Mortality within ventilator-associated pneumonia prevention studies using topical antibiotics

Online Data Supplement

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Supplemental file contents:

Table S1: Mortality data: observational studies

Author	Year	Ref	Notes	Age [a]	Patients (n)	Vap (n)	Vap (%)	Mortality (n)	Mortality (%)
Akça	2000	1		44	260	81	31.2	66	25.4
Apostolopoulou	2003	2		52	175	56	32.0	62	35.4
Bercault_all	2005	3		58	236	43	18.2	72	30.5
Bochicchio	2004	4	T	43	714	125	17.5	82	11.5
Bonten'96	1996	5		58	141	31	22.0	50	35.5
Boots	2005	6		56	794	131	16.5	121	15.2
Bronchard	2004	7	T	34	109	45	41.3	20	18.3
Chastre	1998	8		62	243	84	34.6	97	39.9
Craven'86	1986	9		55	233	49	21.0	95	40.8 (L)
Croce	2003	10	T	41	9721			243	2.5
Daumal	1999	11		63	364	54	14.8	20	5.5
Eggimann	2003	12		63	452	127	28.1	76	17
Fagon'96	1996	13	<90	58	1978	328	16.6	542	27.4
Georges	2000	14		64	135	35	25.9	45	33.3
Guimaraes	2006	15		52	278	106	38.1	126	45.3
Ibrahim'00	2000	16		57.7	3668	397	10.8	589	16.1 (L)
Ibrahim'01	2001	17	<90	69.3	880	132	15.0	301	34.2 (L)
Ibrahim'02	2002	18		58	150	60	40.0	35	23.3 (L)
Jaimes	2007	19		41	270	60	22.2	50	18.5
Jimenez	1989	20		55	77	18	23.4	21	27.3
Kanafani	2003	21		60.5	70	33	47.1	24	34.3
Kappstein	1992	22	T	44	270	78	28.9	45	16.7
Kollef' 93	1993	23		63.1	277	43	15.5	36	13.0
Kollef '95	1995	24		60.6	314	87	27.7	119	37.9 (L)
Kollef '97	1997	25		57.4	521	77	14.8	131	25.1 (L)
Langer	1989	26	<90	50.5	724	168	23.2	172	23.8
Lowy	1987	27		67	78	35	44.9	22	28.2
Moine	2002	28	<90	63	764	89	11.6	188	24.6
Myny	2005	29		60	385	89	23.1	109	28.3
Noor	2005	30		45	250	70	28.0	100	40.0
OUTCOMEREA*	2019	31		66	7735	1161	15	2077	26.9
Rello'91	1991	32		46.4	264	58	22.0	101	38.3
Rodriguez	1991	33	T	36	294	130	44.2	64	21.8
Sofianou	2000	34			198	67	33.8	49	24.7
Stéphan	2006	35	T	35	175	78	44.6	34	19.4
Timsit	1996	36		65	387	56	14.5	168	43.4 (L)
Torres	1990	37		54.5	322	78	24.2	73	22.7
Valles	2007	38		62	101	40	39.6	35	34.7
van der Kooi	2007	39		61	1516	220	14.5	360	23.7
Violan	1998	40		52.9	314	82	26.1	67	21.3
Warren	2003	41		69	819	127	15.5	301	36.8
Woske	2001	42		53	103	49	47.6	36	35.0 (L)
Zygun	2006	43	T	38	134	60	44.8	38	28.4 (L)

Table S1 Footnotes

Age – Group mean (or median) age (years)

T – Data originating from a study for which the majority of ICU admission were for trauma

<90 – less than 90% of patients received > 24 hours of MV

L – Late mortality being day 28 or hospital mortality

* - Indicate study identified and included from outside a systematic review

Studies derived from the following systematic reviews;

- Safdar N, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med* 2005;33(10):2184-93.
- Melsen WG, Rovers MM, Bonten MJM: Ventilator-associated pneumonia and mortality: A systematic review of observational studies. *Crit Care Med* 2009, 37:2709–2718.
- Agrafiotis M, Siempos II, Ntaidou TK, Falagas ME. Attributable mortality of ventilator-associated pneumonia: a meta-analysis. *Internat J Tuberculosis Lung Dis*. 2011;15(9):1154-63.

The studies below within these systematic review met the following exclusion criteria;

ARDS population

- Delclaux C, Roupie E, Blot F, et al: Lower respiratory tract colonization and infection during severe acute respiratory distress syndrome: Incidence and diagnosis. Am J Respir Crit Care Med 1997; 156:1092–1098
- Markowicz P, Wolff M, Djedaini K, et al: Multicenter prospective study of ventilator associated pneumonia during acute respiratory distress syndrome. Incidence, prognosis, and risk factors. ARDS study Group. Am J Respir Crit Care Med 2000; 161:1942–1948
- Sutherland KR, Steinberg KP, Maunder RJ, et al: Pulmonary infection during the acute respiratory distress syndrome. Am J Respir Crit Care Med 1995; 152:550–556

Cardiac or cardio-thoracic population or < 50% receiving MV

- Bouza E, Perez A, Munoz P, et al: Ventilator- associated pneumonia after heart surgery: A prospective analysis and the value of surveillance. Crit Care Med 2003; 31: 1964–1970
- Ensminger SA, Wright RS, Baddour LM, et al: Suspected ventilator-associated pneumonia in cardiac patients admitted to the coronary care unit. Mayo Clin Proc 2006; 81:32–35
- Kollef MH, Vlasnik J, Sharpless L, et al: Scheduled change of antibiotic classes: A strategy to decrease the incidence of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1997; 156:1040–1048
- Pawar M, Mehta Y, Khurana P, Chaudhary A, Kulkarni V, Trehan N. Ventilator-associated pneumonia: incidence, risk factors, outcome, and microbiology. J Cardiothorac Vasc Anesth 2003; 17: 22–28.
- Simsek S, Yurtseven N, Gercekogalu H, et al: Ventilator-associated pneumonias in a cardiothoracic surgery centre postoperative intensive care unit. J Hosp Infect 2001; 47: 321–324
- Stoller JK, Orens DK, Fatica C, et al: Weekly versus daily changes of in-line suction catheters: Impact on rates of ventilator-associated pneumonia and associated costs. Respir Care 2003; 48:494–499

Case control design

- Baker AM, Meredith JW, Haponik EF. Pneumonia in intubated trauma patients. Microbiology and outcomes. Am J Respir Crit Care Med 1996; 153: 343–349.
- Bercault N, Boulain T. Mortality rate attributable to ventilator associated nosocomial pneumonia in an adult intensive care unit: a prospective case-control study. Crit Care Med 2001;29: 2303–2309.
- Bonten MJ, Froon AH, Gaillard CA, et al. The systemic inflammatory response in the development of ventilator-associated pneumonia. Am J Respir Crit Care Med 1997; 156: 1105–1113.
- Cavalcanti M, Ferrer M, Ferrer R, Morforte R, Garnacho A, Torres A. Risk and prognostic factors of ventilator-associated pneumonia in trauma patients. Crit Care Med 2006; 34:1067–1072.
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- Heyland DK, Cook D J, Griffith L, Keenan SP, Brun-Buisson C. The attributable morbidity and mortality of ventilator associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. Am J Respir Crit Care Med 1999; 159: 1249–1256.
- Hugonnet S, Eggimann P, Borst F, Maricot P, Chevrolet JC, Pittet D. Impact of ventilator-associated pneumonia on resource utilization and patient outcome. Infect Control Hosp Epidemiol 2004; 25: 1090–1096.
- Kallel H, Chelly H, Bahloul M, et al. The effect of ventilator associated pneumonia on the prognosis of head trauma patients. J Trauma 2005; 59: 705–710.
- Leone M, Bourgoin A, Giuly E, et al. Influence on outcome of ventilator-associated pneumonia in multiple trauma patients with head trauma treated with selected digestive decontamination. Crit Care Med 2002; 30: 1741–1746.
- Leroy O, Guilley J, Georges H, et al. Effect of hospital-acquired ventilator-associated pneumonia on mortality of severe community-acquired pneumonia. J Crit Care 1999; 14: 12–19.
- Papazian L, Bregeon F, Thirion X, et al. Effect of ventilator associated pneumonia on mortality and morbidity. Am J Respir Crit Care Med 1996; 154: 91–97.
- Rello J, Quintana E, Ausina V, et al: Incidence, etiology, and outcome of nosocomial pneumonia in mechanically ventilated patients. Chest 1991; 100:439–444
- Rincon-Ferrari MD, Flores-Cordero JM, Leal-Noval SR, et al. Impact of ventilator-associated pneumonia in patients with severe head injury. J Trauma 2004; 57: 1234–1240.

Table S2: Mortality data: non-decontamination methods of VAP prevention [a]

Author	Year	Ref	Notes	Age [a]	Patients (n)	Vap (n)	Vap (%)	Mortality (n)	Mortality (%)
control groups									
Acosta-escribano	2010	44	T	41	54	31	57.4	9	16.7 (L)
Amrein	2014	45		65	238			63	26.5
Barquist	2006	46		49.9	31			5	16.1
Barraud	2010	47		60.7	80	15	18.8	21	26.3
Ben-Menachem	1994	48	<90	59	100	6	6.0	19	19.0
Blot	2009	49		58	62	31	50.0	20	32.3 (L)
Bonten '95	1995	50		58.6	74	16	21.6	24	32.4
Boots	1997	51		53	33	8	24.2	7	21.2
Boots'06_HME	2006	52		58	190			29	15.1
Cheadle	1985	53		58	100			7	7.0
Combes	2000	54	T	43.8	54	4	7.4	15	27.8
Cook	1998	55		58.8	596	114	19.1	140	23.5
Darvas	2003	56		63.8	53	10	18.9	17	32.0 (L)
David	2011	57		44	100			47	47.0
Davies	2002	58		53.5	39	1	2.6	5	12.8
Davies	2012	59		54	89	19	21.3	12	13.5 (L)
Deppe BAMC	1990	60	T	54.4	18	4	22	4	22
Deppe BTGH	1990	60		52.1	20	7	35	7	35
Drakulovic	1999	61		67	47	11	23.4	13	27.7
Dreyfuss	1995	62		62	70	8	11.4	12	17.1
Driks	1987	63		55.2	69	16	23.2	32	46.4
Eddleston '91	1991	64		54.1	30	10	33.3	7	23.3
Fabian	1993	65	T	35	179	52	29.1	32	17.9
Fink	1990	66	T	28.5	48	19	39.6	8	16.7
G'-Bourboulis	2009	67	T	55.9	36	16	44.4	5	13.9
Grau	2011	68		65	68			13	19.1
Hanisch	1998	69	T	55	57	10	17.5	7	12.3
Hanisch	1998	69		53	44	10	22.7	12	27.3
Heyland	1999	70		55.2	59	7	11.9	7	11.9
Holzapfel_C_99	1999	71		60.8	200	51	25.5	80	40.0 (L)
Hurni	1997	72		52.6	56	7	12.5	19	33.9
Ibrahim '02	2002	73		56.5	75	37	49.3	15	20.0 (L)
Kearns_C	2000	74		49	23	3	13.0	6	26.1 (L)
Knight	2009	75		49.5	129	17	13.2	34	26.4
Kollef '98	1998	76		59	147	15	10.2	39	26.5 (L)
Kollef'08	2008	77		62	743	56	7.5	198	26.6 (L)
Kortbeek	1999	78	T	34.7	43	18	41.9	3	7.0
Kotzampassi	2006	79	T	55.9	30	24	80.0	9	30.0
Lacherade '05	2005	80		54.7	184	53	28.8	63	34.2

Table S2 (continued): Mortality data: non-decontamination methods of VAP prevention [a]

author	Year	Ref	Notes	Age [a]	Patients (n)	Vap (n)	Vap (%)	Mortality (n)	Mortality (%)
control groups									
Lacherade '10	2010	81		70	164	42	25.6	65	39.6
Leaf	2014	82		58	31			6	19.4
Liu	2006	83			45	30	66.7	18	40.0
Loan	2012	84		34	112			11	9.8
Lorente '03	2003	85		58.1	116	26	22.4	28	24.1
Lorente'05	2005	86		58.2	233	31	13.3	50	21.5
Lorente'06	2006	87		55.9	51	8	15.7	12	23.5
Lorente'06	2006	88		59.2	221	31	14.0	30	13.1
Lorente'07	2007	89		60	140	31	22.1	32	22.9
Mahul	1992	89		57.9	75	21	28.0	16	21.3
Mahul	1992	90		57.9	72	17	23.6	16	22.2
Maier	1994	91			51			11	21.6
Manzano	2008	92		47	63	16	25.4	16	25.4 (L)
Martin	1990	93		54	42	8	19.0	11	26.2
Martin	1993	94		60	66	6	9.1	7	10.6 (L)
Memish	2001	95		46	120	19	15.8	30	25.0
Misset	1991	96		49	26			16	61.5
Montecalvo_G	1992	97		44.8	19	2	10.5	5	26.3
Montejo	2002	98		59	51	20	39.2	22	43.1
Montejo	2010	99		60	165			26	15.8
Morrow	2010	100		52.5	68	28	41.2	12	17.6
Nair *	2015	101		56	25			4	16
Nseir	2011	102		62	61	16	26.2	20	32.8
Ntoumenopoulos	2002	103		65.1	36	14	38.9	3	8.3
O'Keefe	1998	104	T	34.2	49	14	28.6	11	22.4
Patman	2009	105		41.1	72			14	19.4
Pickworth	1993	106	T	27.3	44	5	11.4	4	9.1
Rayes	2007	107			40			1	2.5
Roustan	1992	108		49.3	61	9	14.8	15	24.6
Rumbak	2004	109		63	60	15	25.0	37	61.7
Ryan_C	1993	110		65	56	7	12.5	19	33.9 (L)
Smulders	2002	111		62.8	75	12	16.0	10	13.3
Spindler-Vessel	2007	112	T	31	31	11	35	1	3
Spindler-Vessel	2007	112	T	36	29	12	41	2	7
Staudinger	2010	113		60	75	17	22.7	18	24.0
Sugerman	1997	114			59			11	18.6
Terragni	2010	115		61.3	210			66	31.4
Thomachot	1998	116		47	66	21	31.8	11	16.7
Thomachot	2002	117		46	84	22	26.2	27	32.1 (L)

