Herd effects of topical antibiotic prophylaxis among ICU patients. Simulating a cluster randomized trial using published studies.

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Oceania Stata Conference

THE UNIVERSITY OF MELBOURNE

Disclosures

James Hurley has no conflicts of interest to declare

Talk outline

The ICU patient

The research question

Herd effects

The data

- linear scale
- logit scale

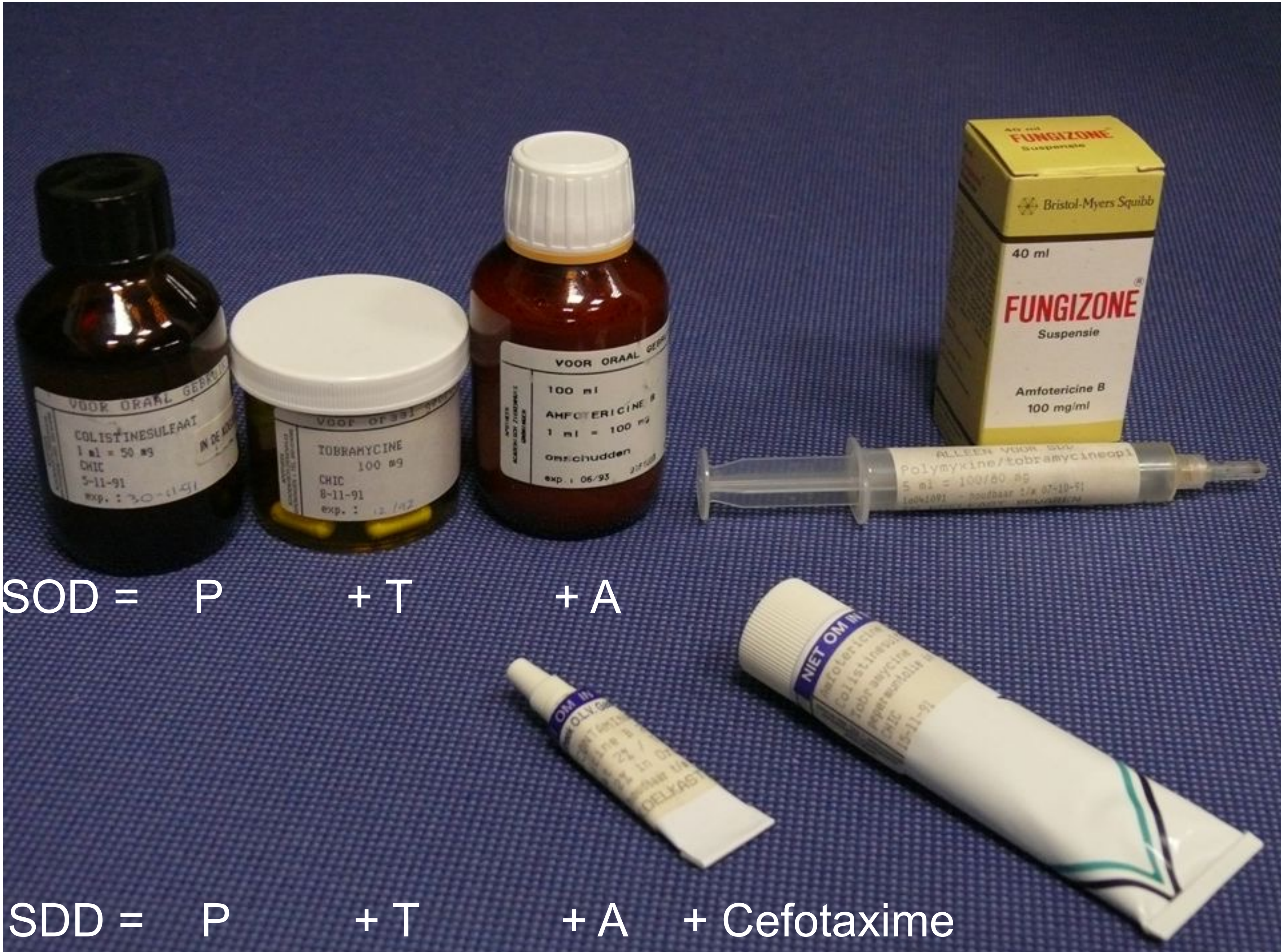
Data available in

Hurley JC. Discrepancies in Control Group Mortality Rates Within Studies Assessing Topical Antibiotic Strategies to Prevent Ventilator-Associated Pneumonia: An Umbrella Review. Critical care explorations. 2020 Jan;2(1).

The mechanism?

The ICU patient on MV

SDD/SOD


COLISTINESULFAAT
1 ml = 50 mg
CHIC
5-11-91
TOBRAMYCINE
100 mg
CHIC
8-11-91
VOOR ORAAL
100 ml
1 ml = 100 mg
exp. : 06/93
Bristol-Myers Squibb
40 ml
FUNGIZONE
Suspensie
Amfotericine B
100 mg/ml
Polymyxine/tobramycineopl
5 ml = 100/80 mg
SOD = P + T + A
SDD = P + T + A + Cefotaxime

Cochrane Library

Cochrane Database of Systematic Reviews

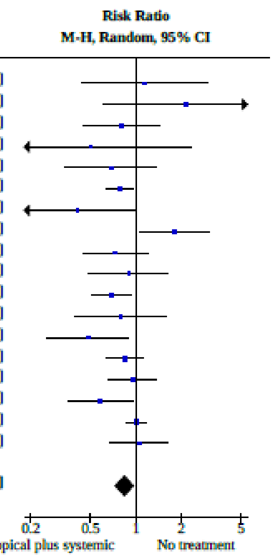
Topical antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving mechanical ventilation (Review)

Minozzi S, Pifferi S, Brazzi L, Pecoraro V, Montrucchio G, D'Amico R

Minozzi S, Pifferi S, Brazzi L, Pecoraro V, Montrucchio G, D'Amico R.
Topical antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving mechanical ventilati
Cochrane Database of Systematic Reviews 2021, Issue 1. Art. No.: CD000022.
DOI: 10.1002/14651858.CD000022.pub4.

Analysis 1.1. Comparison 1: Topical plus systemic prophylaxis versus placebo or no treatment, Outcome 1: Overall mortality

Study or Subgroup	Favours treatment Events	Favours treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Abele-Horn 1997	11	58	5	30	1.8%	1.14 [0.44 , 2.97]
Aerdts 1991	4	18	4	39	1.1%	2.17 [0.61 , 7.70]
Blair 1991	17	126	22	130	4.2%	0.80 [0.44 , 1.43]
Boland 1991	2	15	4	15	0.8%	0.50 [0.11 , 2.33]
Cockerill 1992	11	75	16	75	3.1%	0.69 [0.34 , 1.38]
de Jonge 2003	113	466	146	468	12.5%	0.78 [0.63 , 0.96]
de la Cal 2005	6	53	15	54	2.2%	0.41 [0.17 , 0.97]
Finch 1991	15	20	10	24	4.7%	1.80 [1.05 , 3.08]
Jacobs 1992	14	36	23	43	5.3%	0.73 [0.44 , 1.19]
Kerver 1988	14	49	15	47	3.9%	0.90 [0.49 , 1.65]
Krueger 2002	52	265	75	262	9.3%	0.69 [0.50 , 0.93]
Palomar 1997	10	41	13	42	3.1%	0.79 [0.39 , 1.59]
Rocha 1992	10	47	24	54	3.7%	0.48 [0.26 , 0.89]
Sanchez-Garcia 1998	51	131	65	140	10.2%	0.84 [0.63 , 1.11]
Stoutenbeek 2007	42	201	44	200	7.6%	0.95 [0.65 , 1.38]
Ulrich 1989	15	48	28	52	5.4%	0.58 [0.36 , 0.95]
de Smet 2009 (1)	258	805	249	783	14.9%	1.01 [0.87 , 1.16]
Verwaest 1997	34	193	31	185	6.2%	1.05 [0.68 , 1.64]
Total (95% CI)		**2647**		**2643**	**100.0%**	**0.84 [0.73 , 0.96]**
Total events:	679		789			

