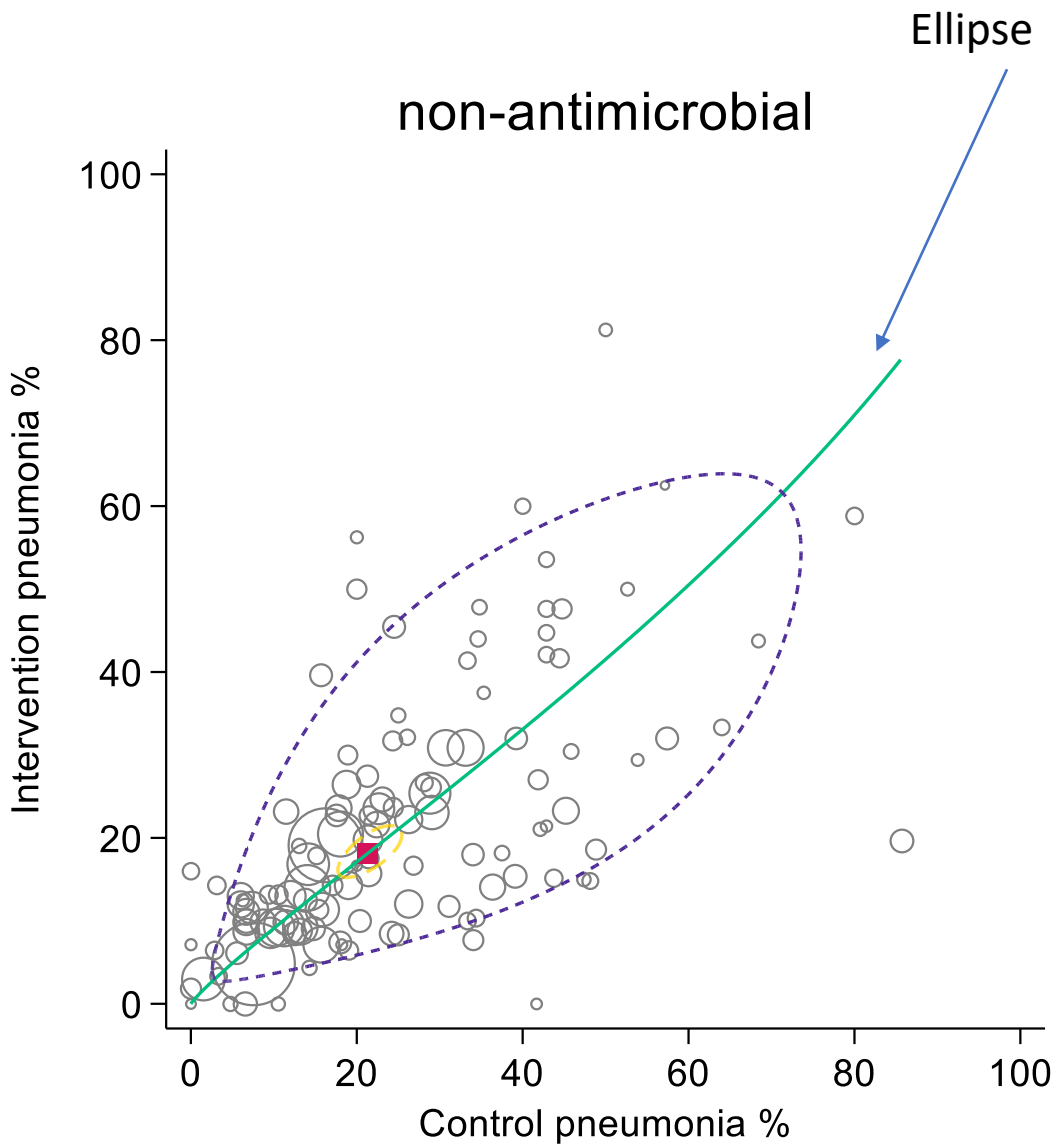
Interpretations

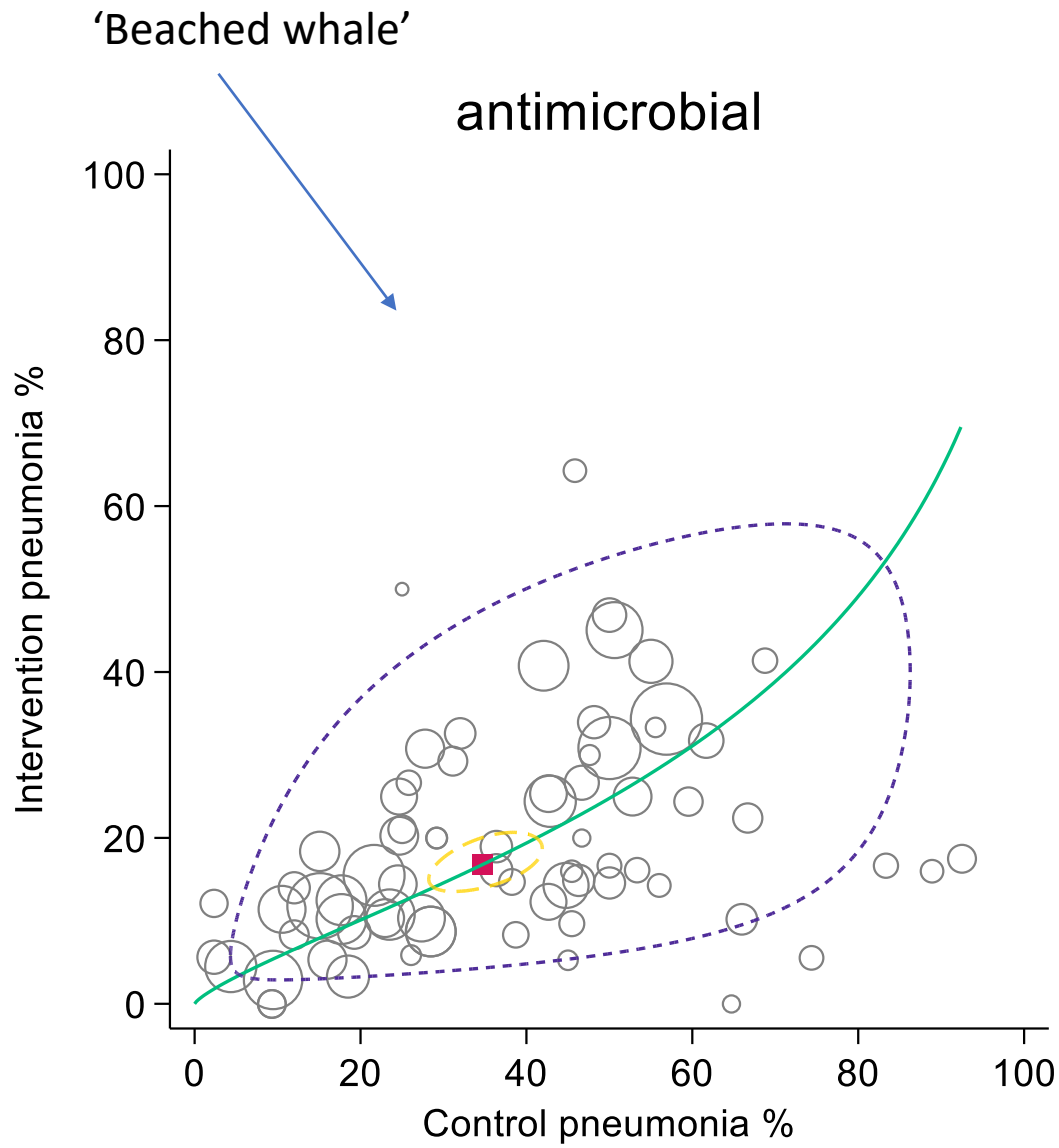
- Q*
- SROC curve
- 95% confidence ellipse





Harbord RM, Whiting P. **Metandi**: meta-analysis of diagnostic accuracy using hierarchical logistic regression. *Stata J*. 2009;9(2):211–29.
Nyaga VN, Arbyn M. **Metadta**: a Stata command for meta-analysis and meta-regression of diagnostic test accuracy data–a tutorial. *Archives of Public Health*. 2022;80(1):1–5.