Table S2 (continued): Mortality data: non-decontamination methods of VAP prevention [a]

author	Year	Ref	Notes	Age [a]	Patients (n)	Vap (n)	Vap (%)	Mortality (n)	Mortality (%)
control groups									
Thomasen A	1996	118	T	32.9	80	30	37.5	10	12.5
Thomasen R	1996	118	T	31	82	27	32.9	19	23.2
Topeli	2004	119		67.9	37	9	24.3	25	67.6
Tryba	1987	120		43.7	50	11	22.0	17	34.0 (L)
Valencia	2007	121		64	69	10	14.5	16	23.2
Valles	1995	122		63.1	77	25	32.5	28	36.4
van Nieuwenhoven	2006	123		63	109	8	7.3	33	30.3
Zheng	2008	124			31	16	51.6	12	38.7

Table S2 (continued): Mortality data: non-decontamination methods of VAP prevention [a]

author	Year	Ref	Notes	Age [a]	Patients (n)	Vap (n)	Vap (%)	Mortality (n)	Mortality (%)
Intervention groups									
Acosta-escribano	2010	44	T	35	50	16	32.0	6	12.0 (L)
Amrein	2014	45		65	237			54	22.8
Barquist	2006	46		53.7	29			2	6.9
Barraud	2010	47		59.1	87	23	26.4	21	24.1
Ben-Menachem	1994	48	<90	59.6	100	12	12.0	11	11.0
Ben-Menachem	1994	48	<90	60.1	100	6	6.0	12	12.0
Blot	2009	49		55	61	30	49.2	21	34.4 (L)
Bonten '95	1995	50		57.3	67	15	22.4	26	38.8
Boots ‘97	1997	51		52	42	6	14.3	6	14.3
Boots ‘97	1997	51		49	41	7	17.1	4	9.8
Boots'06_DHW	2006	52		56	97			21	21.6
Boots’06_SHW	2006	52		55	94			13	13.8
Cheadle	1985	53		58	100			5	5.0
Combes	2000	54	T	43	50	10	20.0	13	26.0
Cook	1998	55		58.7	604	98	16.2	138	22.8
Darvas	2003	56		65.8	48	13	27.1	15	31.3 (L)
David	2011	57		42	100			42	42.0
Davies	2002	58		55.7	34	2	5.9	4	11.8
Davies	2012	59		51	91	18	19.8	13	14.3 (L)
Deppe BAMC	1990	60	T	54.4	23	7	30	3	13
Deppe BTGH	1990	60		52.1	23	5	22	9	39
Drakulovic	1999	61		63	39	2	5.1	7	17.9
Dreyfuss	1995	62		58	61	6	9.8	17	27.9
Driks	1987	63		53.9	61	7	11.5	18	29.5
Eddleston '91	1991	64		44.3	30	3	10.0	8	26.7
Fabian	1993	65	T	34	99	15	15.2	16	16.2
Fink	1990	66	T	35	51	7	13.7	10	19.6
G’-Bourboulis	2009	67	T	52.9	36	15	41.7	10	27.8
Grau	2011	68		68	59			9	15.3
Hanisch_plac	1998	69	T	58	57	12	21.1	12	21.1
Heyland	1999	70	T	55.2	61	3	4.9	15	24.6
Holzapfel_I_99	1999	71		60.7	199	37	18.6	60	30.2 (L)
Hurni	1997	72		59.5	59	5	8.5	17	28.8
Ibrahim '02	2002	73		59.1	75	23	30.7	20	26.7 (L)
Kearns_I	2000	74		54	21	4	19.0	5	23.8 (L)
Knight	2009	75		50	130	12	9.2	28	21.5
Kollef '98	1998	76		57.8	163	15	9.2	40	24.5 (L)
Kollef'08_silverETT	2008	77		60.9	766	37	4.8	233	30.4 (L)
Kortbeek	1999	78	T	33.6	37	10	27.0	4	10.8
Kotzampassi	2006	79	T	52.9	35	19	54.3	5	14.3
Lacherade '05	2005	80		55.2	186	47	25.3	61	32.8

Table S2 (continued): Mortality data: non-decontamination methods of VAP prevention [a]

author	Year	Ref	Notes	Age [a]	Patients (n)	Vap (n)	Vap (%)	Mortality (n)	Mortality (%)
Intervention groups									
Lacherade '10	2010	81		67	169	25	14.8	71	42.0
Leaf	2014	82		68	36			7	19.4
Liu	2006	83			41	14	34.1	13	31.7
Loan	2012	84		38	117			17	14.5
Lorente '03	2003	85		57.1	114	29	25.4	37	32.5
Lorente'05	2005	86		59.4	210	33	15.7	52	24.8
Lorente'06	2006	87		55.5	53	21	39.6	13	24.5
Lorente'06	2006	88		59.6	236	33	14.0	31	13.5
Lorente'07	2007	89		60.6	140	11	7.9	26	18.6
Mahul	1992	90		57.9	70	13	18.6	17	24.3
Mahul	1992	90		57.9	70	9	12.9	17	24.3
Maier	1994	91			47			6	12.8
Manzano	2008	92		44	64	6	9.4	19	29.7 (L)
Martin	1993	93		59	65	2	3.1	8	12.3
Martin	1990	94		61	31	2	6.5	7	22.6 (L)
Memish	2001	95		47	123	14	11.4	40	32.5
Misset	1991	96		53	30			13	43.3
Montecalvo_J	1992	97		50.5	19			5	26.3
Montejo	2010	98		65	157			31	19.7
Montejo	2002	99		57	50	16	32.0	19	38.0
Morrow	2010	100		54.6	70	13	18.6	15	21.4
Nair *	2015	101		48	25			5	20
Nseir	2011	102		59	61	6	9.8	16	26.2
Ntoumenopoulos	2002	103		65	24	2	8.3	6	25.0
O'Keefe	1998	104	T	34.2	47	10	21.3	6	12.8
Patman	2009	105		45.8	72			7	9.7
Pickworth	1993	106	T	26.8	39	6	15.4	2	5.1
Rayes	2007	107			40			1	2.5
Roustan	1992	108		52.7	55	5	9.1	10	18.2
Rumbak	2004	109		63	60	3	5.0	19	31.7
Ryan_S	1993	110		62	58	8	13.8	22	37.9 (L)
Smulders	2002	111		63.7	75	3	4.0	12	16.0
Spindler-Vessel	2007	112	T	41	26	11	42	2	8
Spindler-Vessel	2007	112	T	48	26	4	15	2	8
Staudinger	2010	113		59	75	8	10.7	22	29.3
Sugerman	1997	114			53			13	24.5
Terragni	2010	115		61.8	209			55	26.3
Thomachot	1998	116		45	70	26	37.1	12	17.1
Thomachot	2002	117		42	71	10	14.1	29	40.8 (L)

Table S2 (continued): Mortality data: non-decontamination methods of VAP prevention [a]

author	Year	Ref	Notes	Age [a]	Patients (n)	Vap (n)	Vap (%)	Mortality (n)	Mortality (%)
Intervention groups									
Thomason	1996	118	T	27.7	80	30	37.5	10	12.5
Topeli	2004	119		60.6	41	13	31.7	27	65.9
Tryba	1987	120		44.9	50	3	6.0	15	30.0 (L)
Valencia	2007	121		64	73	11	15.1	20	27.4
Valles	1995	122		62.9	76	14	18.4	30	39.5
van Nieuwenhoven	2006	123		69.8	112	13	11.6	33	29.5
Zheng	2008	124			30	9	30.0	8	26.7

Table S2 footnotes

Age – Group mean (or median) age (years)

T – Data originating from a study for which the majority of ICU admission were for trauma

<90 – less than 90% of patients received > 48 hours of MV

L – Late mortality being day 28 or hospital mortality

* - Indicate study identified and included from outside a systematic review

These studies were sourced from the following systematic reviews.

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- Roquilly A, Marret E, Abraham E, Asehnoune K. Pneumonia prevention to decrease mortality in intensive care unit: a systematic review and meta-analysis. *Clin Infect Dis.* 2014;60(1):64-75.
- Melsen WG, Rovers MM, Koeman M, Bonten MJ. Estimating the attributable mortality of ventilator-associated pneumonia from randomized prevention studies. *Crit Care Med* 2011;39(12):2736-42.
- Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, Hanisch EW, Klarin B, Koeman M, Krueger WA, Lacherade JC. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect Dis.* 2013;13(8):665-71.
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The studies below within these systematic review met the following exclusion criteria;

Cardiac or cardio-thoracic population or < 50% receiving MV

- Apte NM, Karnad DR, Medhekar TP, Tilve GH, Morye S, Bhave GG. Gastric colonization and pneumonia in intubated critically ill patients receiving stress ulcer prophylaxis: a randomized, controlled trial. Crit Care Med. 1992; 20:590–3.
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Pancreatitis

- Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJ, Rosman C, Ploeg RJ, Brink MA, Schaapherder AF, Dejong CH, Wahab PJ, van Laarhoven CJ, van der Harst E, van Eijck CH, Cuesta MA, Akkermans LM, Gooszen HG, Dutch Acute Pancreatitis Study Group: Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 371:651-659

ARDS

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Table S3: Mortality data: Topical anti-septic methods of VAP prevention [a]

author	Year	Ref	Notes	Age [a]	Patients (n)	Vap (n)	Vap (%)	Mortality (n)	Mortality (%)
control groups									
Bellissimo-Rodrigues	2009	125	<90	54	96	17	17.7	33	34.4
Berry	2011	126		59	78	1	1	17	22
Cabov	2010	127	<90	52	30	6	20.0	3	10
Caruso	2009	128		63	132	31	23.5	65	49.2
Chua	2004	129		55	20	8	40	10	50.0 (L)
Fourrier'00	2000	130		50	30	15	50.0	7	23.3
Fourrier'05	2005	131		61	114	12	10.5	24	21.1
Klarin	2008	132		70	23	1	4.3	5	21.7
Koeman	2006	133		62	130	23	27.7	38	29.2
Kollef'06	2006	134		58	347	63	18.2	63	18.2
MacNaughton	2004	135		56	88	21	23	33	37.5
Meinberg [*]	2012	136		41	24	11	45.8	9	37.5 (L)
Munro	2009	137		47	51			9	17.6
Özçaka	2012	138		61	34	22	64.7	20	59.5
Panchabhai	2009	139			262	15	5.7	78	29.8
Scannapieco	2009	140		50	49	12	24.5	8	16.3
Seguin	2006	141	T	40	62	25	40.3	16	25.8
Tantipong	2008	142		60	105	10	9.5	37	35.2

Table S3: Mortality data: Topical anti-septic methods of VAP prevention (continued) [a]

Author	Year	Ref	Notes	Age [a]	Patients (n)	Vap (n)	Vap (%)	Mortality (n)	Mortality (%)
intervention groups - other									
Bellissimo-Rodrigues - chlx	2009	125	<90	63	98	16	16.3	35	35.7
Berry	2011	126		60	76	4	5	13	17
Berry	2011	126		58	71	4	6	17	24
Cabov –chlx	2010	127	<90	57	30	1	3.3	1	3
Camus M-chlx	2005	143		65	130	24	18.5	36	27.7
Caruso - saline	2009	128		65	130	14	10.8	67	51.5
Chua- PVI	2004	129		51	22	6	27	12	54.5 (L)
Fourrier'00 –chlx	2000	130		51	30	5	16.7	3	10.0
Fourrier'05 –chlx	2005	131		61	114	13	11.4	31	27.2
Klarin–chlx	2008	132		70	21	3	14.3	4	19.0
Koeman-chlx	2006	133		61	127	13	10.2	49	38.6
Kollef - Iseganan	2006	134		61	362	80	22.1	80	22.1
MacNaughton -chlx	2004	135		58	91	21	21	36	39.5
Meinberg –chlx *	2012	136		40	28	18	64.3	13	46.5 (L)
Munro –chlx	2009	137		47	44			13	29.5
Munro –chlx	2009	137		46	49			10	20.4
Munro –chlx	2009	137		47	48			12	25.0
Özçaka –chlx	2012	138		56	32	12	37.5	19	58.5
Panchabhai –chlx	2009	139			250	14	5.6	70	28.0
Pobo –chlx	2009	144		53	74	15	20.3	16	21.6
Pobo –chlx	2009	144		55	73	18	24.7	23	31.5
Scannapieco –chlx	2009	140		48	47	7	14.9	8	17.0
Scannapieco –chlx	2009	140		45	50	7	14.0	8	16.0
Seguin-PVI	2006	141	T	38	36	3	8.3	6	16.7
Tantipong -chlx	2008	142		57	102	5	4.9	36	35.3
Wittekamp *	2018	145		61	664			2108	31

Table S3 footnotes

Age – Group mean (or median) age (years)

T – Data originating from a study for which the majority of ICU admission were for trauma

<90 – less than 90% of patients received > 48 hours of MV

L – Late mortality being day 28 or hospital mortality

* - Indicate study identified and included from outside a systematic review

Topical anti-septic intervention regimens were chlorhexidene in various concentrations and preperations in all studies except; saline installation before tracheal suction (Caruso et al [S126]); povidone-iodine (Chua et al [S127] & Seguin [S139]) and iseganan (Kollef et al [S132]).

Data for MacNaughton obtained as abstracted as a personal communication within Chan EY, Ruest A, Meade MO, Cook DJ. Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis. *BMJ*. 2007;334(7599):889.

These studies were sourced from the following systematic reviews.

- Chan EY, Ruest A, Meade MO, Cook DJ. Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis. *BMJ*. 2007;334(7599):889.
- Roquilly A, Marret E, Abraham E, Asehnoune K. Pneumonia prevention to decrease mortality in intensive care unit: a systematic review and meta-analysis. *Clin Infect Dis.* 2014;60(1):64-75.
- Melsen WG, Rovers MM, Koeman M, Bonten MJ. Estimating the attributable mortality of ventilator-associated pneumonia from randomized prevention studies. *Crit Care Med* 2011;39(12):2736-42.
- Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, Hanisch EW, Klarin B, Koeman M, Krueger WA, Lacherade JC. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect Dis.* 2013;13(8):665-71.
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- Klompas M, Speck K, Howell MD, Greene LR, Berenholtz SM. Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: systematic review and meta-analysis. *JAMA Intern Med*. 2014;174(5):751-61.