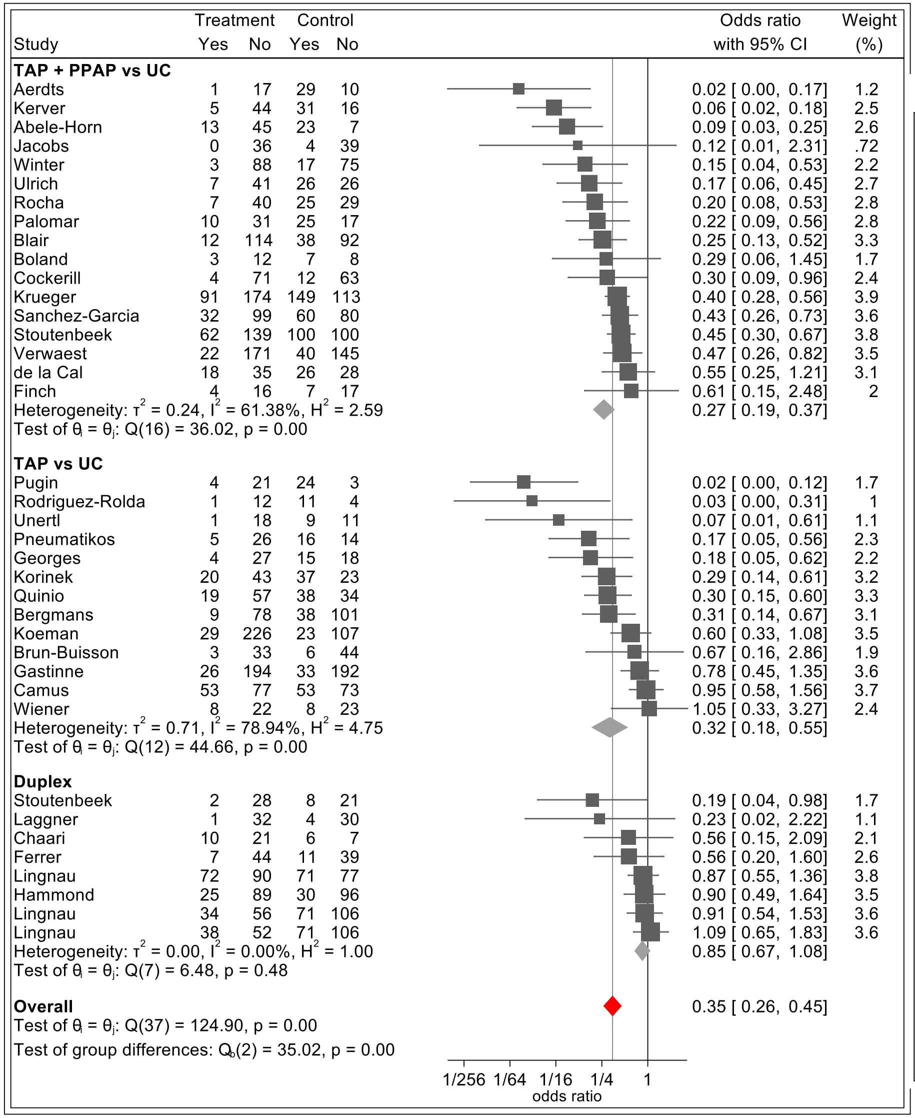


Heterogeneity: Tau² = 0.03; Chi² = 28.46, df = 17 (P = 0.04); I² = 40%
Test for overall effect: Z = 2.55 (P = 0.01)
Test for subgroup differences: Not applicable

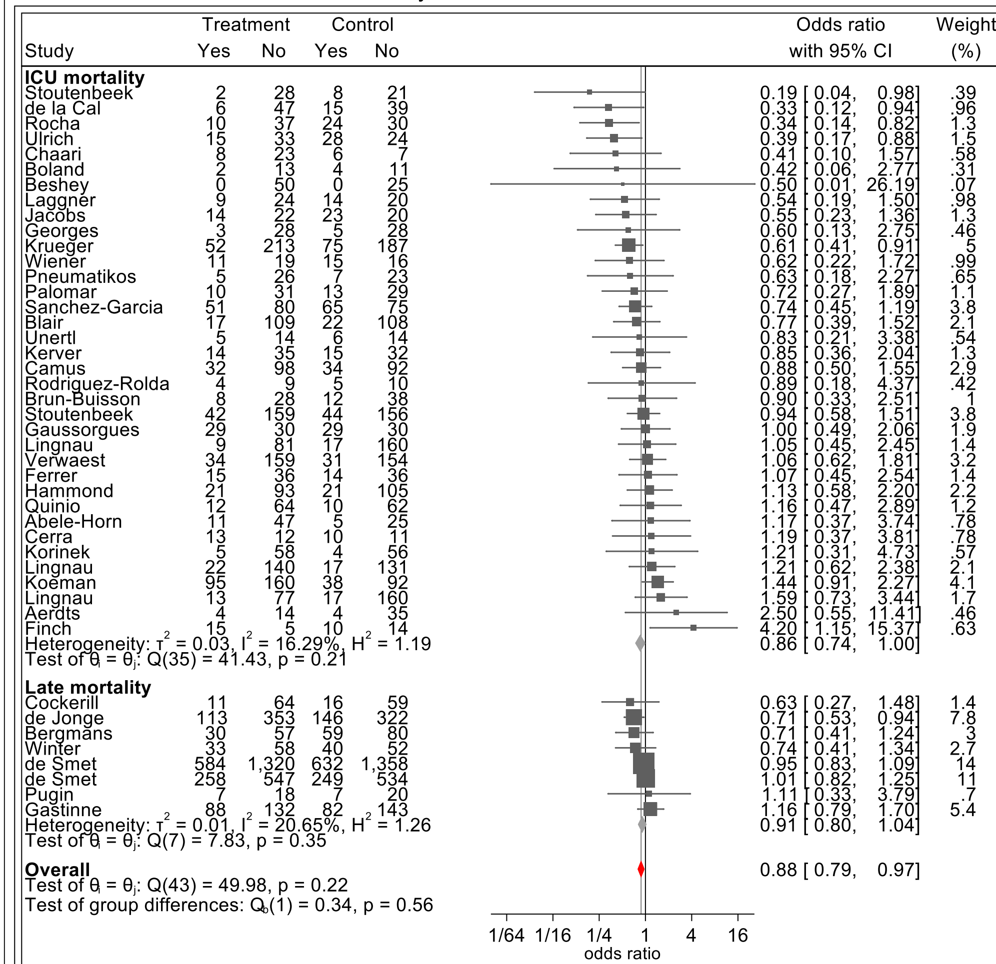
Footnotes
(1) We adjusted the sample size of the cluster-RCT by calculating the effective sample size according to #Section 23.1.4 of the Handbook

Pneumonia and mortality prevention effect size from RCCT's

Pnemonia: Antibiotic interventions



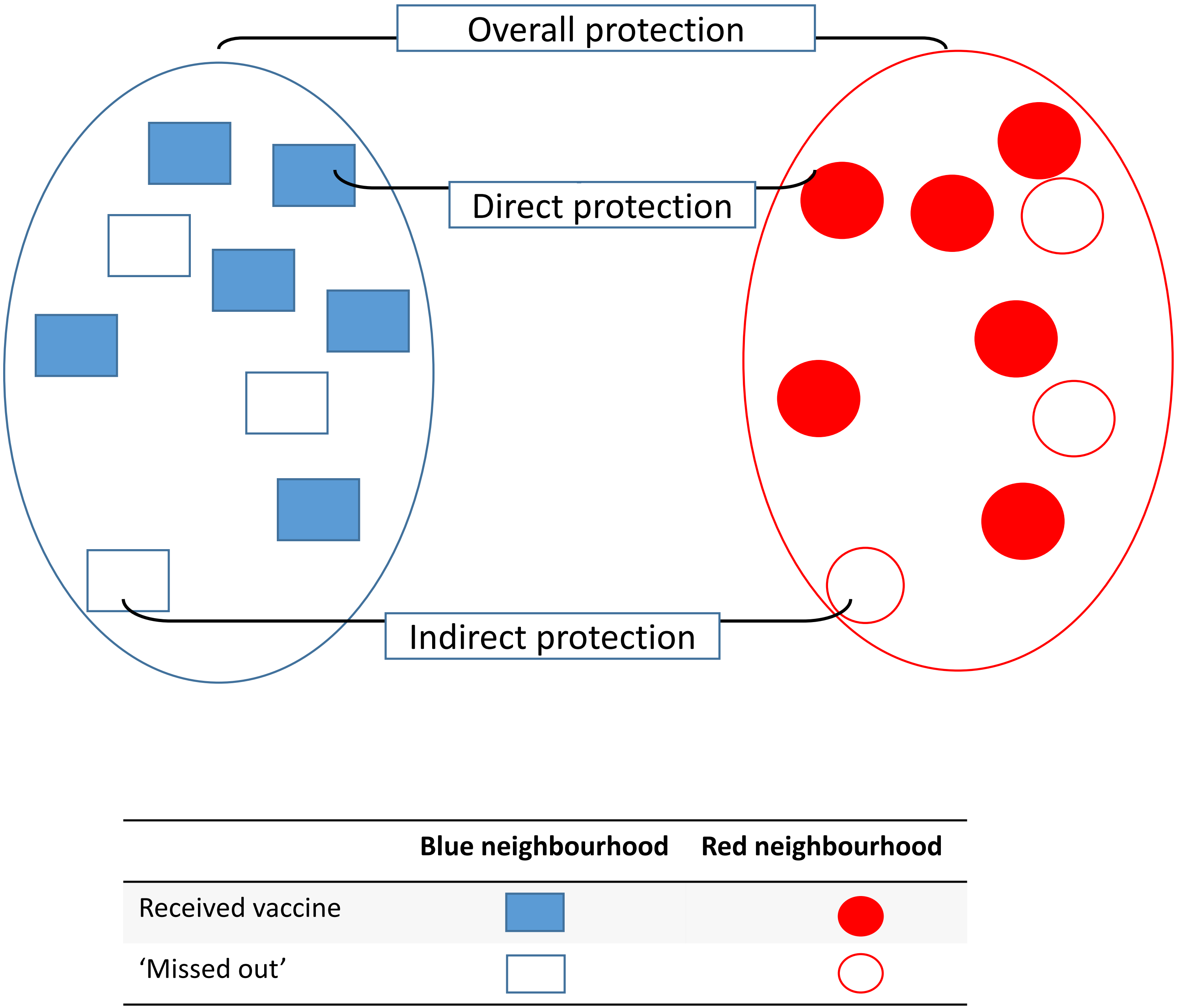
Mortality: Antibiotic interventions



Pneumonia and mortality prevention effect size from RCCT's

The research question

- Does Topical antibiotic prophylaxis (TAP) engender indirect (herd) effects on concurrent ICU patients?


Overall protection
Direct protection
Indirect protection
Blue neighbourhood
Red neighbourhood
Received vaccine
'Missed out'

Neighborhoods in Kolkata, India.