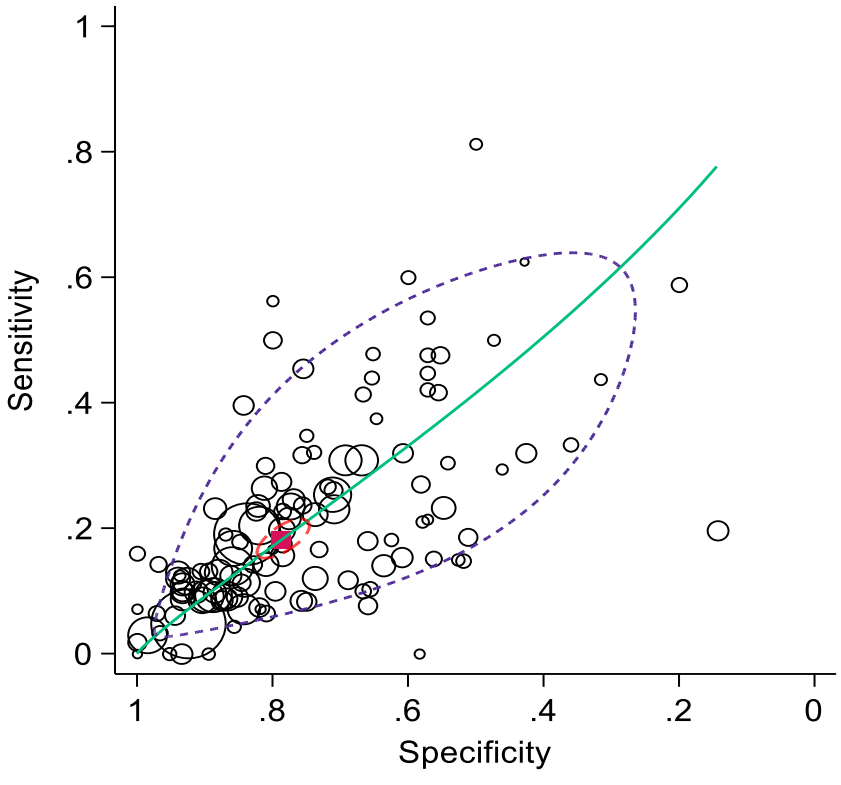
<u>Non-antimicrobial;</u>
DOR 0.82 (0.71-0.94)
N = 122
TPR = 'sensitivity' = 18.1
TNR = (1-specificity) = 21.4

<u>Antimicrobial;</u>
DOR 0.38 (0.31-0.47)
N = 68
TPR = 'sensitivity' = 16.8
TNR = (1-specificity) = 34.8