The studies below within these systematic review met the following exclusion criteria;

Cardiac or cardio-thoracic population or < 50% receiving MV

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- Jacomo AD, Carmona F, Matsuno AK, Manso PH, Carlotti AP. Effect of oral hygiene with 0.12% chlorhexidine gluconate on the incidence of nosocomial pneumonia in children undergoing cardiac surgery. *Infect Control Hosp Epidemiol* 2011;32:591-6

Table S4: Mortality data: Topical antibiotic methods of VAP prevention

author	Year	Ref	Notes	Age [a]	Patients (n)	Vap (n)	Vap (%)	Mortality (n)	Mortality (%)
Non-concurrent control (NCC) groups									
Bergmans NC	2001	146		58.7	61	14	23.0	26	42.6
Bonten	1994	147		65	54	7	13	14	26
Brun Buisson	1989	148		57	124	19	14.7	25	19.4
De Jonge	2003	149		59.5	468			107	22.9
de Smet	2009	150	<90	61.4	1990			443	22.3 (L)
Godard	1990	151	<90	51	84	13	15.5	15	17.9
Hartenauer [a]	1991	152, 153	PP	55	101	46	45.5	46	45.5
Konrad	1989	154		52	83	22	26.5	18	21.7
Landelle [*]	2018	155		62	291	67	23	68	23.4
Ledingham	1988	156		52	161	18	11.2	39	24.2
Rouby [*]	1994	157		51	251	100	39.8	31	12.4
Schardey	1989	158		58	55	26	47.3	29	52.7 (L)
Stoutenbeek [a]	1984	159		37	59	35	59.3	5	8.5
Stoutenbeek [a]	1987	160		37	59	35	59.3	5	8.5
Tissot van Patot [*]	1996	161		70	142	89	63	42	40
Winter	1992	162		57.3	84	11	13.1	34	40.5 (L)
Wittekamp [*]	2018	145		62	2251			691	30.7
Concurrent control (CC) groups									
Abele-Horn	1997	163	T	44.7	30	20	66.7	5	16.7
Aerdts	1991	164		48	39	27	69.2	6	15.4 (L)
Bergmans CC	2001	146		58.1	78	24	30.8	27	34.6
Blair	1991	165		46.5	130	37	28.5	22	16.9
Boland [b]	1991	166	T		32	17	53.1	4	12.5
Bonten	1994	147		62	21	0	0	6	28.6
Brun Buisson	1989	148		59.7	50	6	8.8	12	24
Camus	2005	143		67	126	30	23.8	41	32.5
Cerra	1992	167			21	15	71.4	10	47.6
Claridge	2007	168	T	35.6	52	24	46.2	6	11.5
Cockerill	1992	169	<90	65	75	4	5.3	16	21.3
de la Cal	2005	170	T, <90	48.1	54	26	48.1	15	27.8 (L)
Ferrer	1994	171	PP	59	41	10	24.4	11	26.8
Finch	1991	172			25	7	28	10	40
Gastinne	1992	173		53.9	225	34	15.1	67	29.8
Gaussorgues	1991	174			59			29	49.2
Georges	1994	175	T	31	33	15	45.5	5	15.2
Greenfield	1973	176			25	4	16.0	6	24.0

Table S4: Mortality data: Topical antibiotic methods of VAP prevention

author	Year	Ref	Notes	Age [a]	Patients (n)	Vap (n)	Vap (%)	Mortality (n)	Mortality (%)
Concurrent control (CC) (Continued)									
Hammond [c]	1992	177	PP	43.5	160	30	19	31	19
Jacobs	1992	178		54.5	43	4	8.7	23	54.0
Karvouniaris	2015	179		58	84	25	29.8	29	34.5
Kerver	1988	180		56.1	47	40	85.1	15	31.9
Klastersky	1974	181	T	43.5	42	17	40.5	16	38.1
Koeman	2006	133		62.1	130	23	17.7	38	29.2
Korinek [d]	1993	182		46.6	95			17	17.9
Krueger	2002	183		53.7	262	29	11.1	75	28.6
Laggner	1994	184	PP	53.7	34	4	11.8	14	41.2
Lingnau	1997	185	PP, T	38.9	148	61	41.2	16	10.8
Lode	1992	186			77			25	32.5 (L)
Luiten	1995	187	T	55	55			18	32.7 (L)
Palomar	1997	188	T	45	42	21	50.0	13	31.0
Palomar Ctx	1997	188	PP	47	46	14	30.4	10	21.7
Pneumatikos	2002	189	T	36.9	30	16	53.3	7	23.3
Pugin [e]	1991	190	T	46	41	21	77.8	11	26.8 (L)
Quinio	1995	191	T	33	72	37	51.4	10	13.9
Rios	2005	192			49	17	34.6	21	42.8
Rocha	1992	193	T	44.1	54	25	46.3	24	44.4
Rodriguez_Roldan	1990	194		49	15	11	73.3	5	33.3
Sanchez-Garcia [f]	1998	195		55.1	140	57	40.7	65	47.1
Stoutenbeek ’96 [b]	1996	196	T		42	8	19.0	8	19.0
Stoutenbeek '07	2007	197	T	40.6	200	46	23.0	44	22.0
Ulrich	1989	198	<90	60	52	26	50.0	28	53.8
Unertl	1987	199		46	20	9	45.0	6	30.0
Verwaest	1997	200		56.1	185	40	21.6	31	16.8
Wiener	1995	201		59	31	8	25.8	15	48.4
Winter	1992	162		59.9	92	17	18.5	40	43.5 (L)
Wood	2002	202	T	41	20	13	65.0	6	30.0

Table S4: Mortality data: Topical antibiotic methods of VAP prevention

author	Year	Ref	Notes	Age [a]	Patients (n)	Vap (n)	Vap (%)	Mortality (n)	Mortality (%)
Intervention groups topical antibiotic alone (= SOD)									
Bergmans PGV	2001	146		56.6	87	9	10.3	25	28.7
Bonten PTA	1994	147		67	22	0	0	7	31.8
Brun Buisson PNeoNal	1989	148		58	36	3	4.6	8	22
Camus PT	2005	143		70	130	15	11.5	39	30.0
Camus PT&MCh	2005	143		68	129	10	7.8	28	21.7
Cerra NorNys	1992	167			25	12	48.0	13	52.0
Claridge Cz(Ae)	2007	168	T	37.3	53	21	39.6	7	13.2
de Smet SOD	2009	150		61.4	1904			416	21.8 (L)
Garbino PNV	2002	203		56	101	11	10.9	41	40.6
Garbino PNVFl	2002	203		53	103	9	5.8	40	38.8
Gastinne PTA	1992	173		55.7	220	26	11.8	75	34.1
Gaussorgues PGA	1991	174			59			29	49.2
Godard P	1990	151	<90	47	97	2	2.1	12	12.4
Greenfield G	1973	176			33	2	6.1	4	12.1
Karvouniaris P	2015	179		60	84	14	16.7	25	29.8
Klastersky G	1974	181	T	51.2	43	5	11.6	23	53.5
Koeman ChC	2006	133		62.4	128	16	12.5	46	35.9
Korinek PTAV [d]	1993	182	T	44.4	96			22	22.9
Landelle PTNy [*]	2018	155		64	413	45	10.9	43	10.4
Landelle PTNy [*]	2018	155		61	356	13	3.7	73	20.5
Lode G	1992	169			85			23	27.1 (L)
Nardi PTA	2001	204	T	53.7	119	9	7.6	25	21.0
Nardi PTAM	2001	204	T	51.9	104	20	19.2	26	25.0
Oostdijk SOD	2014	205	<90	63	5957			1530	25.7 (L)
Pneumatikos PTA	2002	189	T	39.1	31	5	16.1	5	16.1
Pugin PNeoVan [e]	1991	190	T	38	25	4	16.0	10	26.3 (L)
Quinio PGA	1995	191	T	35.5	76	19	25.0	13	17.1
Rios PG	2005	192			47	17	36.2	18	38.3
Rodriguez_Roldan PTA	1990	193		54	13			4	30.8
Rouby P [*]	1994	157		53	347	97	28	42	12.1
Schardey PTNeBA	1989	160		53	41	4	9.8	10	24.4 (L)
Stoutenbeek PTA	1987	158		40	42	23	54.8	3	7.1
Unertl PGA	1987	199		53	19	1	5.3	5	26.3
Wiener PGNy	1995	201		60	30	8	26.7	11	36.7
Wittekamp PTNy [*]	2018	145		61.6	2224			685	30.8
Wittekamp PTNy [*]	2018	145		62.8	2082			645	31.0
Wood Cz(ae)	2002	202	T	38	20	6	30.0	3	15.0

Table S4: Mortality data: Topical antibiotic methods of VAP prevention

author	Year	Ref	Notes	Age [a]	Patients (n)	Vap (n)	Vap (%)	Mortality (n)	Mortality (%)
Intervention groups topical antibiotic + PPAP (= SDD)									
Abele-Horn PTA-Ctx	1997	163	T	39.9	58	13	22.4	11	19.0
Aerdts PNoA-Ctx	1991	164		45	17	1	5.9	2	11.8
Blair PTA-Ctx	1991	165		49.3	126	11	8.7	17	13.5
Boland PTNy-Ctx [b]	1991	166	T		32	14	43.8	2	6.3
Cockerill PGNy-Ctx	1992	167	<90	65.5	75	3	4.0	11	14.7
De Jonge PTA-Ctx	2003	147		60.4	466			69	14.8
de la Cal PTA-Ctx	2005	170	T, <90	41.5	53	18	34.0	5	9.4 (L)
de Smet SDD	2009	150		62.4	2045			440	21.5 (L)
Ferrer PTA-Ctx	1994	171		62	39	7	17.9	12	30.8
Finch PGA-Ctx	1991	173			24	4	16.1	15	61
Georges PNA-AmClav	1994	175		34	31	3	9.7	3	9.7
Hammond PTA-Ctx [g]	1992	177		43.5	162	25	15	34	21
Hartenauer PTA-Ctx [a]	1991	152, 153		53	99	10	10.1	34	34.3
Jacobs PTA-Ctx	1992	178		36	45	0	0	14	39
Kerver PTA-Ctx	1988	179		55.2	49	6	12.2	14	28.6
Konrad PTA-Ctx	1989	154		52	82	5	6.1	25	30.5
Krueger PG-Cip	2002	183		52.7	265	6	2.3	52	19.6
Laggner GA-AmClav	1994	184		52.7	33	1	3.0	9	27.3
Ledingham PTA-Ctx	1988	156		51	163	3	1.8	39	23.9
Lingnau_PCiproA-Cipro	1997	185	T	38.4	82	26	31.7	10	12.2
Lingnau_PTA-cipro	1997	185	T	35.6	80	31	38.8	9	11.3
Luiten PNoA-Ctx	1995	187	T	56	54			11	20.4 (L)
Oostdijk SDD	2014	205	<90	63.2	6040			1439	23.8 (L)
Palomar PTA-Ctx	1997	188		45	41	7	17.1	10	24.4
Rocha PTA-Ctx	1992	193	T	42.8	47	7	14.9	10	21.3
Sanchez-Garcia PGA-Ctx [f]	1998	195		55	131	38	29.0	51	38.9
Silvestri'04 PTA-Ctx	2004	206		69.5	42	19	45.2	15	35.7
Silvestri'04 PTAV-Ctx	2004	206		72	42	22	52.4	12	28.6
Stoutenbeek ’84 PTA-Ctx	1984	160		35	63	5	7.9	0	0
Stoutenbeek ‘96 PTA-Ctx [b]	1996	196	T		49	2	4.1	2	4.1
Stoutenbeek '07 PTA-Ctx	2007	197	T	38.1	201	19	9.5	42	20.9
Ulrich PNoA-Tri	1989	198	<90	64.3	48	7	14.6	15	31.3
Tissot van Patot PTA-Cfu [*]	1996	161		70	138	28	20.3	55	39.9
Verwaest OA-O	1997	200		56.5	193	22	11.4	34	17.6
Verwaest PTA-Ctx	1997	200		55.6	200	31	15.5	31	15.5
Winter PTA-Cz	1992	162		58.4	91	3	3.3	33	36.1 (L)

Table S4 Footnotes

Age – Group mean (or median) age (years)

PP- Control group received protocolized parenteral antibiotic prophylaxis (all SDD intervention groups received protocolized parenteral antibiotic prophylaxis)

T – Data originating from a study for which the majority of ICU admission were for trauma

<90 – less than 90% of patients received > 24 hours of MV

L – Late mortality being day 28 or hospital mortality

* - Indicate study identified and included from outside a systematic review

Notes;

a. There appears to be duplication among six groups of four studies and the duplicates are handled in the singular within the analysis; Hartenauer 1990, 1991, and Stoutenbeek 1984, 1987.

b. For Boland 1991 and Stoutenbeek 1996, the mortality listed here includes 23 and 32 early exclusions respectively including early deaths as clarified as personal communications recorded in Liberati A, D'Amico R, Pifferi, et al. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev. 2009; 4: CD000022.

c. For Hammond 1992, the mortality listed here includes 83 early exclusions with 28 deaths (34%) as detailed in the original publication and clarified as personal communications recorded in Liberati A, D'Amico R, Pifferi, et al. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev. 2009; 4: CD000022.

d. For Korinek, the mortality listed here includes 68 early exclusions with 29 deaths (43%) as detailed in the original publication and as recorded in Liberati A, D'Amico R, Pifferi, et al. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev. 2009; 4: CD000022.

e. For Pugin, the mortality listed here includes 27 early exclusions with 7 deaths (26%) as detailed in the original publication and as recorded in Liberati A, D'Amico R, Pifferi, et al. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev. 2009; 4: CD000022.

f. For Sanchez-Garcia, the mortality listed here includes 45 early exclusions with 12 deaths (27%) as detailed in the original publication and as recorded in Liberati A, D'Amico R, Pifferi, et al. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev. 2009; 4: CD000022.