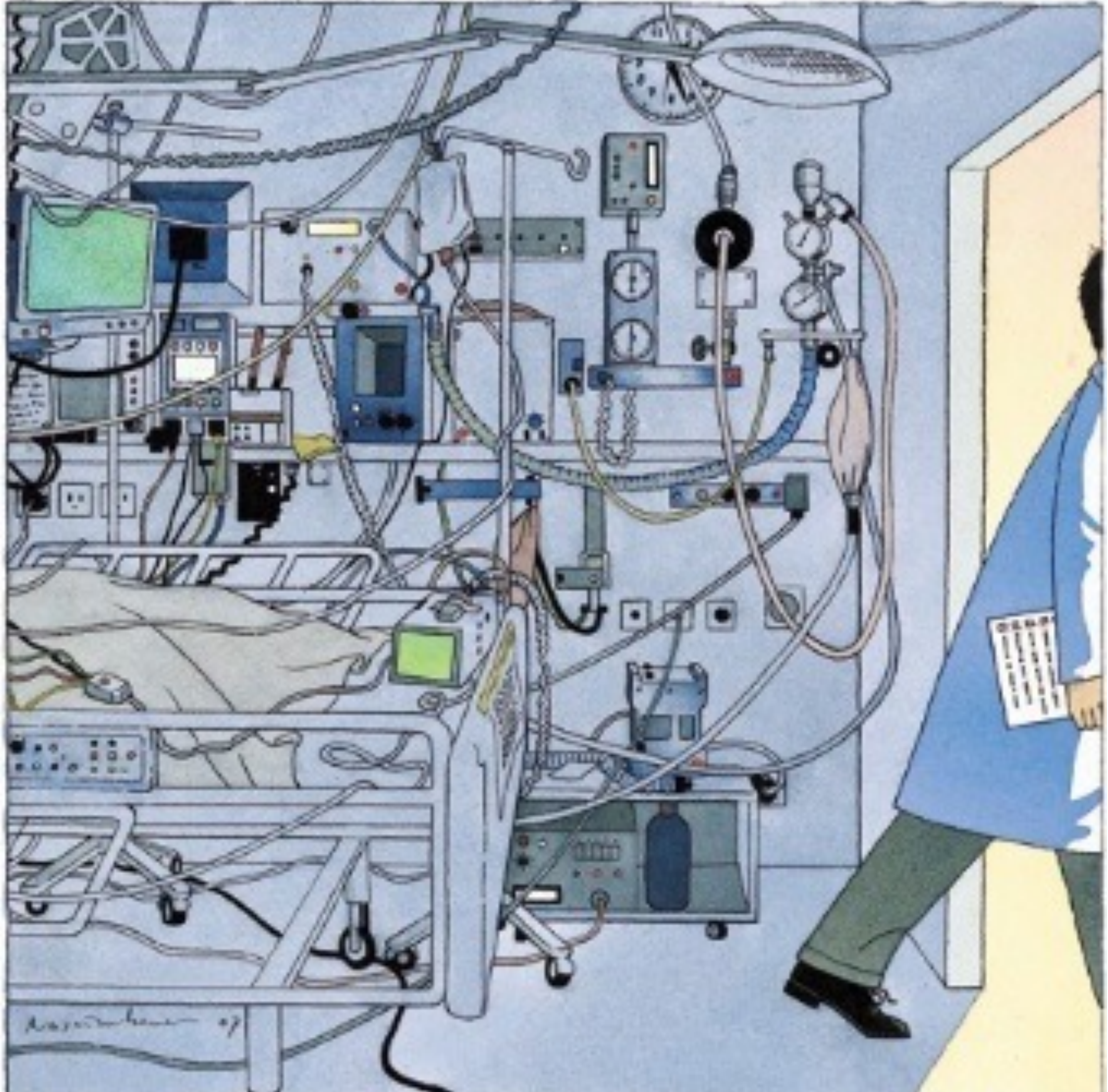
80 neighbourhoods
61280 people
37673 vaccinated

2 years follow up

Vi typhoid protection;
Direct = 61%; 41-75
Indirect = 44%; 2-69

Sur D, Ochiai RL, Bhattacharya SK, Ganguly NK, Ali M, Manna B, Dutta S, Donner A, Kanungo S, Park JK, Puri MK.
A cluster-randomized effectiveness trial of Vi typhoid vaccine in India.
N Engl J Med 2009;361:335-344.

The NEW ENGLAND JOURNAL of MEDICINE



The data:

Interventions to prevent infections (n = numbers of studies)

UGIT (n = 121)

Toews_I, George_AT, Peter_JV, Kirubakaran_R, Fontes_LES, Ezekiel_JPB, Meerpohl_JJ. Interventions for preventing upper gastrointestinal bleeding in people admitted to intensive care units. ***Cochrane Database of Systematic Reviews*** 2018, Issue 6. Art. No.: CD008687.

Feeding [EN vs TPN] (n = 46)

Lewis SR, Schofield-Robinson OJ, Alderson P, Smith AF. Enteral versus parenteral nutrition and enteral versus a combination of enteral and parenteral nutrition for adults in the intensive care unit. ***Cochrane Database of Systematic Reviews*** 2018, Issue 6. Art. No.: CD012276.

Padilla PF, Martínez G, Vernooij RW, Urrútia G, i Figuls MR, Cosp XB. Early enteral nutrition (within 48 hours) versus delayed enteral nutrition (after 48 hours) with or without supplemental parenteral nutrition in critically ill adults. ***Cochrane Database of Systematic Reviews*** 2019(10).

Alkhawaja S, Martin C, Butler RJ, Gwadry-Sridhar F. Post-pyloric versus gastric tube feeding for preventing pneumonia and improving nutritional outcomes in critically ill adults. ***Cochrane Database of Systematic Reviews*** 2015(8).

Airway management (n = 61)

Wang L, Li X, Yang Z, Tang X, Yuan Q, Deng L, Sun X. Semi-recumbent position versus supine position for the prevention of ventilator-associated pneumonia in adults requiring mechanical ventilation. ***Cochrane Database Syst Rev*** 2016(1). DOI: 10.1002/14651858.CD009946.pub2.

Gillies D, Todd DA, Foster JP, Batuwitage BT. Heat and moisture exchangers versus heated humidifiers for mechanically ventilated adults and children**. *Cochrane Database Syst Rev***. 2017(9). DOI: 10.1002/14651858.CD004711.pub3.

Solà I, Benito S. Closed tracheal suction systems versus open tracheal suction systems for mechanically ventilated adult patients. ***Cochrane Database of Systematic Reviews*** 2007, Issue 4. Art. No.: CD004581.

Tokmaji G, Vermeulen H, Müller MCA, Kwakman PHS, Schultz MJ, Zaat SAJ. Silver-coated endotracheal tubes for prevention of ventilator-associated pneumonia in critically ill patients. ***Cochrane Database of Systematic Reviews*** 2015, Issue 8. Art. No.: CD009201.

Probiotics (n = 8)

Bo L, Li J, Tao T, Bai Y, Ye X, Hotchkiss RS, Kollef MH, Crooks NH, Deng X. Probiotics for preventing ventilator-associated pneumonia. ***Cochrane Database of Systematic Reviews*** 2014, Issue 10. Art. No.: CD009066.

Anti-septics / oral care (n = 40)

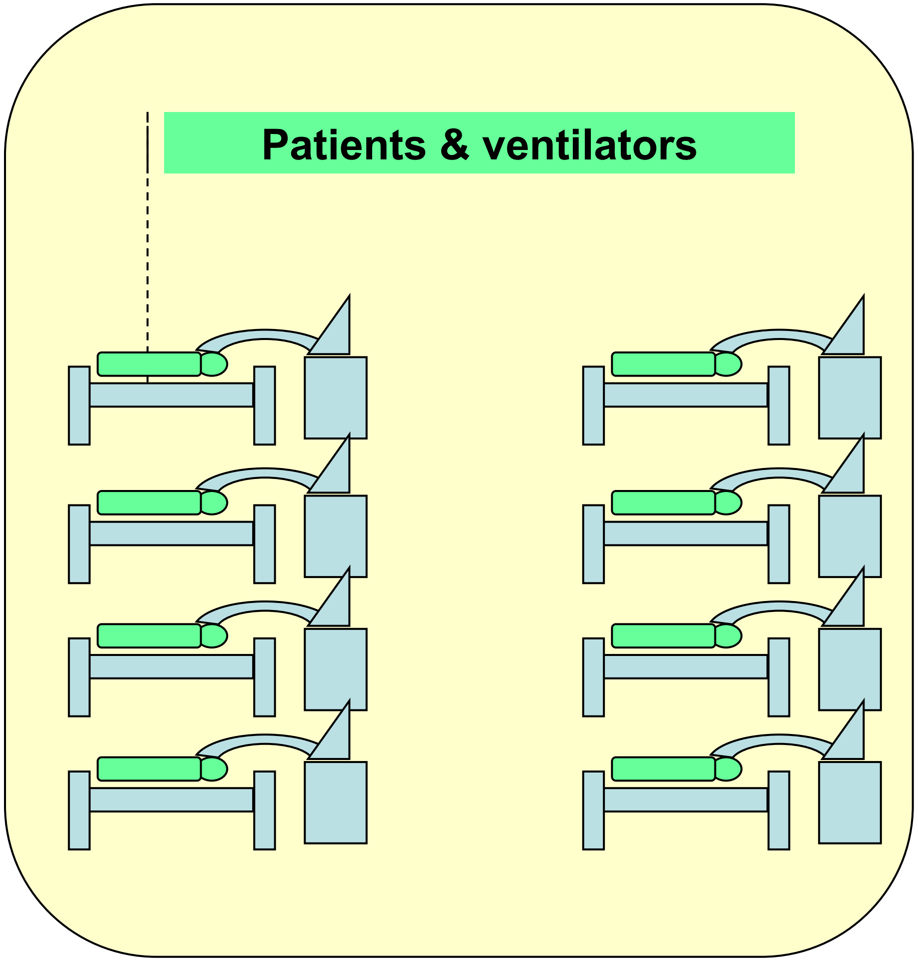
Hua F, Xie H, Worthington HV, Furness S, Zhang Q, Li C. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. ***Cochrane Database of Systematic Reviews*** 2016, Issue 10. Art. No.: CD008367.