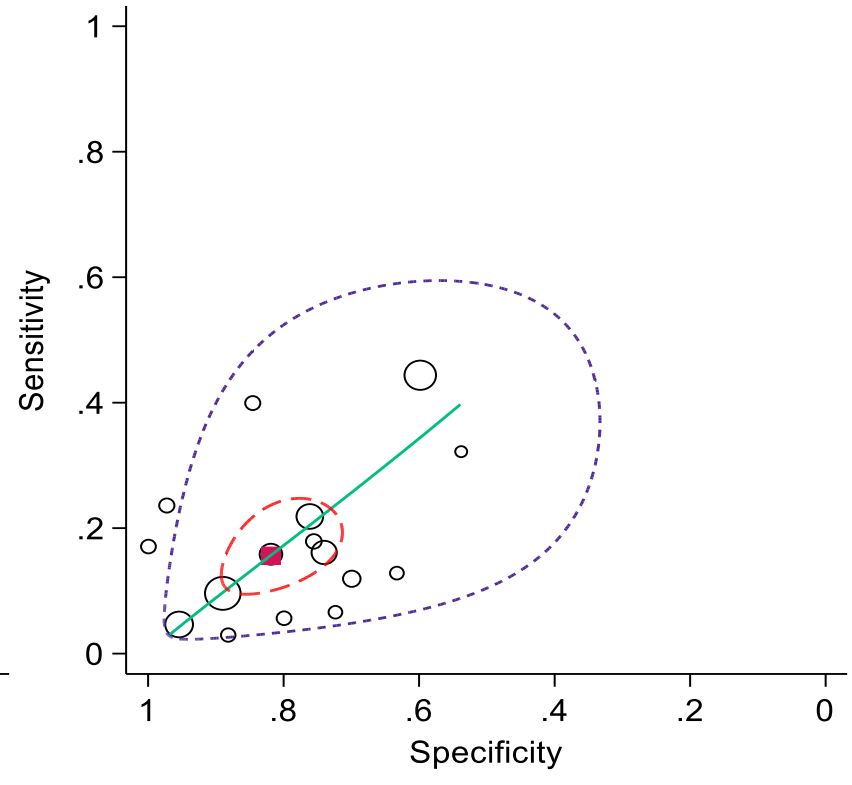
```
metandiplot vap_n cvapn vap_m cvapm if Cochrane0==100,
legend(off) ti(non-antimicrobial) xtitle(Control pneumonia %)
xlab(1 "0" .8 "20" .6 "40" .4 "60" .2 "80" 0 "100") ylab(0 "0"
.2 "20" .4 "40" .6 "60" .8 "80" 1 "100")  ytitle(Intervention
pneumonia %)
```

```
 metandiplot vap_n cvapn vap_m cvapm if Cochrane0==700,
legend(off) ti(antimicrobial)  xtitle(Control pneumonia %)
xlab(1 "0" .8 "20" .6 "40" .4 "60" .2 "80" 0 "100") ylab(0 "0"
.2 "20" .4 "40" .6 "60" .8 "80" 1 "100")  ytitle(Intervention
pneumonia %)
```

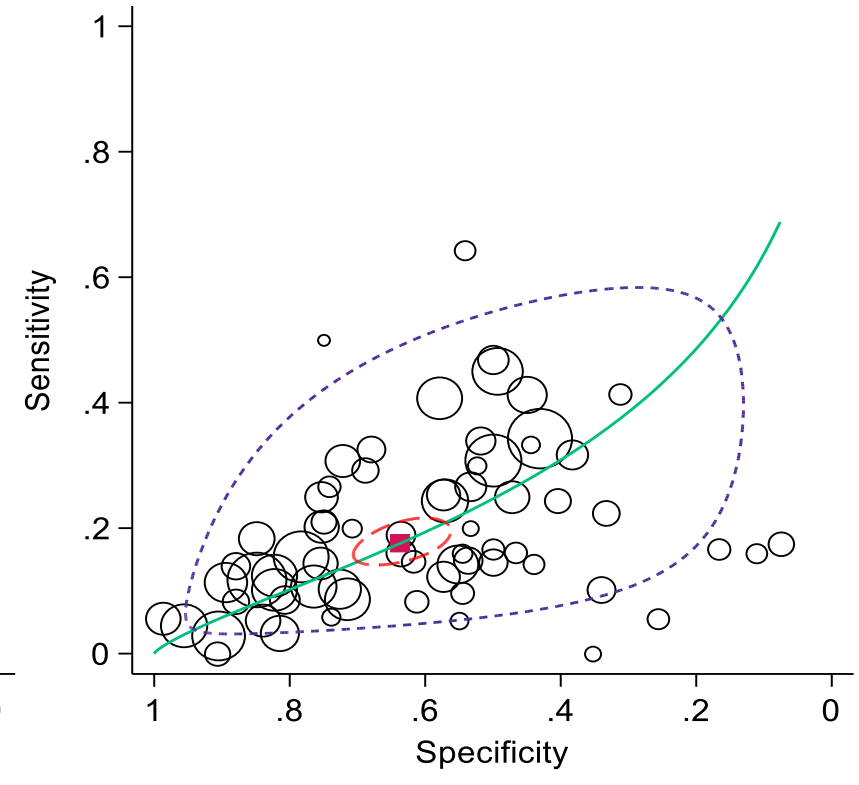
non-antimicrobial



antimicrobial - duplex



antimicrobial



Conclusion

- SUTVA (= spillover) no formal test exists
  - Visual?
- SROC enables a visual test (shape of 95% PI).
- SROC analogous to L'abbe plot
  - with improvement

References

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