SDD/SOD intervention regimens. For the purpose of this analysis, a SDD/SOD regimen was any regimen of topical antibiotic porphylaxis with (SDD) or without (SOD) additional protocolized parenteral antibiotic prophylaxis. SOD regiemns included the following;

- PGV (P, topical polymyxin; G, topical gentamicin; V, topical vancomycin),
- PNeoNal (P, topical polymyxin; Neo, topical neomyxin; Nal = Nalidixic acid),
- PT (P, topical polymyxin; T, topical tobramycin),
- PTChM (P, topical polymyxin; T, topical tobramycin; Ch, topical chlorhexidene; topical mupirocin),
- NorNys (Nor, Norfloxacin; Nys, Nystatin),
- Cz(Ae) = Aerosolized ceftazidime;
- PTA (P, topical polymyxin; T, topical tobramycin; A, topical amphotericin).
- PGA (P, topical polymyxin; G, topical gentamicin; A, topical amphotericin),
- P (P = polymyxin either aerosolized or topical),
- G = gentamicin,
- ChC (Ch, topical chlorhexidine; C, topical colistin),
- PTAM (P, topical polymyxin; T, topical tobramycin; A, topical amphotericin; topical mupirocin),

- PNeoVan (P, topical polymyxin; Neo, topical neomycin; Van, topical vancomycin),
- PGA (P, topical polymyxin; G, topical gentamicin; A, topical amphotericin),
- PGNy (P, topical polymyxin; G, topical gentamicin; Ny, topical nystatin).

SDD regiemns included the following;

- PTA-Ctx (P, topical polymyxin; T, topical tobramycin; A, topical amphotericin; Ctx, parenteral cephalosporin),
- PNoA-Ctx (P, topical polymyxin; No, topical norfloxacin; A, topical amphotericin; Ctx, parenteral cephalosporin),
- PGNy-Ctx (P, topical polymyxin; G, topical gentamicin; Ny, topical nystatin; Ctx, parenteral cephalsporin),
- PTNy-Ctx (P, topical polymyxin; T, topical tobramycin; Ny, topical nystatin; Ctx, parenteral cephalsporin),
- PNA-AmClav (P, topical polymyxin; N, topical netilmicin; A, topical amphotericin; Ctx, parenteral amoxicillin-clavulinate),
- PG-Cip (P, topical polymyxin; G, topical gentamicin; Cip, parenteral ciprofloxacin),
- GA- AmClav (G, topical gentamicin; A, topical amphotericin),
- PCA-Cip (P, topical polymyxin; C, topical ciprofloxacin; A, topical amphotericin; Cip, parenteral ciprofloxacin),
- PTA-Cip (P, topical polymyxin; T, topical tobramycin; A, topical amphotericin; Cip, parenteral ciprofloxacin),
- PTA-Cef (P, topical polymyxin; T, topical tobramycin; A, topical amphotericin; Ctx, parenteral cefuroxime),
- PGA-Ctx (P, topical polymyxin; G, topical gentamicin; A, topical amphotericin; Ctx, parenteral ceftriaxone),
- PTAV-Ctx (P, topical polymyxin; T, topical tobramycin; A, topical amphotericin; Van, topical vancomycin; Ctx, parenteral cephalosporin),
- PNoA-Tri (P, topical polymyxin; No, topical norfloxacin; A, topical amphotericin; trimethoprim),
- OA-O (O = topical ofloxacin, A = topical amphotericin; O = parenteral ofloxacin),
- PTA-Cz (P, topical polymyxin; T, topical tobramycin; A, topical amphotericin; Ctx, parenteral cephalosporin).

These studies were sourced from the following systematic reviews.

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- Cardiac or cardio-thoracic population or < 50% receiving MV

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- Fox MA, Peterson S, Fabri BM. Selective decontamination of the digestive tract in cardiac surgical patients. *Crit Care Med* 1991;19(12):1486-90**.**
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- Liver transplant population

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Table S5: Intention to treat mortality data: as reported in Liberati et al [a]

author	Year	Ref	Notes	Patients (n)	Mortality (n)	Mortality (%)
control groups						
Aerdts	1991	164		60	12	20 (L)
Brun Buisson	1989	148		68	15	22
Ferrer	1994	171	PP	50	14	28
Palomar	1997	188	T	49	14	28.1
Rocha	1992	193	T	77	40	51.9
Rodriguez_Roldan	1990	194		17	7	41.2
Ulrich	1989	196	<90	57	33	57.9
Verwaest	1997	200		220	40	18.2
Intervention groups						
Aerdts	1991	164		28	4	14.3 (L)
Brun Buisson	1989	148		65	14	22
Ferrer	1994	171	PP	51	15	29.8
Palomar	1997	188	T	50	14	28
Rocha	1992	193	T	74	27	36.5
Rodriguez_Roldan	1990	194		14	5	35.7
Ulrich	1989	196	<90	55	22	40
Verwaest OA-O	1997	200		220	47	21.4

a. The data here is intention to treat data with outcomes for all patients as randomly assigned to receive or not treatment with topical antibiotics obtained as personal communications from the original authors and reported in Liberati [S218]

Table S6: VAP prevention effect size from meta-analysis

	Effect sizes [a]; 95% CI (n)	Notes
Non-decontamination studies		
	0.69; 0.63 – 0.76 (71)	Figure S2
Topical anti-septic studies		
	0.76; 0.64 – 0.9 (19)	Figure S3
Topical antibiotic studies		
• Topical antibiotic alone (= SOD)	0.43; 0.37 – 0.51 (28)	Figure S4
• Topical antibiotic + PPAP (= SDD)	0.33; 0.28 – 0.38 (31)	Figure S4
• All Topical antibiotic studies (= SDD/SOD)	0.37; 0.34 – 0.41 (59)	Figure S4

Footnotes to Table S6

a. all effect sizes are odds ratios

Table S7: Mortality prevention effect size from meta-analysis versus published effect sizes

Effect sizes; 95% CI (n)	[ref] Notes
Non-decontamination studies	
0.97; 0.90 – 1.04 (86)	[this study; Figure S6]
RR: 0.98; 0.90 – 1.07 (35)	Roquilly [S210]; (‘circuit prophylactic methods’; 4.2.2 – 4.2.22) [b]
RR: 1.00; 0.89 – 1.13 (16)	Roquilly [S210]; (‘ulcer prophylaxis’; 4.1.27)’
Anti-septic studies	
1.04; 0.95 – 1.15 (24)	[this study; Figure S7]
1.25; 1.05 – 1.50 (11)	Price [S220]; ‘Chlorhexidine v control; Table 7
0.96; 0.69 – 1.33 (11)	Chan [S214]; ‘Antiseptics’; Figure 3 [c]
RR: 1.13; 0.99 – 1.29 (9)	Klompas [S216]; ‘non-cardiac surgery studies’; Figure 3

Table S7: Mortality prevention effect size from meta-analysis versus published effect sizes (continued)

Topical antibiotic studies		
• Topical antibiotic alone (= SOD)	0.95; 0.89 – 1.01 (36)	[this study; Figure S8]
	0.97; 0.79 – 1.20 (13)	Liberati [S218] ('2.1.2 topical versus no prophylaxis)
	0.94; 0.71 – 1.24 (14)	Silvestri [S217] ('Enteral only')
	Adj OR [d]: 0.85; 0.73 – 1.0 (3)	Plantinga [S215] Table 3; SOD studies
	RR: 0.95; 0.66 – 1.38 (5)	Roquilly [S210] – 'Aerosolized antibiotics (4.2.2)'
	0.89; 0.64 – 1.25 (6)	Póvoa [S219]
	0.85; 0.74 – 0.97 (4)	Price [S220] (SDD studies)
• Topical antibiotic + PPAP (= SDD)	0.85; 0.78 – 0.93 (33)	[this study; Figure S8]
	0.75; 0.65 – 0.87 (17)	Liberati [S218] – ('1.1 topical plus systemic versus no prophylaxis)
	RRR: 0.18; 0.04 – 0.87 (17)	Van Nieuwenhoven [S221] (quality score >5)
	0.74; 0.61 – 0.91 (17)	Silvestri [S217] ('Parenteral plus enteral')
	Adj OR [d]: 0.74; 0.65 – 0.84 (5)	Plantinga [S215] Table 3; SDD studies
	0.73; 0.64 – 0.84 (15)	Price [S220] (SDD studies)
• All Topical antibiotic studies (= SDD/SOD)	0.91; 0.87 –0.96 (69)	[this study; Figure S8]
	RRR: 0.12; 0.03 – 0.21 (21)	Van Nieuwenhoven [S221]
	0.80; 0.69 – 0.94 (31)	Silvestri [S217] (All)
	RR: 0.84; 0.76 – 0.92 (30)	Roquilly [S210]– 'digestive decontamination (4.1.2)'

Footnotes to Table S7

a. The summary effect sizes listed in the cited systematic reviews have been extracted to correspond to categories for which the majority of studies align with the classification here

b. The summary effect size in Roquilly [S210] includes two studies of a cardiac surgery population and six interventions which included various topical antibiotics (i.e. SOD)

c. The summary effect size in Chan [S214] includes two studies of a cardiac surgery population

d. Adj OR = odds ratio adjusted for admission type; RR = risk ratio; RRR = relative risk reduction; all other effect sizes are odds ratios

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Fig S1. (p 44) **Search method, screening criteria and resulting classification of eligible studies and subsequent decant of component groups.** The four numbered arrows are as follows;

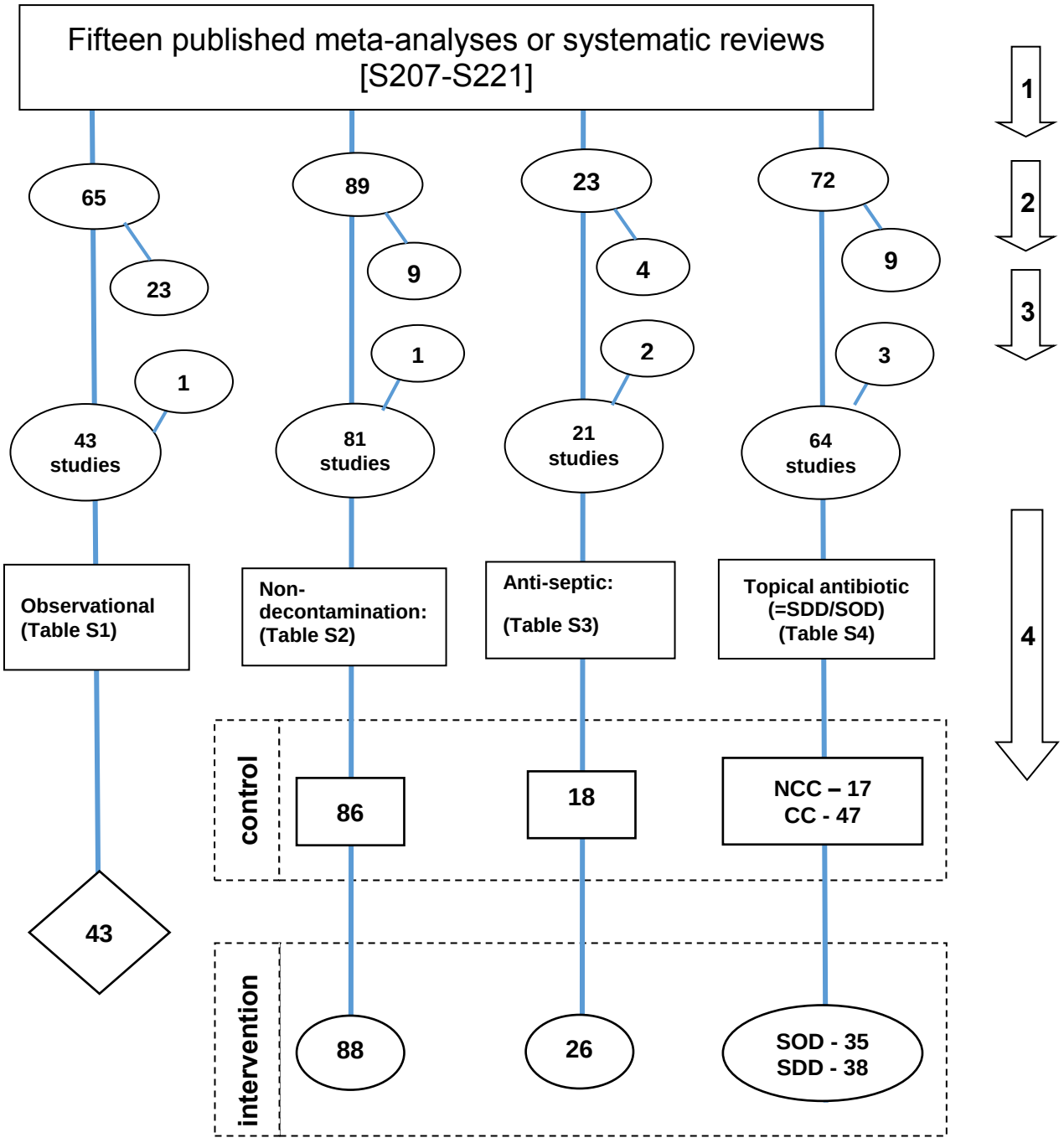
(1) An electronic search for systematic reviews containing potentially eligible studies using search terms; "ventilator associated pneumonia", "mechanical ventilation", "intensive care unit", each combined with either "meta-analysis" or "systematic review" up to December 2018;

(2) The systematic reviews were then searched for studies of patient populations requiring prolonged (> 24 hours) ICU admission in one of four categories; studies in which there was no intervention (observational studies), studies of various non-decontamination methods such as methods delivered either via the gastric route, the airway route or via the oral care route, studies of anti-septic methods and studies with a topical antibiotic (in any formulation) based intervention.

(3) All studies were reviewed for potentially eligible studies and screened against inclusion and exclusion criteria. Any duplicate or ineligible studies were removed and seven studies identified outside of systematic reviews [S31, S101, S136, S145, S155, S157, S161] were included;

(4) The component groups were decanted from each study being control (rectangles), intervention (ovals) and observation (diamond) groups. SOD refers to studies using only topical antibiotics; SDD refers to studies using topical antibiotics and protocolized parenteral antibiotic prophylaxis (PPAP). NCC = non-concurrent control; CC = concurrent control.