Zhao T, Wu X, Zhang Q, Li C, Worthington HV, Hua F. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. ***Cochrane Database of Systematic Reviews*** 2020, Issue 12. Art. No.: CD008367.

Antibiotics (n= 41)

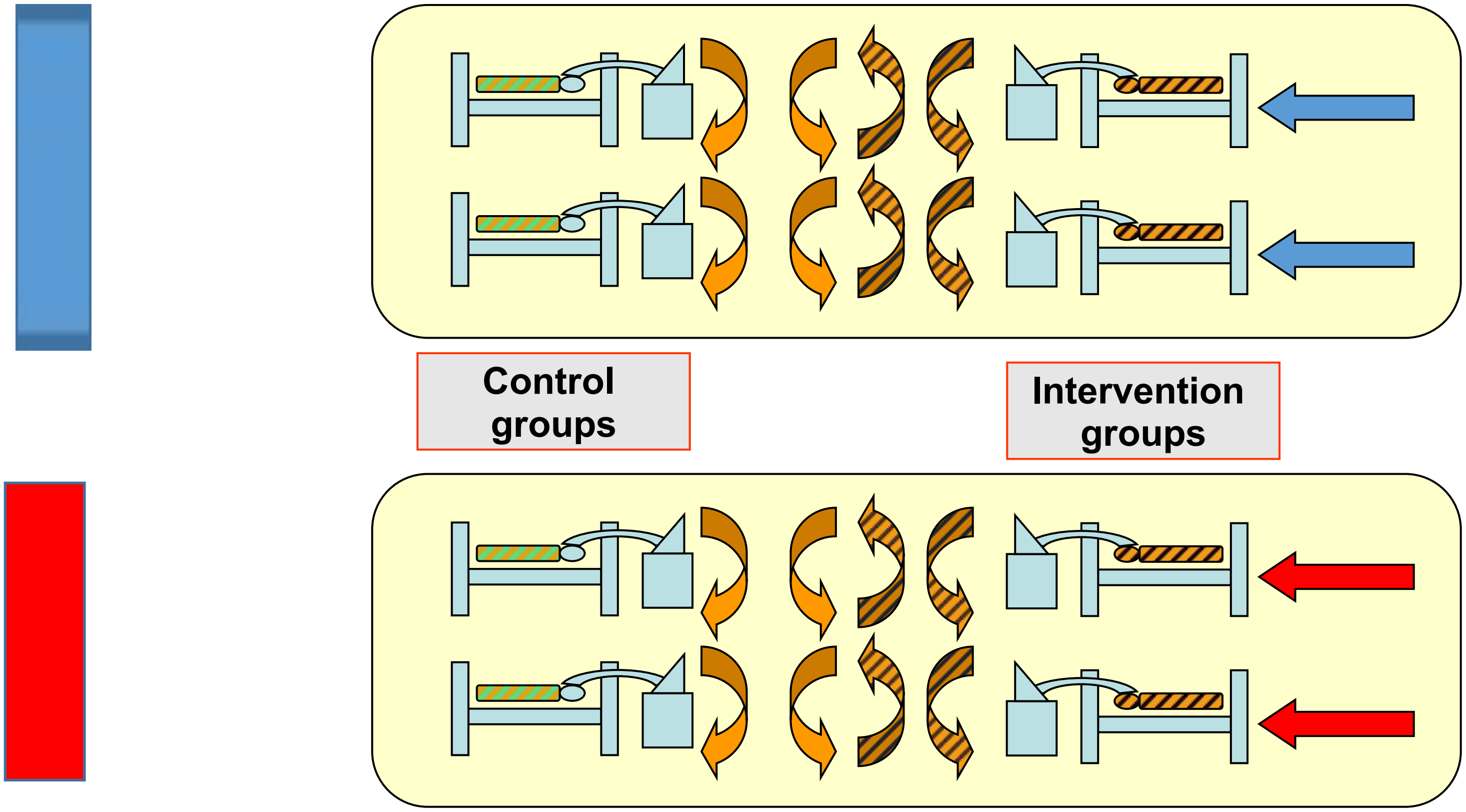
Liberati A, D’Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. ***Cochrane Database of Systematic Reviews*** 2009, Issue 4. Art. No.: CD000022.

Minozzi S, Pieri S, Brazzi L, Pecoraro V, Montrucchio G, D'Amico R. Topical antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving mechanical ventilation. ***Cochrane Database of Systematic Reviews*** 2021, Issue 1. Art. No.: CD000022.

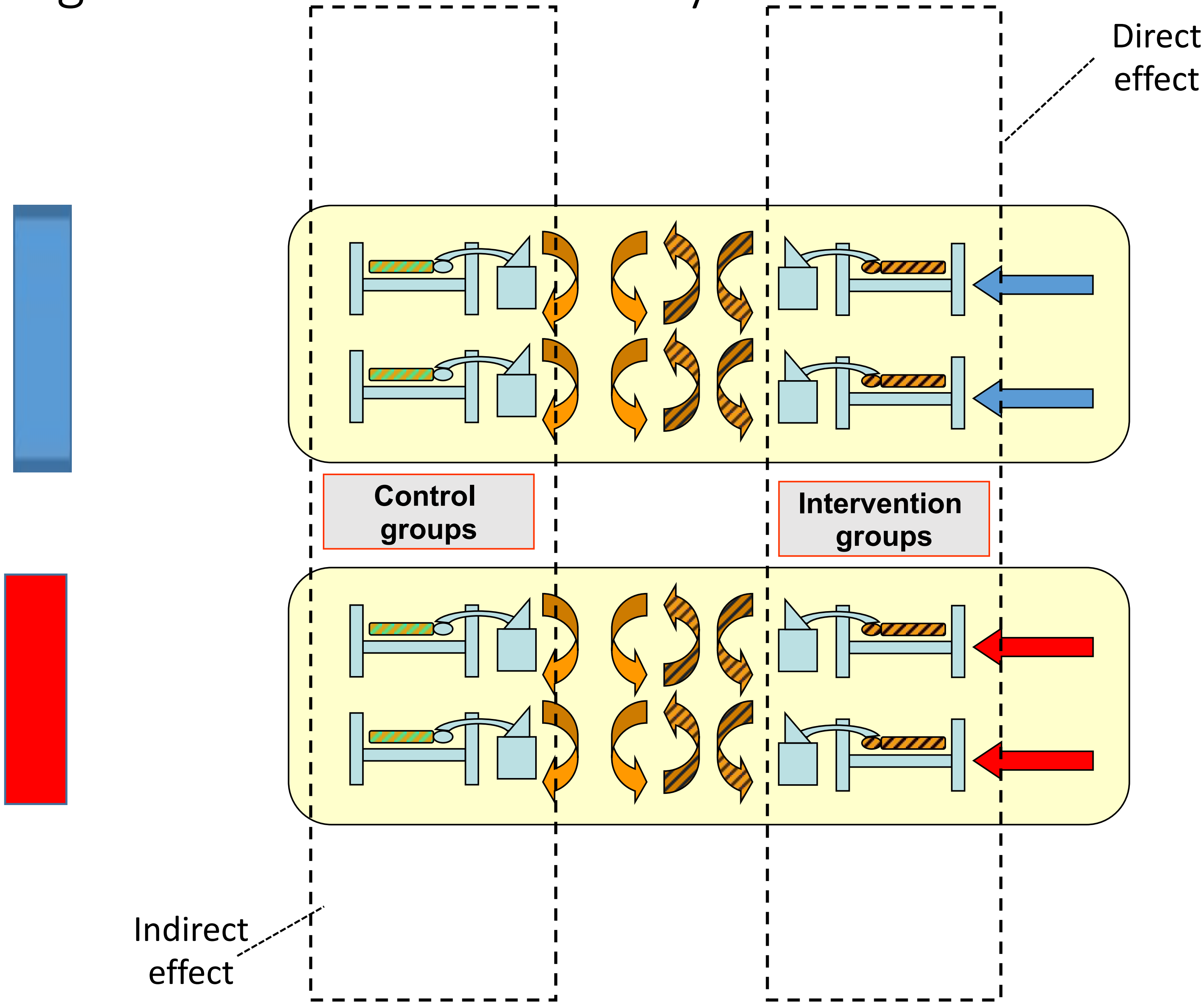


The ICU as a ‘neighbourhood’

‘neighbourhoods’ in RCCT array

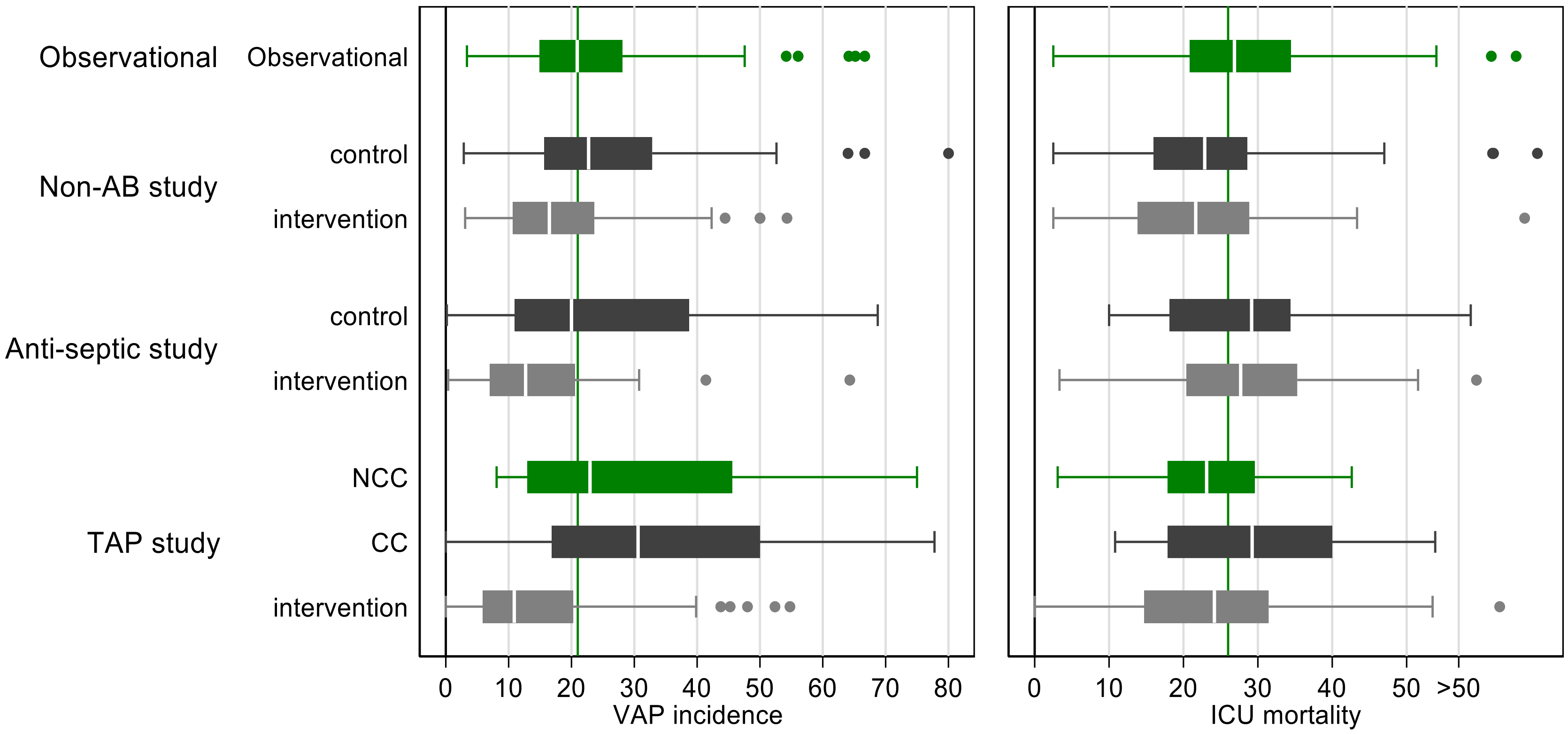


‘neighbourhoods’ in CRT array



(How not to display proportion data)

```
gen vappct = vap_n*100/ vap_d
gen mortpct = m_n*100/ m_d
```



- NCC = non-concurrent control groups; observational = no intervention
- Box plots & linear scale (logit scale would be better)

- Transforming to a logit scale
- Estimating sub-category means from meta-analysis

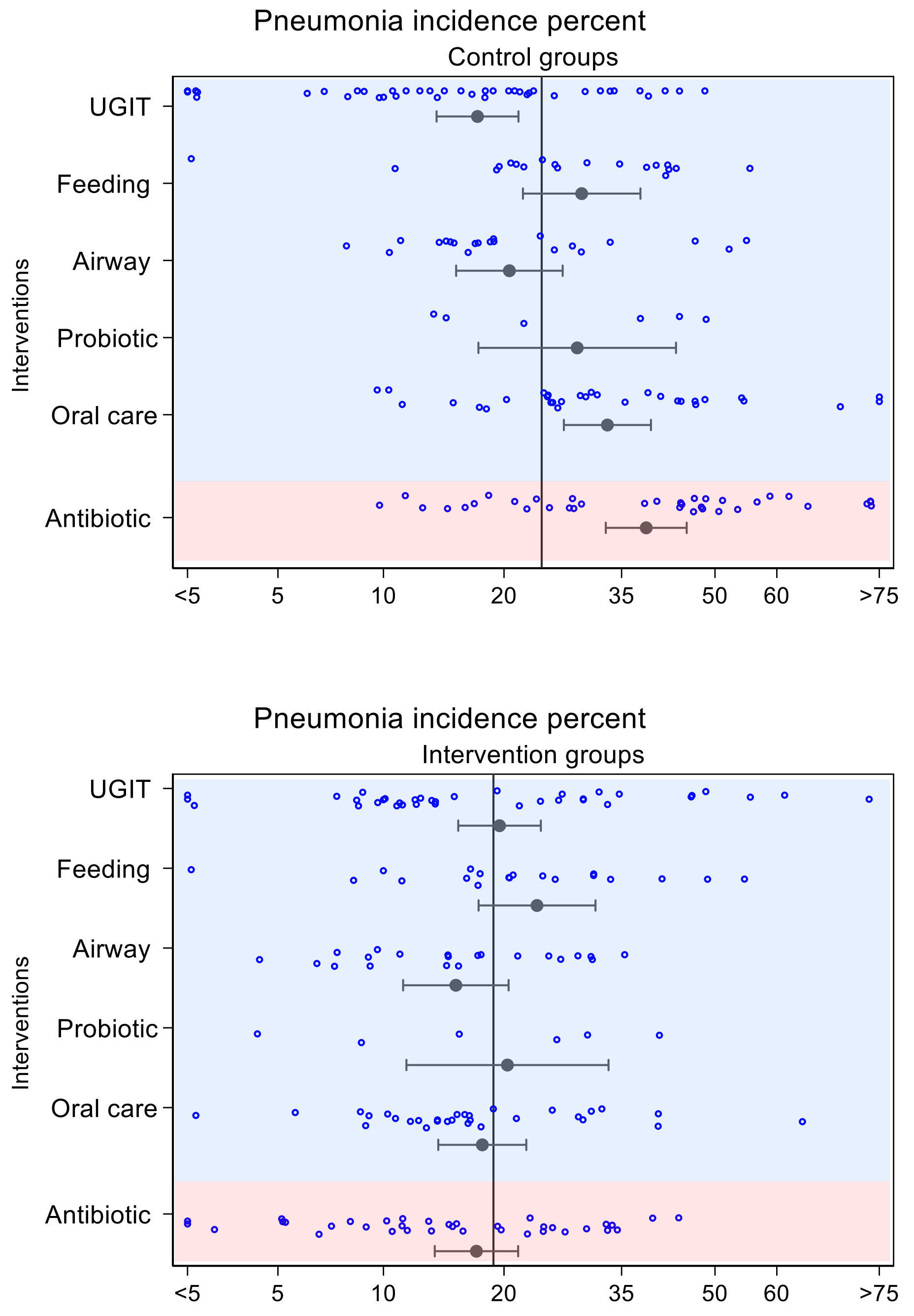
```
///Logit transformation from counts of
/// Pneumonia [vap_n; denominator = vap_d]
/// Mortality [m_n; denominator = m_d]

generate m_m = m_d - m_n
recode m_n (0 = 0.5)
recode m_m (0 = 0.5)
gen mlogodds = ln((m_n)/(m_m))
gen mselogor = sqrt((1/m_n) + (1/m_m))
replace mlogodds = -3.5 if mortpct <3


generate vap_m = vap_d - vap_n
replace vap_n = 0.5 if vap_n == 0
replace vap_m = 0.5 if vap_m == 0
gen vaplogodds = ln((vap_n)/(vap_m))
gen vapselogor = sqrt((1/vap_n) + (1/vap_m))
```

```
///declare data for meta-analysis using generic
effect sizes and standard errors


meta set mlogodds mselogor
(45 missing values generated)

Meta-analysis setting information

 Study information
    No. of studies: 467
       Study label: Generic
        Study size: N/A

       Effect size
              Type: <generic>
             Label: Effect size
          Variable: mlogodds

         Precision
         Std. err.: mselogor
                CI: [_meta_cil, _meta_ciu]
          CI level: 95%

  Model and method
             Model: Random effects
            Method: REML
```

- Estimating sub-category means & 95% CI's from meta-regression
- using 'addplot' with margins

```
 meta regress ib(last).level4 if census==1 & Int==1, random(reml) cformat(%9.3f)

  Effect-size label: Effect size
        Effect size: mlogodds
          Std. err.: mselogor

Random-effects meta-regression                      Number of obs  =        180
Method: REML                                        Residual heterogeneity:
                                                                tau2 =   .3535
                                                              I2 (%) =   79.23
                                                                  H2 =    4.81
                                                       R-squared (%) =    6.34
                                                    Wald chi2(5)   =     14.66
                                                    Prob > chi2    =    0.0119
------------------------------------------------------------------------------------
          _meta_es | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------------+----------------------------------------------------------------
            level4 |
      UGIT control |     -0.540      0.148    -3.66   0.000       -0.829      -0.251
   Feeding control |     -0.477      0.203    -2.35   0.019       -0.875      -0.079
    Airway control |     -0.235      0.194    -1.21   0.225       -0.615       0.145
Probiotic control  |     -0.456      0.331    -1.38   0.169       -1.105       0.194
Oral care control  |     -0.359      0.191    -1.88   0.061       -0.734       0.016
                   |
             _cons |     -0.954      0.119    -7.98   0.000       -1.188      -0.720
------------------------------------------------------------------------------------
 margin level4
[output omitted]

marginsplot, xdimension(level4) horizontal recast(scatter) ytitle("Interventions ") yscale(reverse) xtitle("  ")
xline(-1.32) xlabel(-3.5 "<5" -2.9 "5" -2.2 "10" -1.4 "20" -.62 "35" 0 "50" .41 "60" 1.09 ">75") title(ICU
mortality incidence percent) sub(Control groups) addplot((scatter level3 mlogodds if Int ==1 & census==1 &
level==1000, mcolor(green) msymbol(T))(scatter level3 mlogodds if Int ==1 & census==1 & mvp!= . & dupl!=2 &
level!=1000, mcolor(blue) msymbol(oh) jitter(3) xlabel(  -3.5 "<5" -2.9 "5" -2.2 "10" -1.4 "20" -.62 "35" 0 "50"
.41 "60" 1.09 ">75", ) ylabel(80 "UGIT " 230 "Feeding " 380 "Airway "  530 "Probiotic" 680 "Oral care"  880
"Antibiotic ", labsize(medium) angle(horizontal)) ysc(r(30 )) legend(off)))
```