Note; the total numbers do not tally as some systematic reviews provided studies in more than one category and some studies provided groups in more than one category.


Fifteen published meta-analyses or systematic reviews [S207-S221]
1
2
3
4
65
23
1
43 studies
89
9
1
81 studies
23
4
2
21 studies
72
9
3
64 studies
Observational (Table S1)
Non-decontamination: (Table S2)
Anti-septic: (Table S3)
Topical antibiotic (=SDD/SOD) (Table S4)
control
86
18
NCC – 17
CC - 47
43
intervention
88
26
SOD - 35
SDD - 38

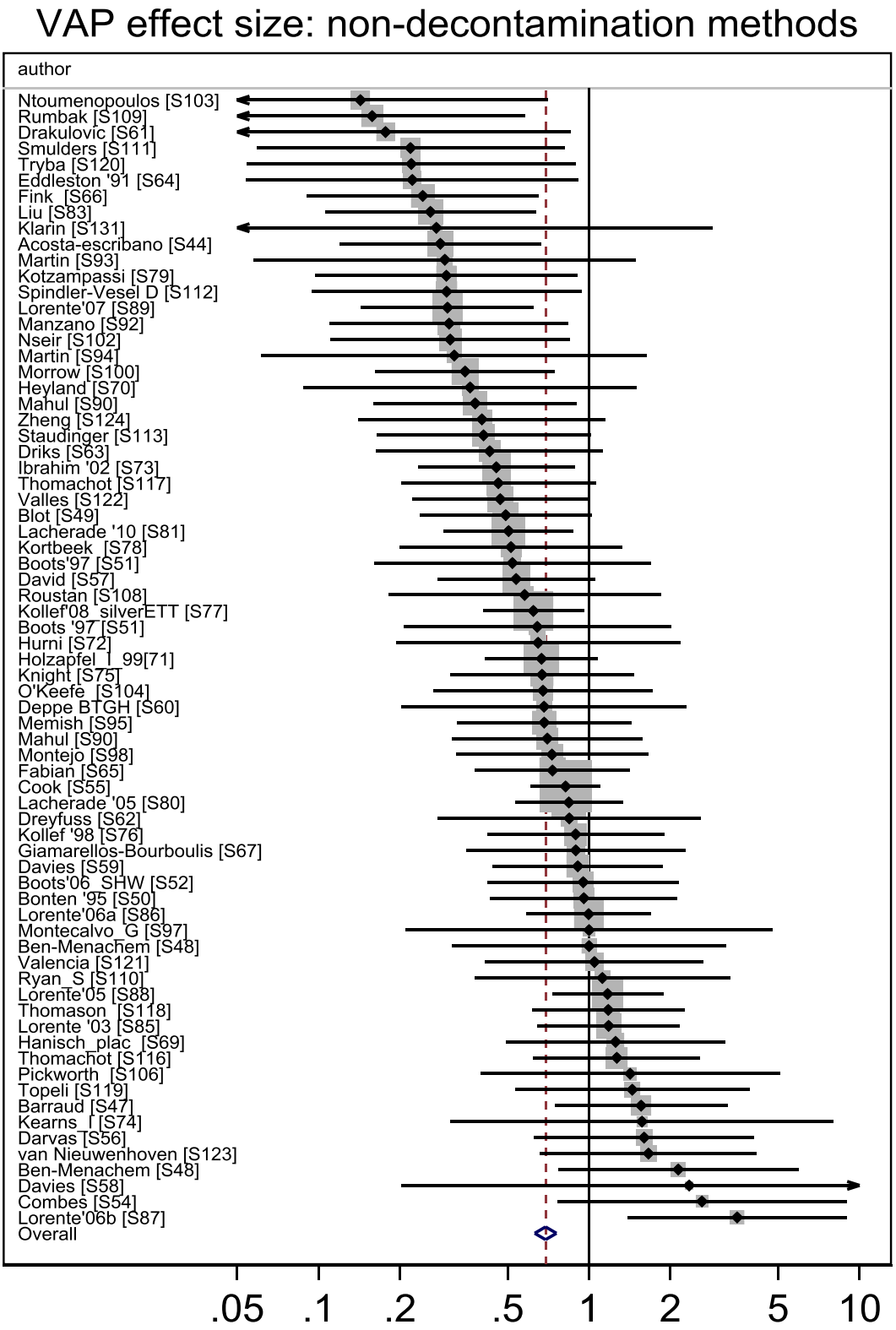


Fig S2

Caterpillar plots of the group specific (small squares) and summary (large open diamond, broken vertical line) VAP prevention effect size and 95 % CI among studies of non-decontamination methods of VAP prevention. Studies are listed in Table S2.

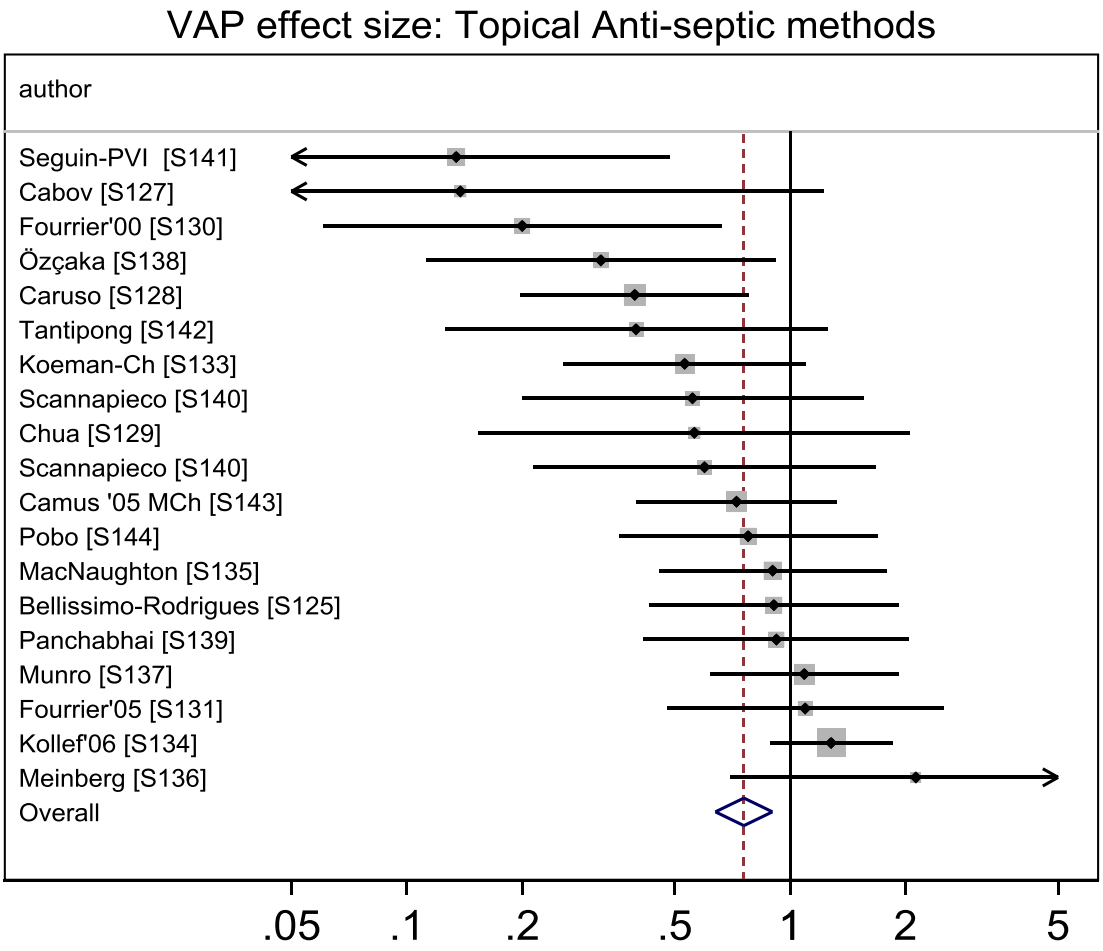


Fig S3

Caterpillar plots of the group specific (small squares) and summary (large open diamonds, broken vertical line) VAP prevention effect size and 95 % CI among studies of Topical anti-septic methods of VAP prevention. CHLX is chlorhexidine and PVI is povidone-iodine. Studies are listed in Table S3.

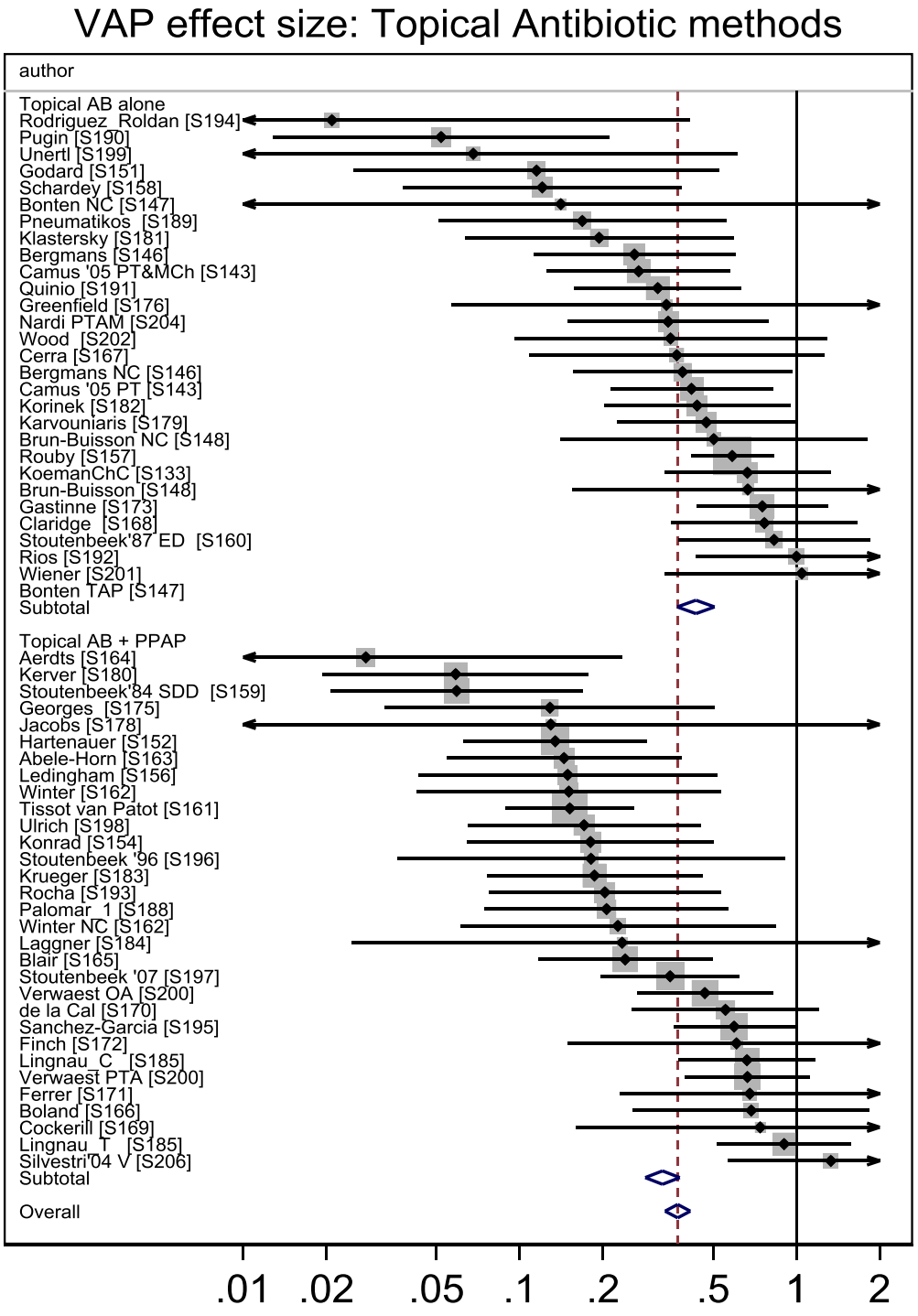


Fig S4

Caterpillar plots of the group specific (small squares), and summary (central broken line and open diamonds) VAP prevention effect size and 95 % CI among studies of Topical antibiotic methods of VAP prevention. Studies are listed in Table S4.