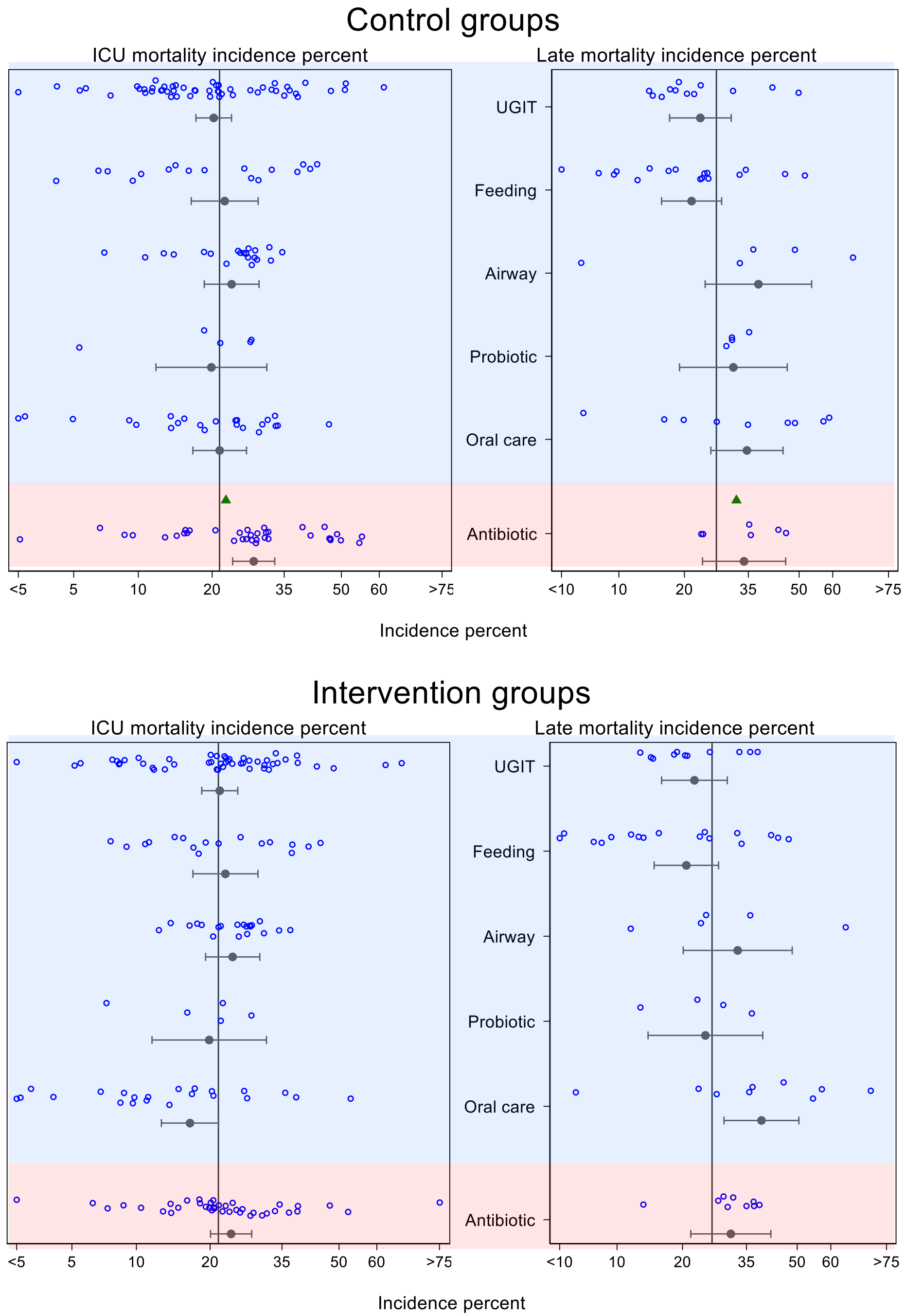
VAP



Adapted from;

Hurley JC. Prophylaxis with enteral antibiotics in ventilated patients: selective decontamination or selective cross infection? Antimicrob. Agents Chemother. 1995;39: 941-947.

Mortality

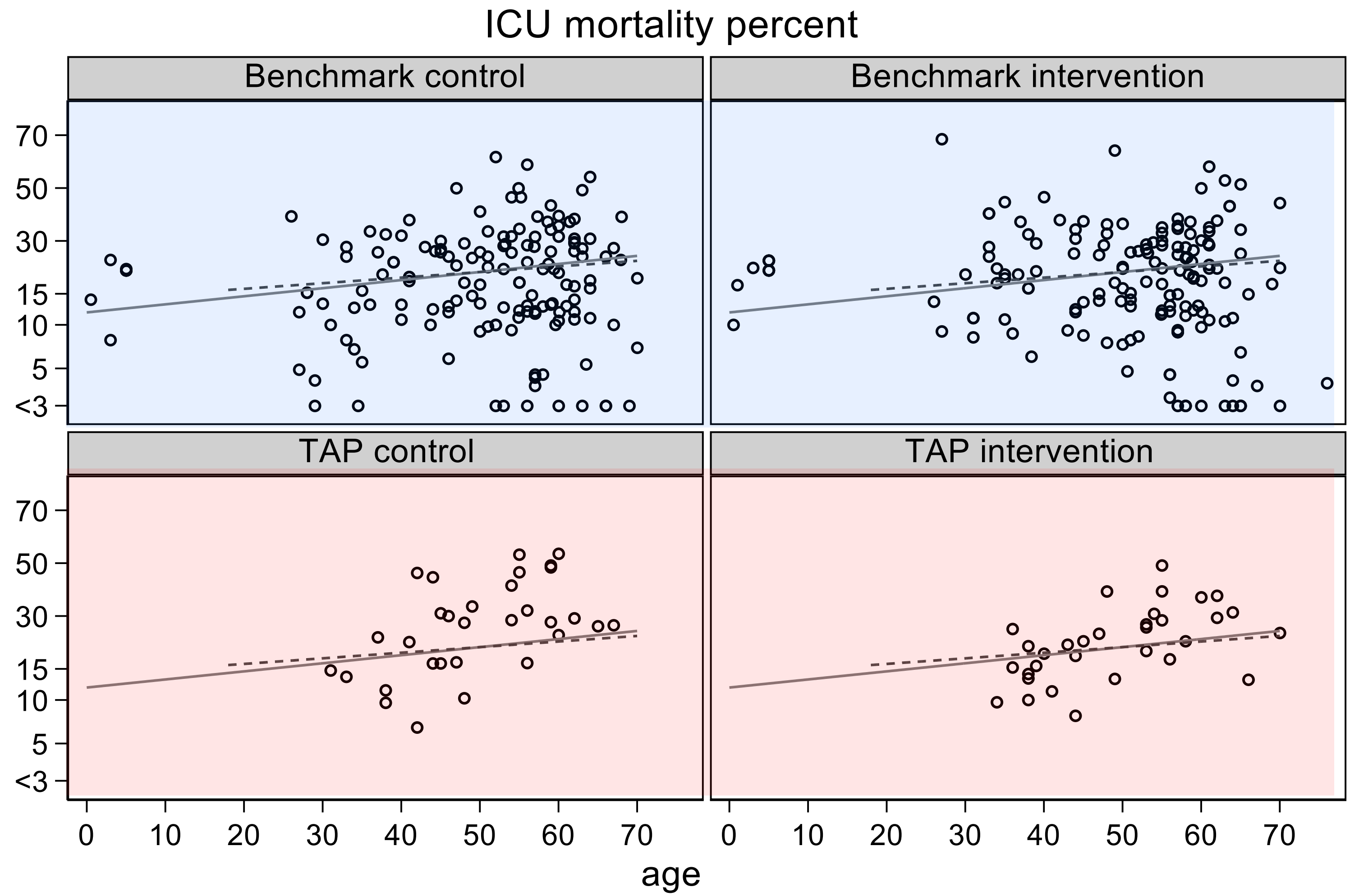


Adapted from;

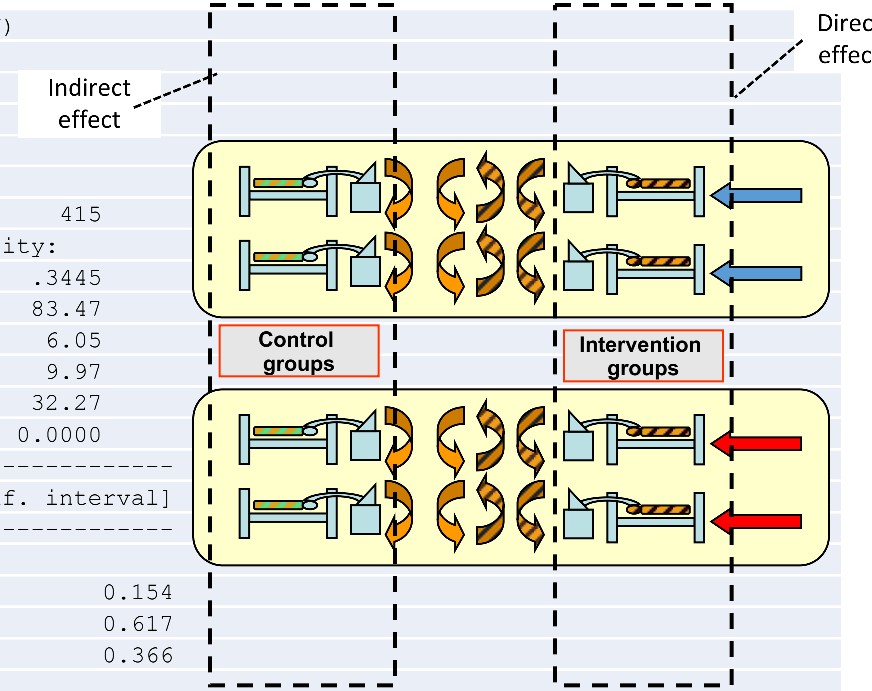
Hurley JC. Prophylaxis with enteral antibiotics in ventilated patients: selective decontamination or selective cross infection? Antimicrob. Agents Chemother. 1995;39: 941-947.

• Meta-regression versus group mean age

```
meta regress i.level5#i.Int i.qs i.census aged if age>18, cformat(%9.3f)

  Effect-size label: Effect size
        Effect size: mlogodds
          Std. err.: mselogor

Random-effects meta-regression                       Number of obs  =        415
Method: REML                                         Residual heterogeneity:
                                                                 tau2 =   .3445
                                                               I2 (%) =   83.47
                                                                   H2 =    6.05
                                                        R-squared (%) =    9.97
                                                     Wald chi2(5)   =     32.27
                                                     Prob > chi2    =    0.0000
---------------------------------------------------------------------------------
         _meta_es | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
------------------+--------------------------------------------------------------
       level5#Int |
500#intervention  |     -0.000      0.079    -0.00   0.999      -0.154       0.154
     900#control  |      0.377      0.123     3.07   0.002       0.136       0.617
900#intervention  |      0.131      0.120     1.09   0.274      -0.104       0.366
                  |
           census |
  Late mortality  |      0.227      0.086     2.65   0.008       0.059       0.395
             aged |      0.128      0.036     3.55   0.000       0.057       0.198 [note aged is age in decades]
            _cons |     -2.010      0.196   -10.24   0.000      -2.395      -1.625
---------------------------------------------------------------------------------

twoway (scatter mlogodds age if census==1 & study!=210, msymbol(oh) mcolor(black)) (scatter mlogodds age if
census==1 & study==210 & Int==1, mcolor(green) msymbol(T)) (function y = -2 + 0.013*(x), range(0 70)) (function y =
-1.8 + 0.009*(x), lpattern(shortdash) range(18 70)), ylabel(-3.5 "<3" -2.9 "5" -2.2 "10" -1.7 "15" -.85 "30" 0 "50"
.85 "70", angle(horizontal)) xlabel(0(10)70) xscale(off) xtitle( age ) ytitle( ) by(level6, imargin(tiny) cols(2))
by(, note("The linear regression lines for ICU mortality versus age in all panels are derived " "using the
Benchmark control groups including [solid line] or not [broken line] the pediatric groups" )) by(, subtitle(ICU
mortality percent)) by(, legend(off))
```



The linear regression lines for ICU mortality versus age in all panels are derived
using the Benchmark control groups including [solid line] or not [broken line] the pediatric groups




```
meta regress i.level5#i.Int i.qs i.census aged if age>18, cformat(%9.3f)

  Effect-size label: Effect size
        Effect size: mlogodds
          Std. err.: mselogor

Random-effects meta-regression                    Number of obs  =        415
Method: REML                                      Residual heterogeneity:
                                                              tau2 =   .3445
                                                            I2 (%) =   83.47
                                                                H2 =    6.05
                                                     R-squared (%) =    9.97
                                                  Wald chi2(5)   =     32.27
                                                  Prob > chi2    =    0.0000
----------------------------------------------------------------------------------
         _meta_es | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-----------------+----------------------------------------------------------------
       level5#Int |
500#intervention  |     -0.000      0.079    -0.00   0.999      -0.154       0.154
      900#control |      0.377      0.123     3.07   0.002       0.136       0.617
900#intervention  |      0.131      0.120     1.09   0.274      -0.104       0.366
                  |
           census |
   Late mortality |      0.227      0.086     2.65   0.008       0.059       0.395
             aged |      0.128      0.036     3.55   0.000       0.057       0.198 [note aged is age in decades]
            _cons |     -2.010      0.196   -10.24   0.000      -2.395      -1.625
-----------------+----------------------------------------------------------------

 nlcom exp((_b[900.level5#2.Int] - _b[500.level5#2.Int])), cformat(%9.2f)
       _nl_1: exp((_b[900.level5#2.Int] - _b[500.level5#2.Int]))                  \\\\\\nlcom to derive direct effect

------------------------------------------------------------------------------
    _meta_es | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
       _nl_1 |       1.00       0.12     8.38   0.000        0.77        1.24
------------------------------------------------------------------------------

 nlcom exp((_b[900.level5#1.Int] - _b[500.level5#1.Int])), cformat(%9.2f)         \\\\\\nlcom to derive indirect effect
       _nl_1: exp((_b[900.level5#1.Int] - _b[500.level5#1.Int]))

------------------------------------------------------------------------------
    _meta_es | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
       _nl_1 |       1.30       0.16     8.15   0.000        0.98        1.61
------------------------------------------------------------------------------
```

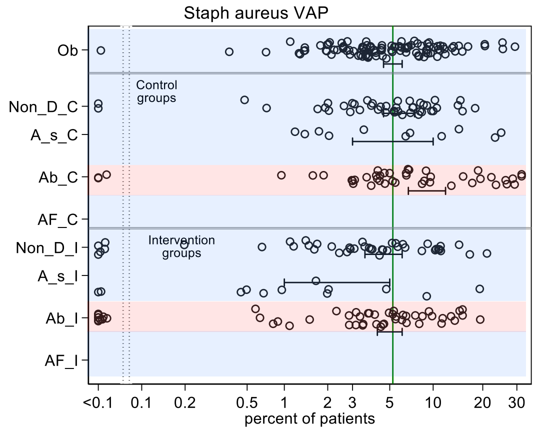
Mechanism?

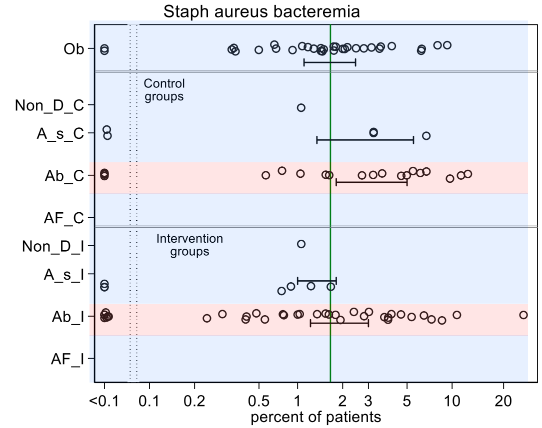
This presentation extends from a presentation to the STATA 2021 on line conference [Structural equation modelling the ICU patient microbiome and risk of bacteremia;

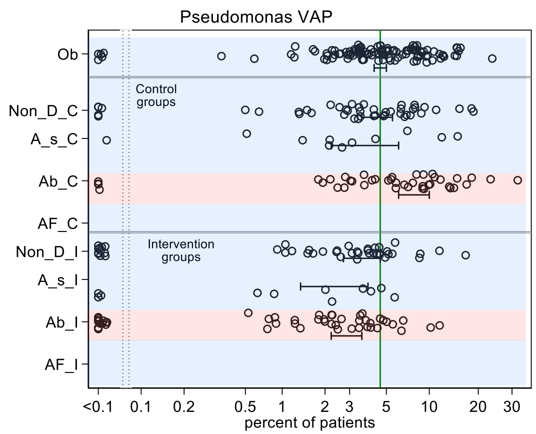
https://www.stata.com/meeting/us21/].

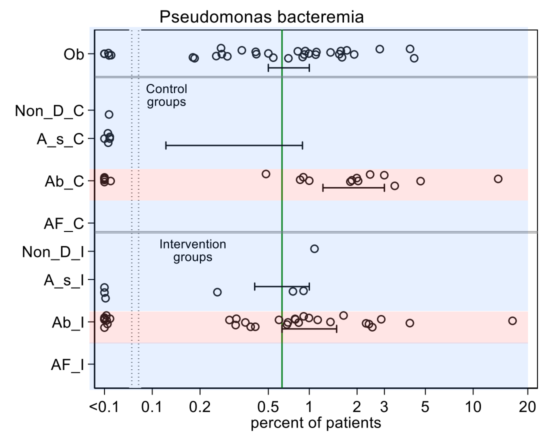
Since published as

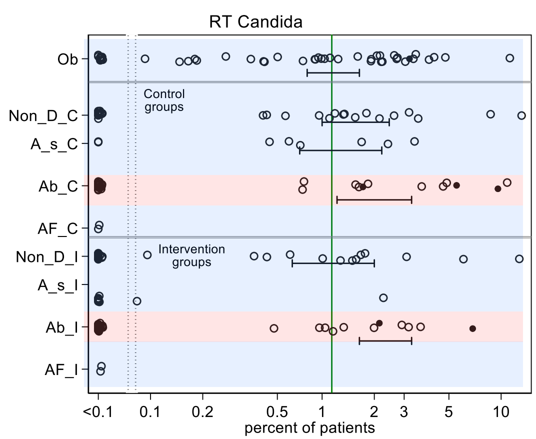
Hurley JC. Structural equation modelling the relationship between anti-fungal prophylaxis and Pseudomonas bacteremia in ICU patients. Intensive Care Medicine Experimental. 2022 Dec;10(1):1-7.