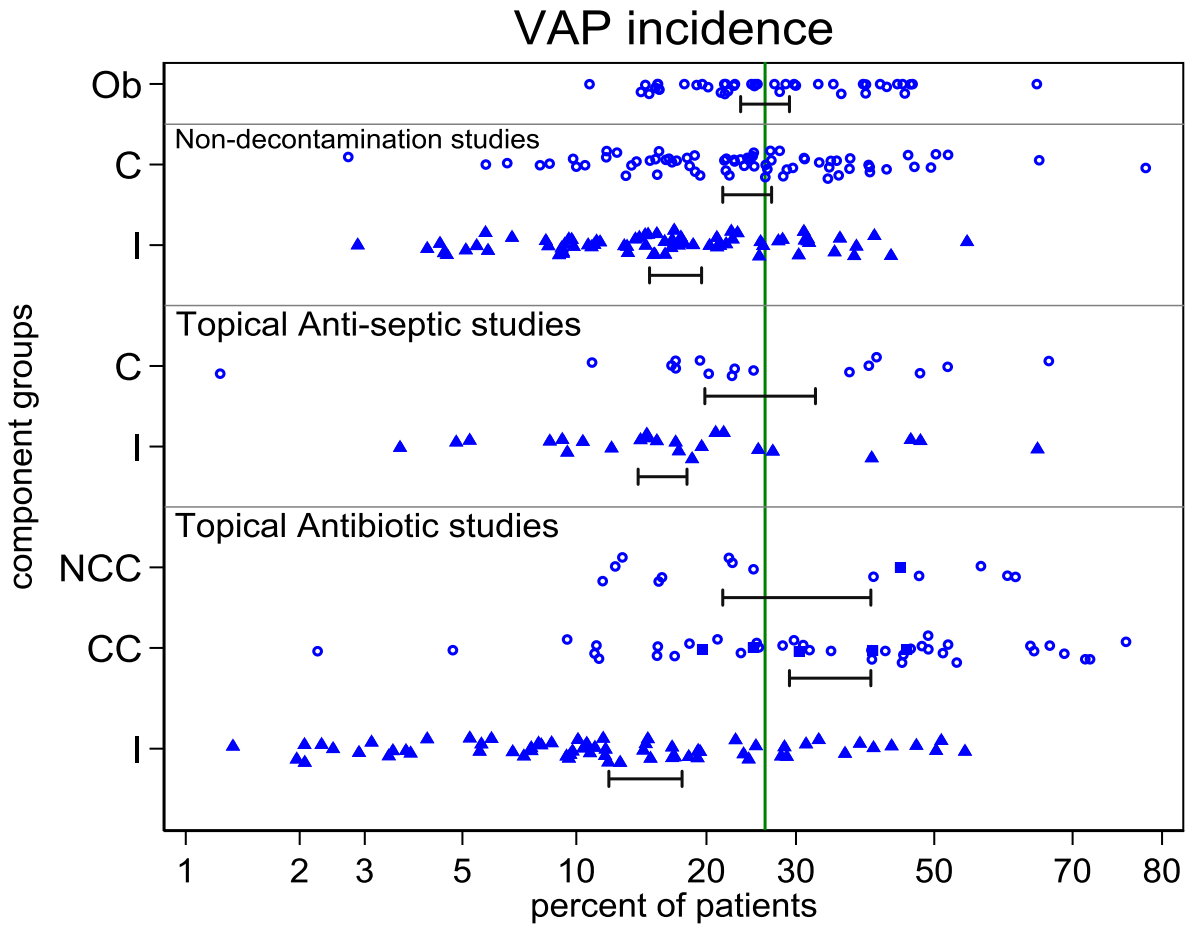


Fig S5

The VAP incidences for the component (C = control; I = intervention; NCC = non-concurrent control: CC = concurrent control) groups of studies of either non- decontamination, topical anti-septic, or topical antibiotic based methods versus the benchmark being the summary mean (central unbroken vertical line) derived from the observation studies (Ob = observational) together with the 95% confidence limits (horizontal error bars) associated with the summary incidence. Shown are incidences from all intervention groups (solid triangles), control groups and observational group incidences (open circles) and control groups that received PPAP (solid squares).

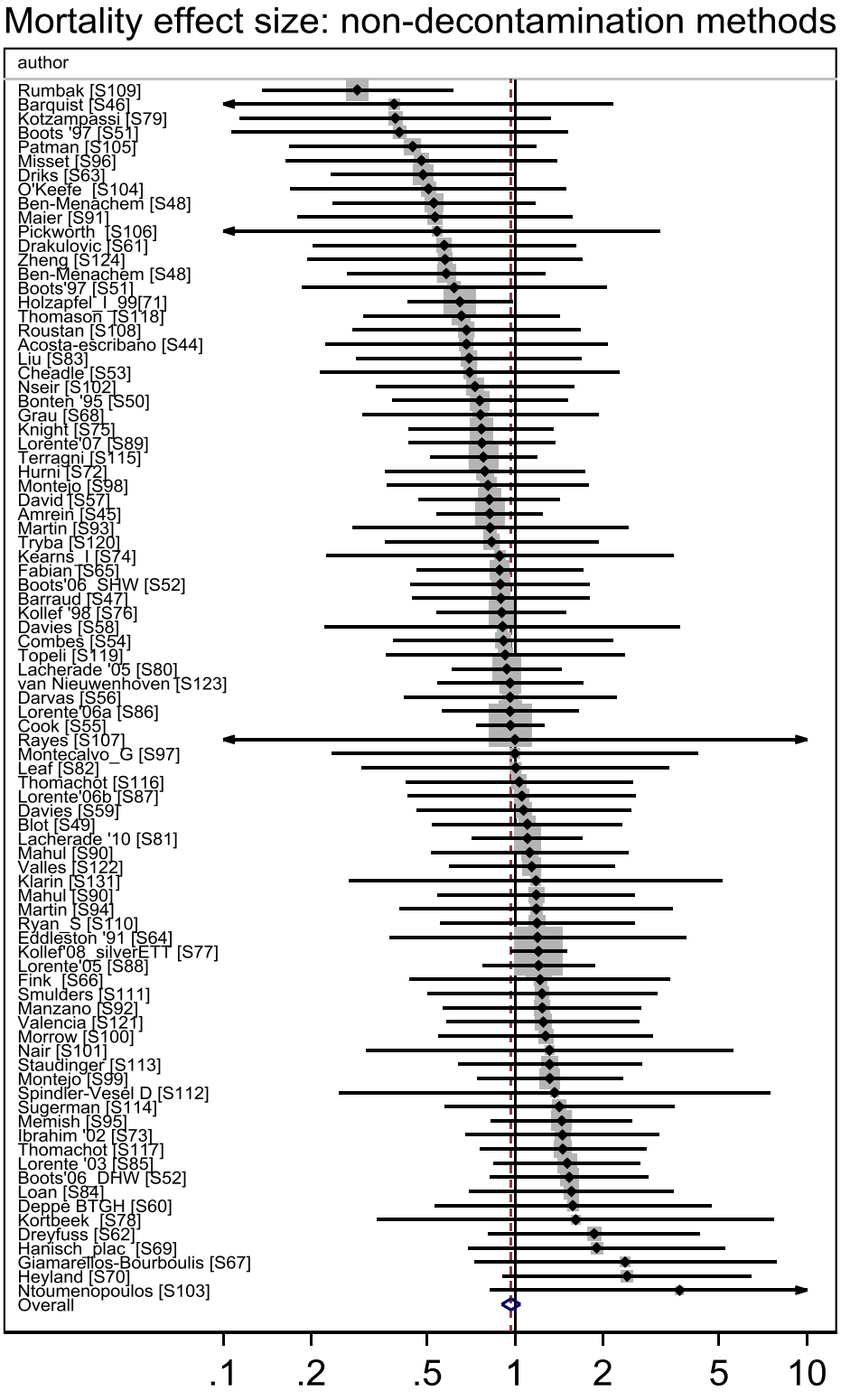


Fig S6

Caterpillar plots of the group specific (small squares) and summary (large open diamond, broken vertical line) effect size on the mortality incidence and 95 % CI among studies of non-decontamination methods of VAP prevention. Studies are listed in Table S2.

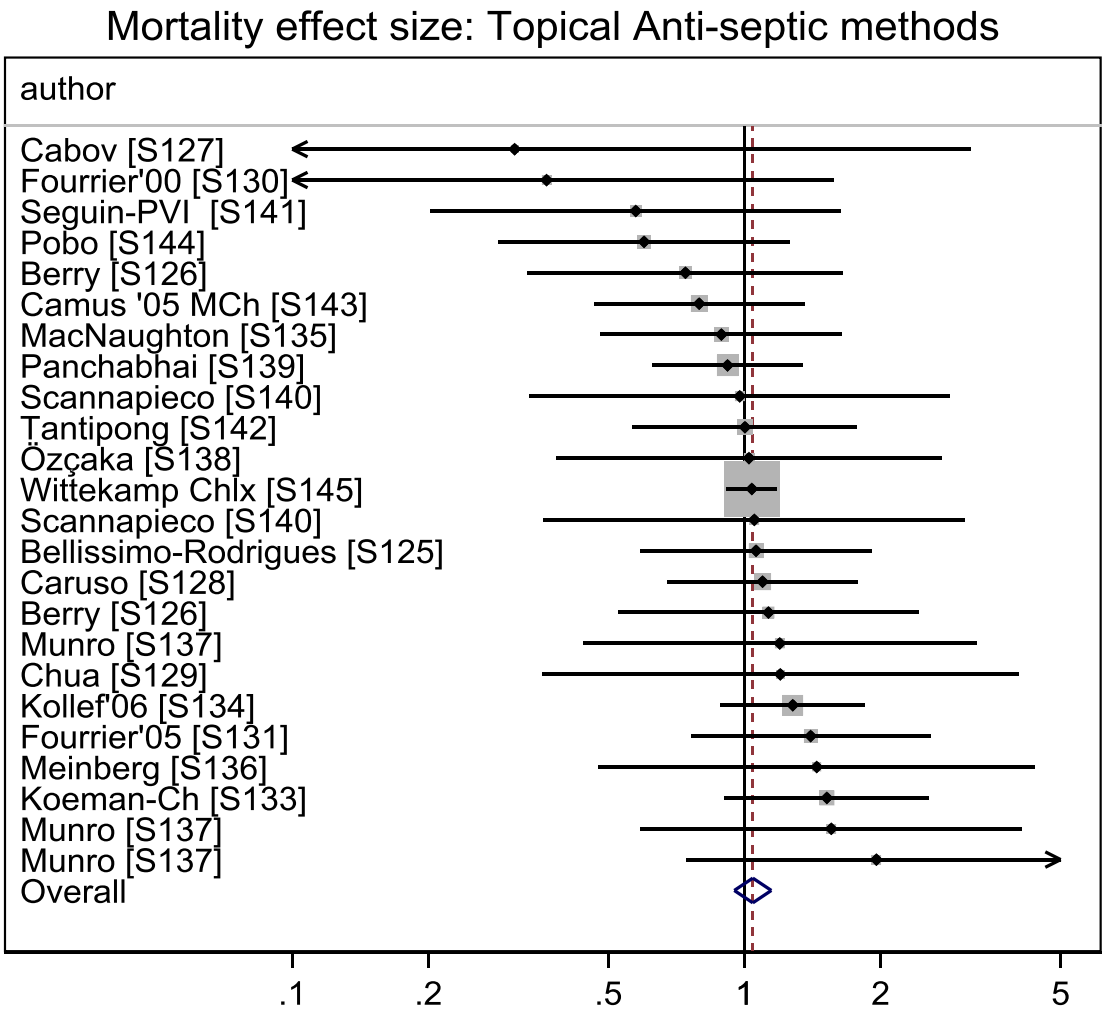


Fig S7

Caterpillar plots of the group specific (small squares) and summary (large open diamonds, broken vertical line) effect size on the mortality incidence and 95 % CI among studies of Topical anti-septic methods of VAP prevention. CHLX is chlorhexidine. Studies are listed in Table S3.

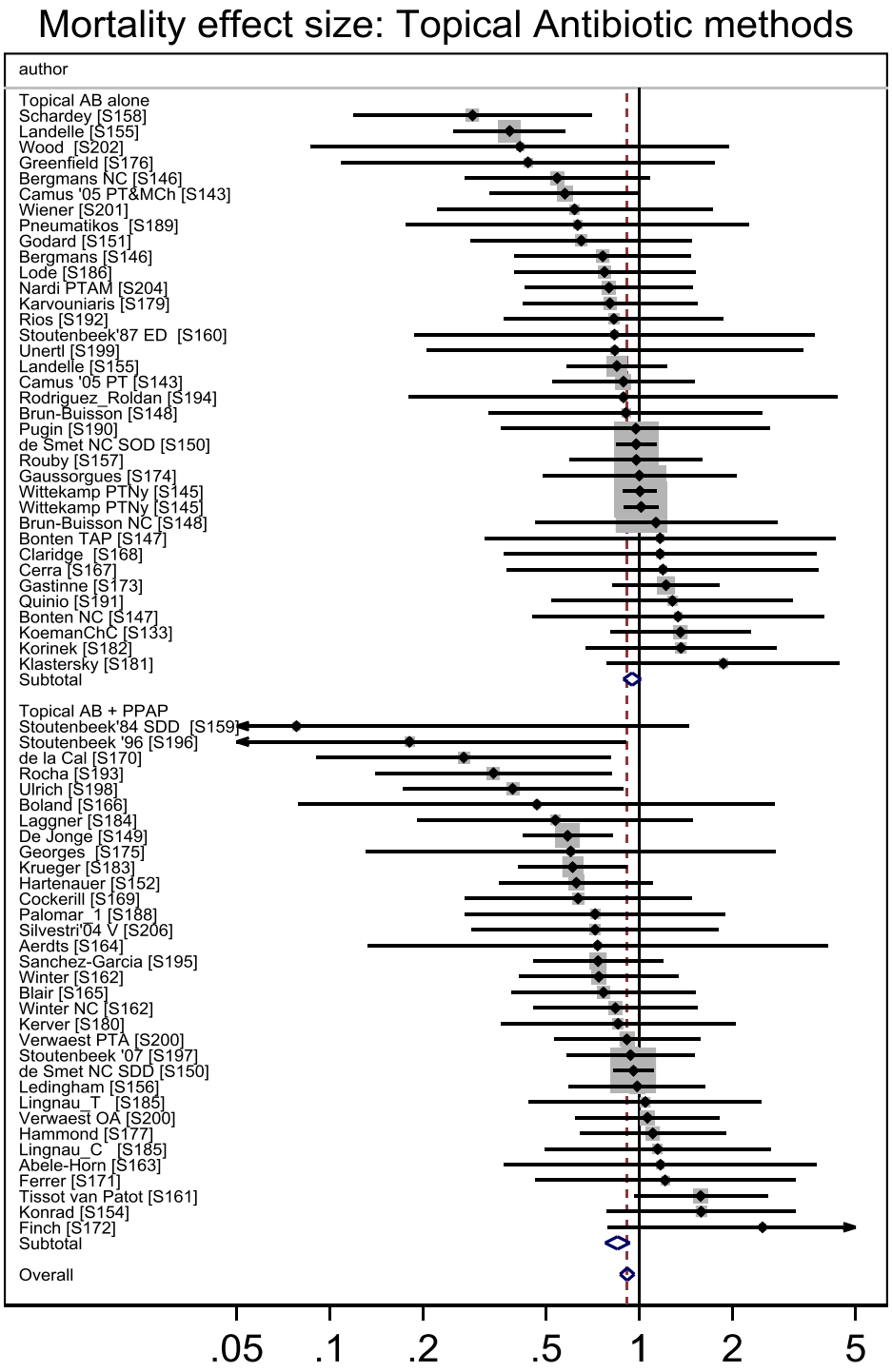


Fig S8

Caterpillar plots of the study specific (small squares) and summary (central broken line and open diamonds) effect size on the mortality incidence and 95 % CI among studies of Topical antibiotic methods of VAP prevention with (top) and without (bottom) PPAP. Studies are listed in Table S4.