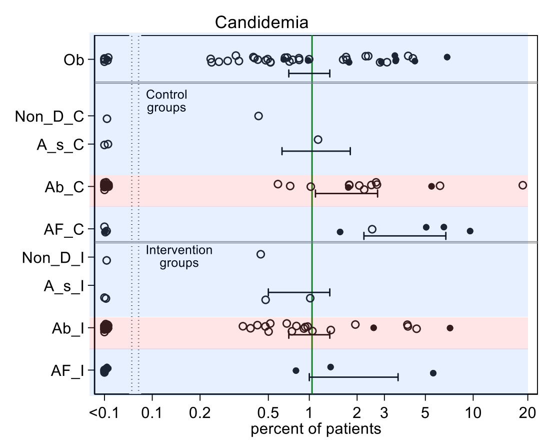

Staph aureus VAP
Ob
Control groups
Non_D_C
A_s_C
Ab_C
AF_C
Intervention groups
Non_D_I
A_s_I
Ab_I
AF_I
<0.1 0.1 0.2 0.5 1 2 3 5 10 20 30
percent of patients


Staph aureus bacteremia
Ob
Control groups
Non_D_C
A_s_C
Ab_C
AF_C
Intervention groups
Non_D_I
A_s_I
Ab_I
AF_I
<0.1 0.1 0.2 0.5 1 2 3 5 10 20
percent of patients


Pseudomonas VAP
Ob
Control groups
Non_D_C
A_s_C
Ab_C
AF_C
Intervention groups
Non_D_I
A_s_I
Ab_I
AF_I
<0.1 0.1 0.2 0.5 1 2 3 5 10 20 30
percent of patients


Pseudomonas bacteremia
Ob
Control groups
Non_D_C
A_s_C
Ab_C
AF_C
Intervention groups
Non_D_I
A_s_I
Ab_I
AF_I
<0.1 0.1 0.2 0.5 1 2 3 5 10 20
percent of patients


RT Candida
Ob
Control groups
Non_D_C
A_s_C
Ab_C
AF_C
Intervention groups
Non_D_I
A_s_I
Ab_I
AF_I
<0.1 0.1 0.2 0.5 1 2 3 5 10
percent of patients


Candidemia
Ob
Control groups
Non_D_C
A_s_C
Ab_C
AF_C
Intervention groups
Non_D_I
A_s_I
Ab_I
AF_I
<0.1 0.1 0.2 0.5 1 2 3 5 10 20
percent of patients

Measurement variables

b_sr_n = Staphylococcus bacteremia (count)

v_sr_n = Staphylococcus VAP (count)

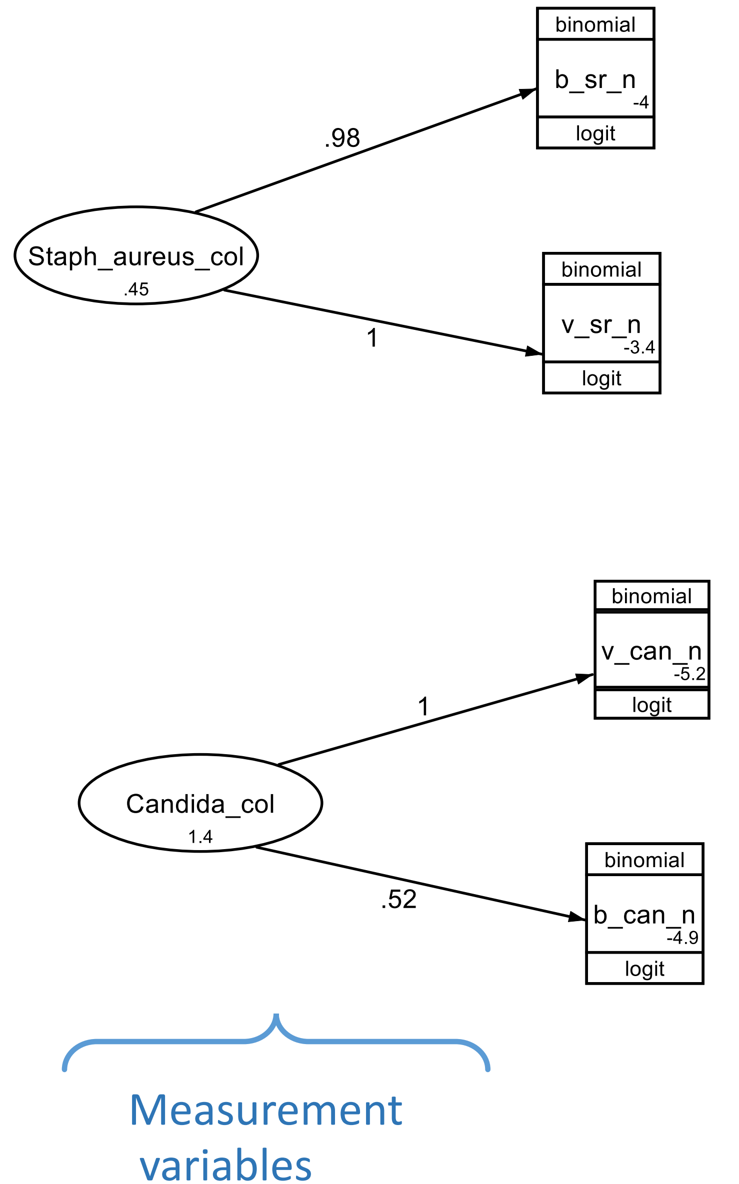
b_ps_n = Pseudomonas bacteremia (count)

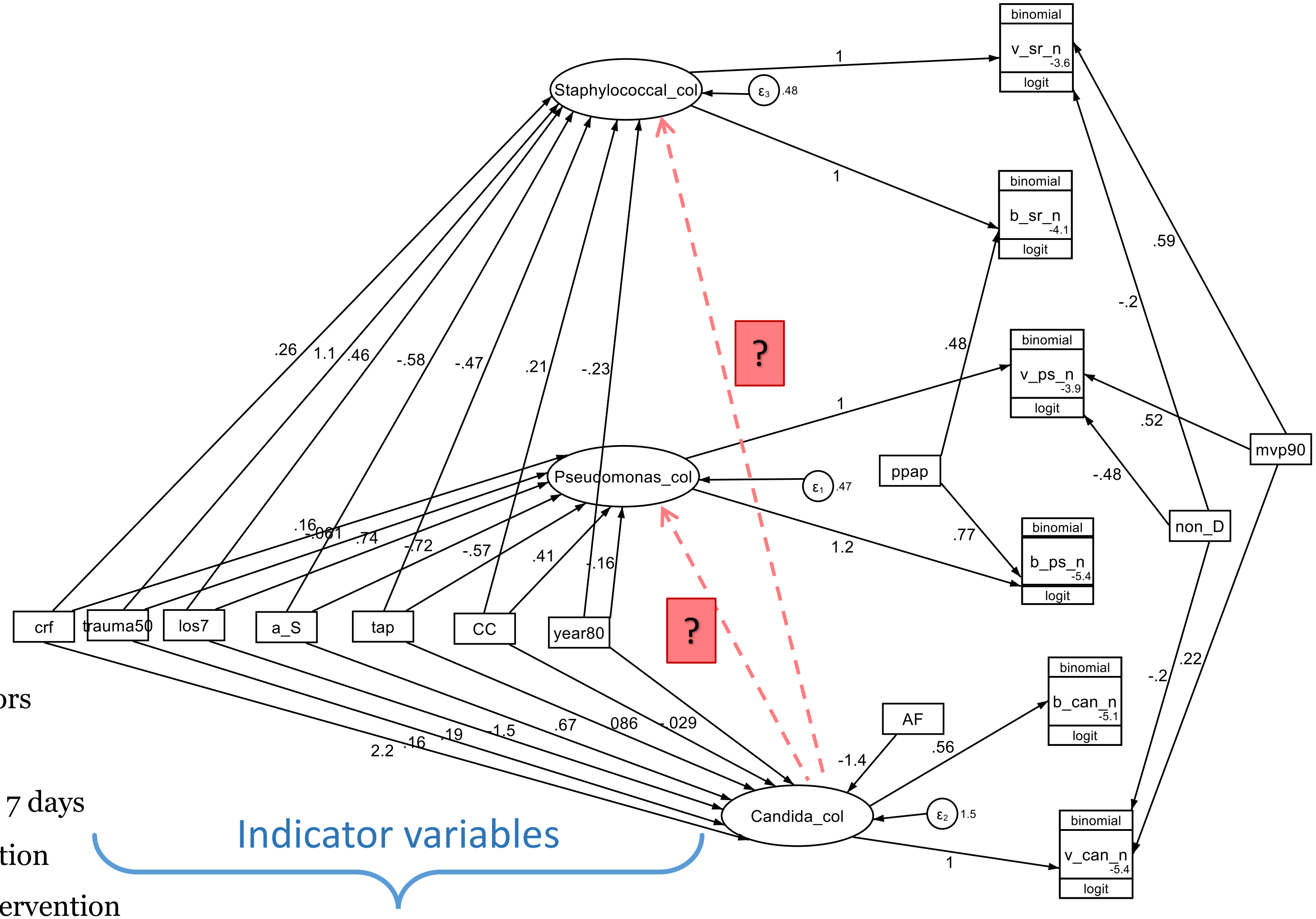
v_ps_n = Pseudomonas VAP (count)

b_can_n = Candidemia (count)

v_can_n = Candida VAP (count)

denominator for all is number of patients





Indicator variables

crf = candidemia risk factors

trauma50 = trauma icu

los7 = mean length of stay 7 days

a_S = anti-septic intervention

tap = topical antibiotic intervention

cc = control group concurrent to tap group

year 80 = year of study publication [decade since 1980]

non_D = non-decontamination/airway intervention

mvp90 = 90% receiving mechanical ventilation

af = anti-fungal intervention

ppap= protocolized parenteral antibiotic intervention

Conclusions

Topical antibiotics as prevention in the ICU

- In RCCT's - appear very effective at preventing VAP [& mortality]
- Contextual effect long postulated – but requires a CRT

Higher event rates among CC groups of topical AB studies [red studies]

- versus groups from blue studies as benchmark

Topical antibiotic as prevention in the ICU context

- Indirect effect stronger than the direct effect
- Mediated through ICU microbiome?

Graphical display using Stata helps to convey