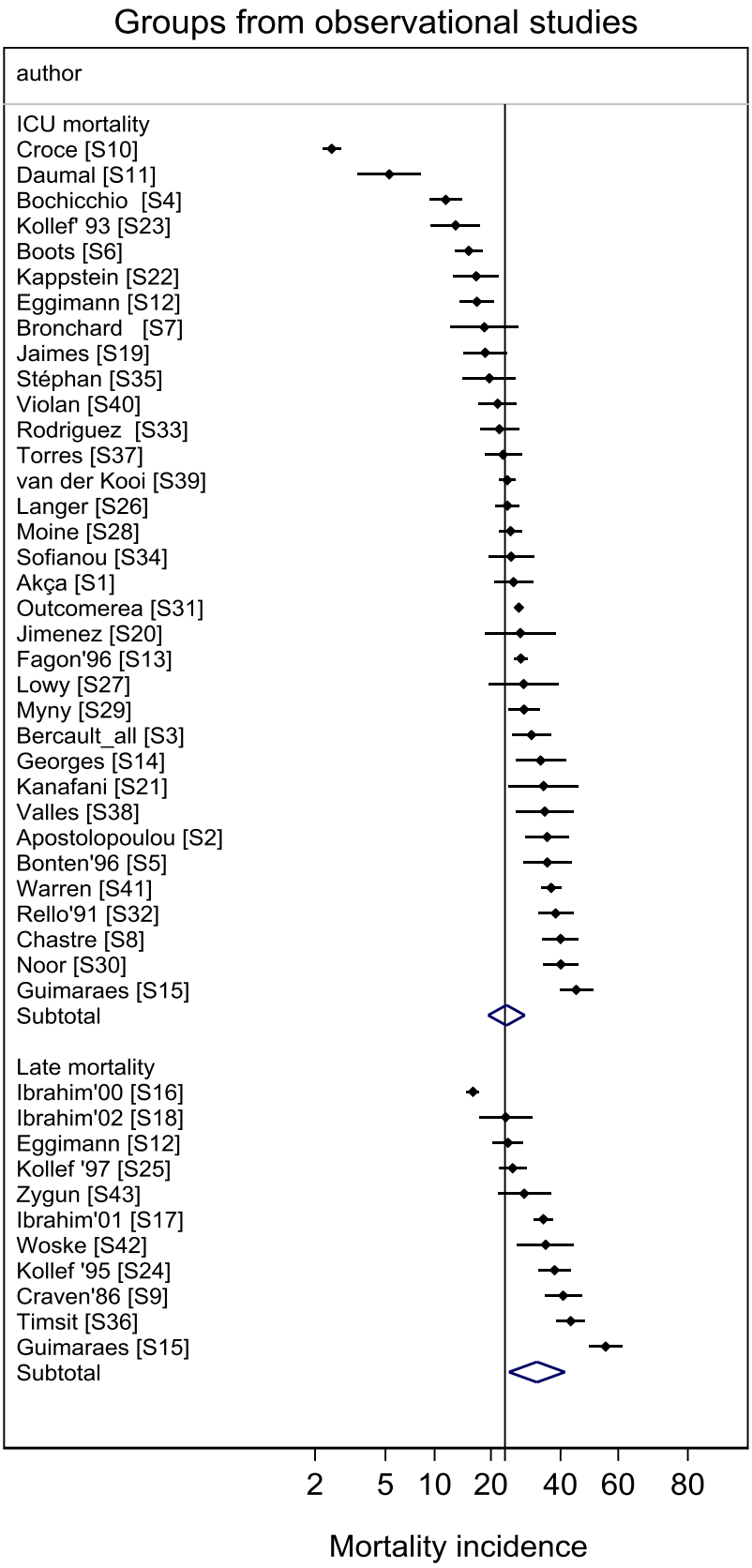


Fig S9

ICU (top) and hospital and late (bottom) mortality incidence among groups from observational studies. Caterpillar plots of the group specific (small diamonds) and summary (central broken line and large open diamond) mortality incidence and 95% CI. Groups are listed in Table S1. Note that the x axis is a logit scale. The central line is derived from groups reporting ICU mortality incidence and is the ICU mortality benchmark.

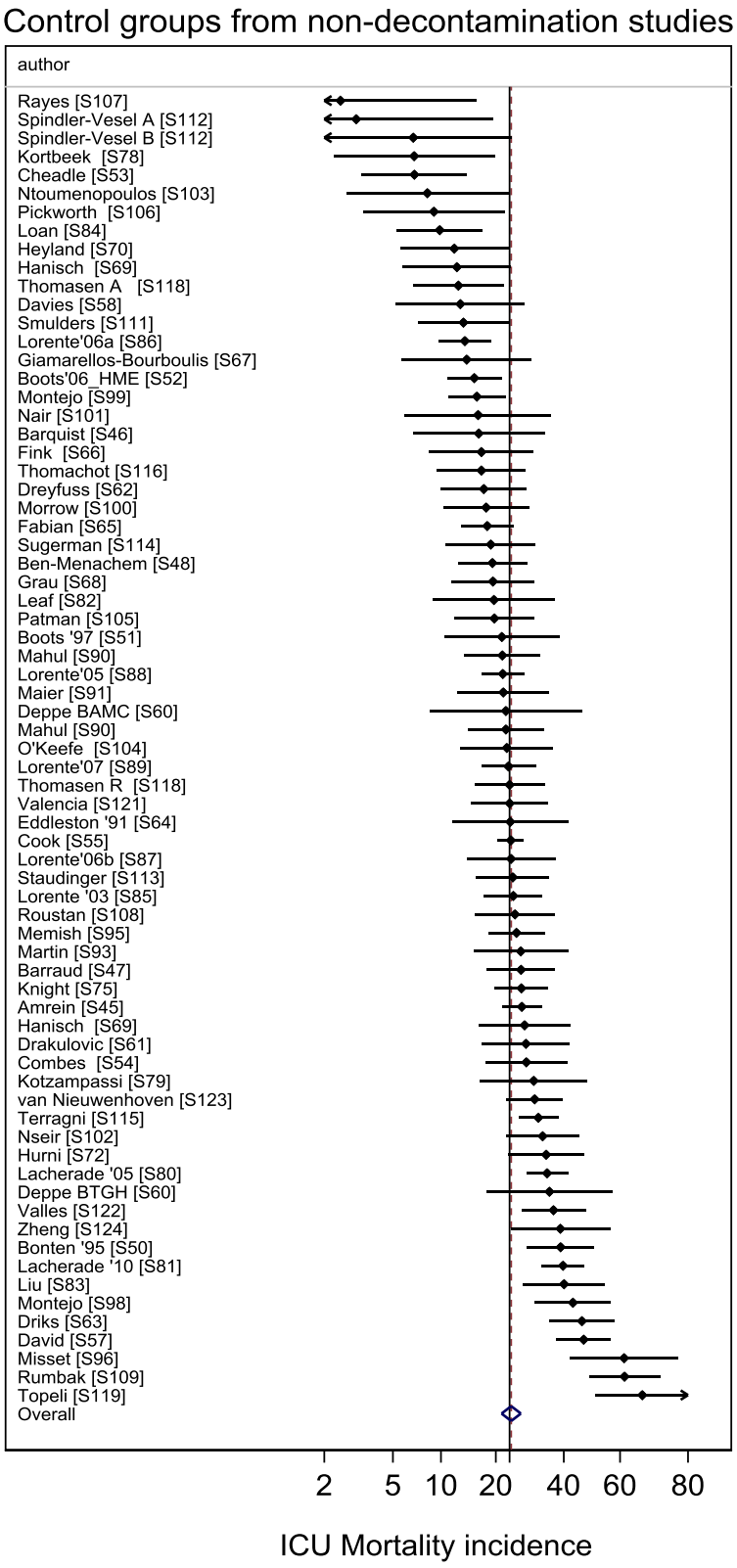


Fig S10

ICU mortality incidence among control groups from studies of non-decontamination methods. Caterpillar plots of the group specific (small diamonds) and summary (central broken line and large open diamond) mortality incidence and 95% CI. Groups are listed in Table S2. Note that the x axis is a logit scale. The central solid line is the ICU mortality incidence benchmark from Figure S9.

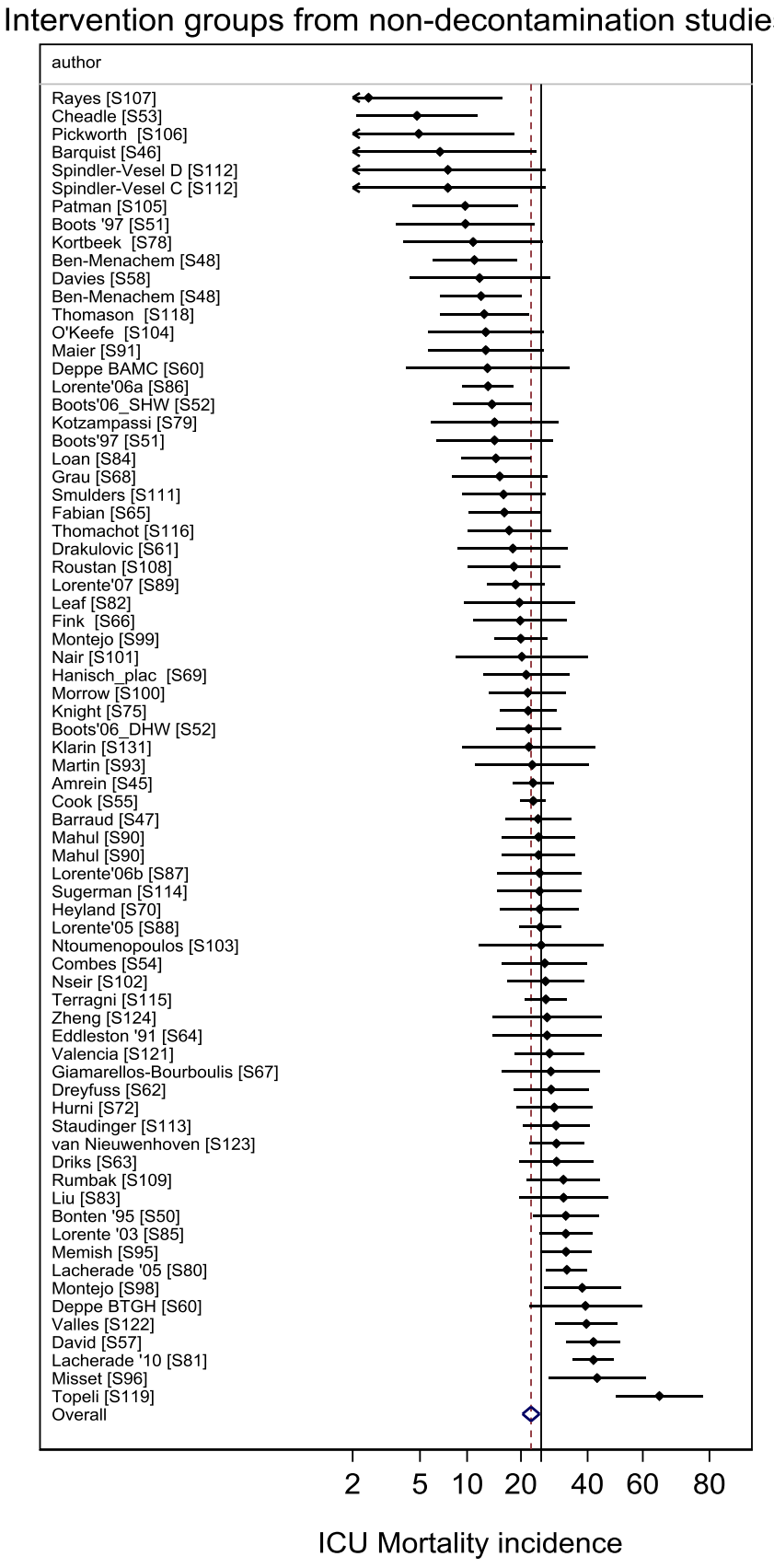


Fig S11

ICU mortality incidence among intervention groups from studies of non-decontamination methods. Caterpillar plots of the group specific (small diamonds) and summary (central broken line and large open diamond) mortality incidence and 95% CI. Groups are listed in Table S2. Note that the x axis is a logit scale. The central solid line is the ICU mortality incidence benchmark from Figure S9.

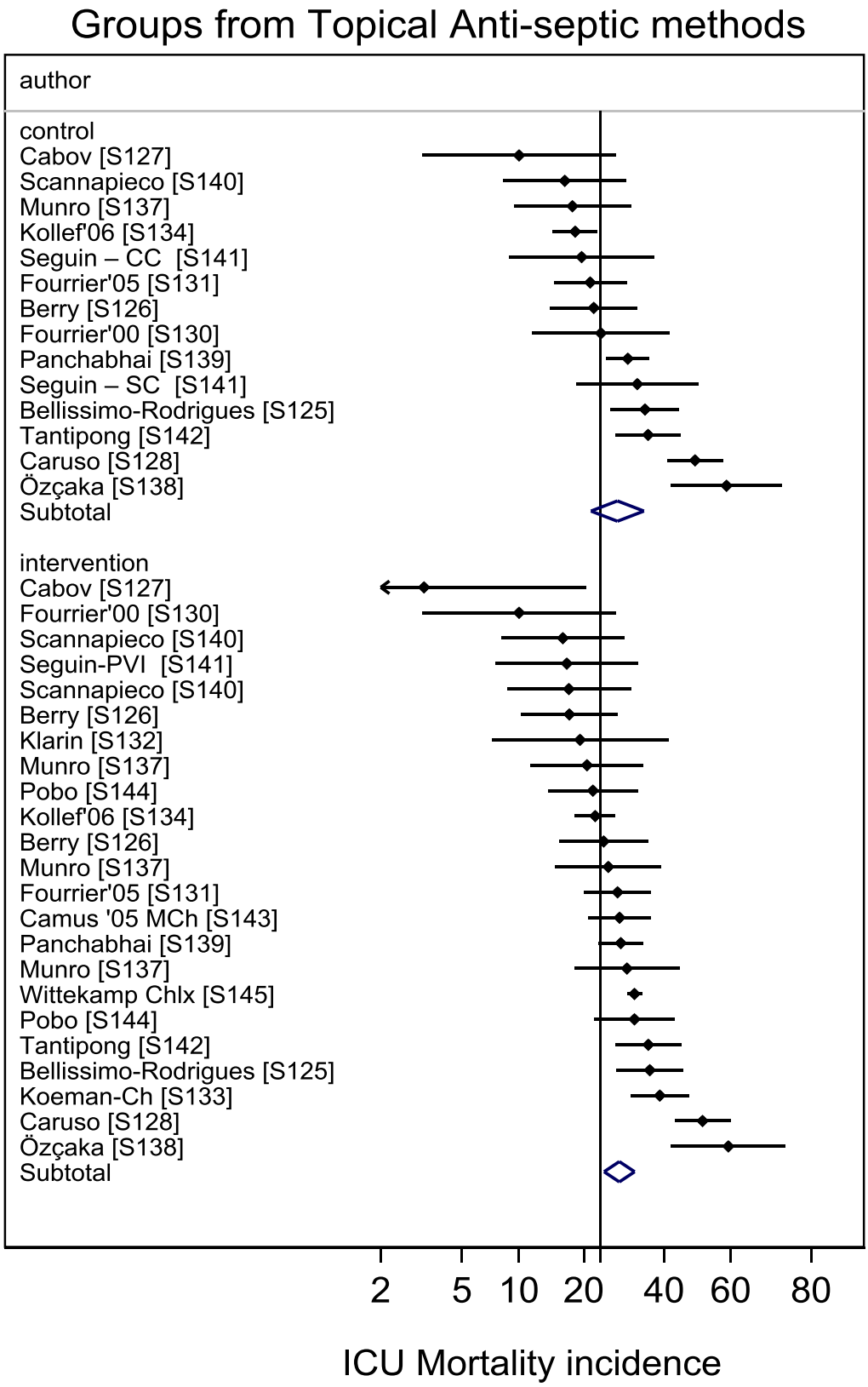


Fig S12. ICU mortality incidence among control and intervention groups from studies of Topical anti-septic methods. CHLX is chlorhexidine. Caterpillar plots of the group specific (small diamonds) and summary (central broken line and large open diamond) mortality incidence and 95% CI. Groups are listed in Table S3. Note that the x axis is a logit scale. The central solid line is the ICU mortality incidence benchmark from Figure S9

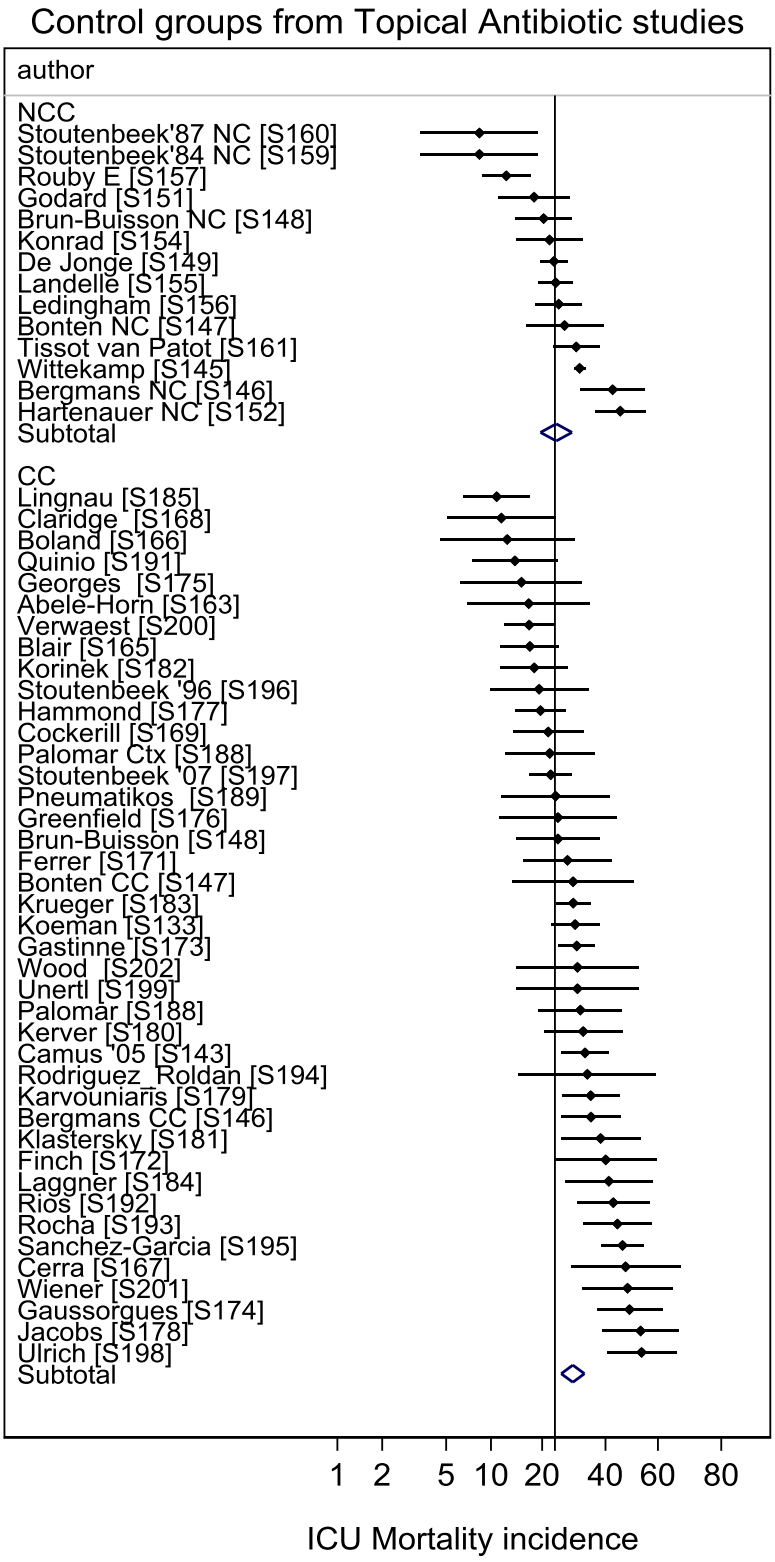


Fig S13. ICU mortality incidence among control groups from NCC (top) and CC (bottom) studies of Topical antibiotic methods. Caterpillar plots of the group specific (small diamonds) and summary (central broken line and large open diamond) mortality incidence and 95% CI. Groups are listed in Table S4. Note that the x axis is a logit scale. The central solid line is the ICU mortality incidence benchmark from Figure S9.

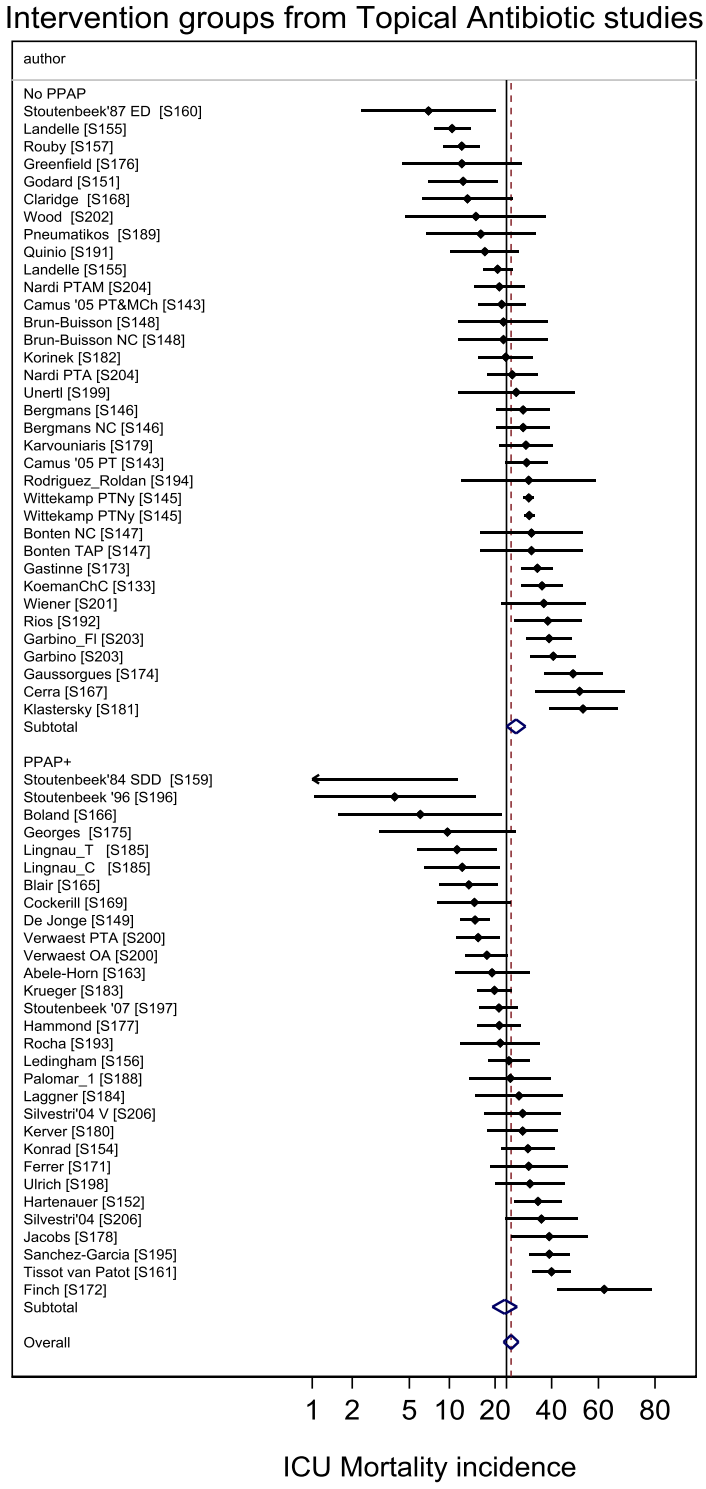


Fig S14 ICU mortality incidence among intervention groups from studies of Topical antibiotic methods stratified by whether PPAP was included in the intervention or not. Caterpillar plots of the group specific (open diamonds) and summary (central broken line and bottom open diamond) mortality incidence and 95% CI. Groups are listed in Table S4. Note that the x axis is a logit scale. The central solid line is the ICU mortality incidence benchmark from Figure S9.

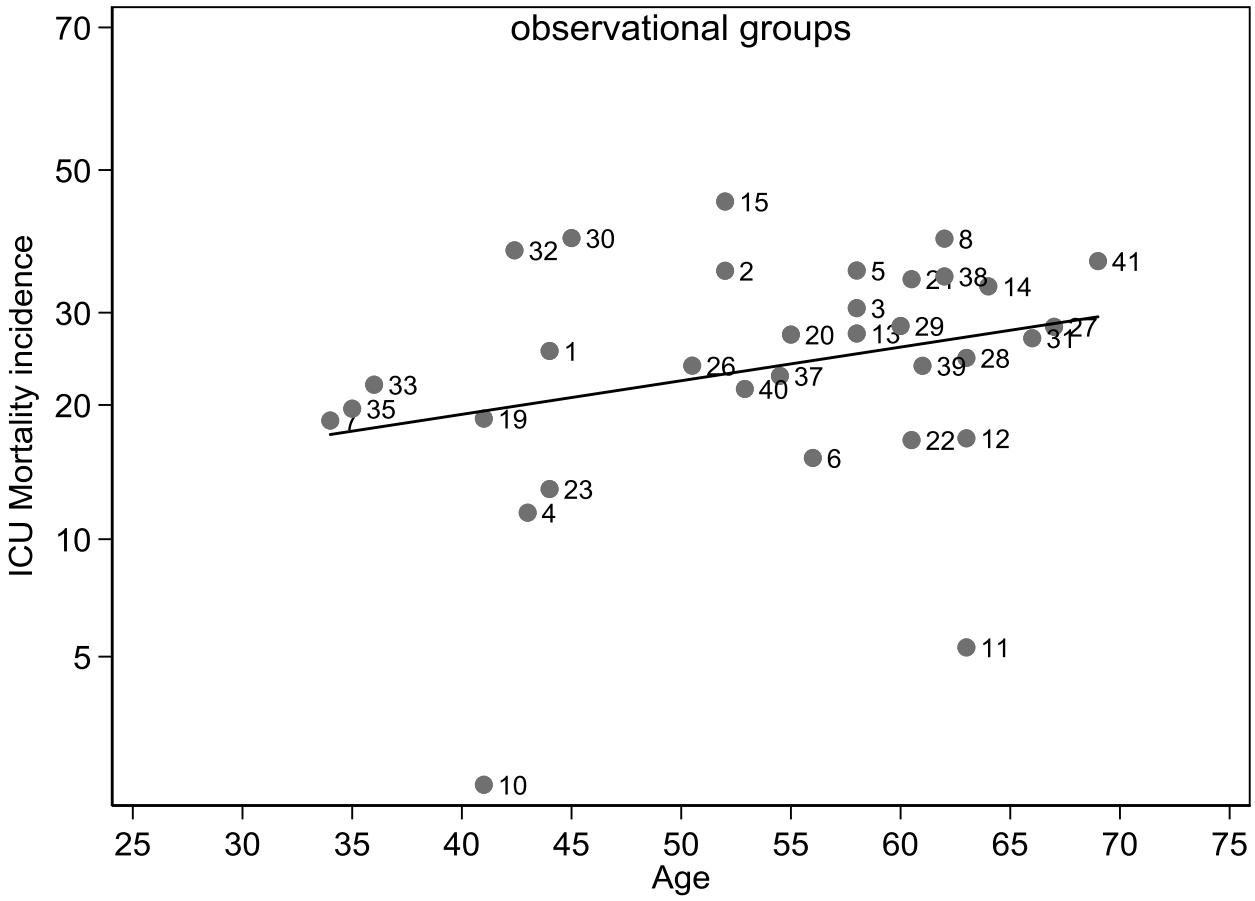
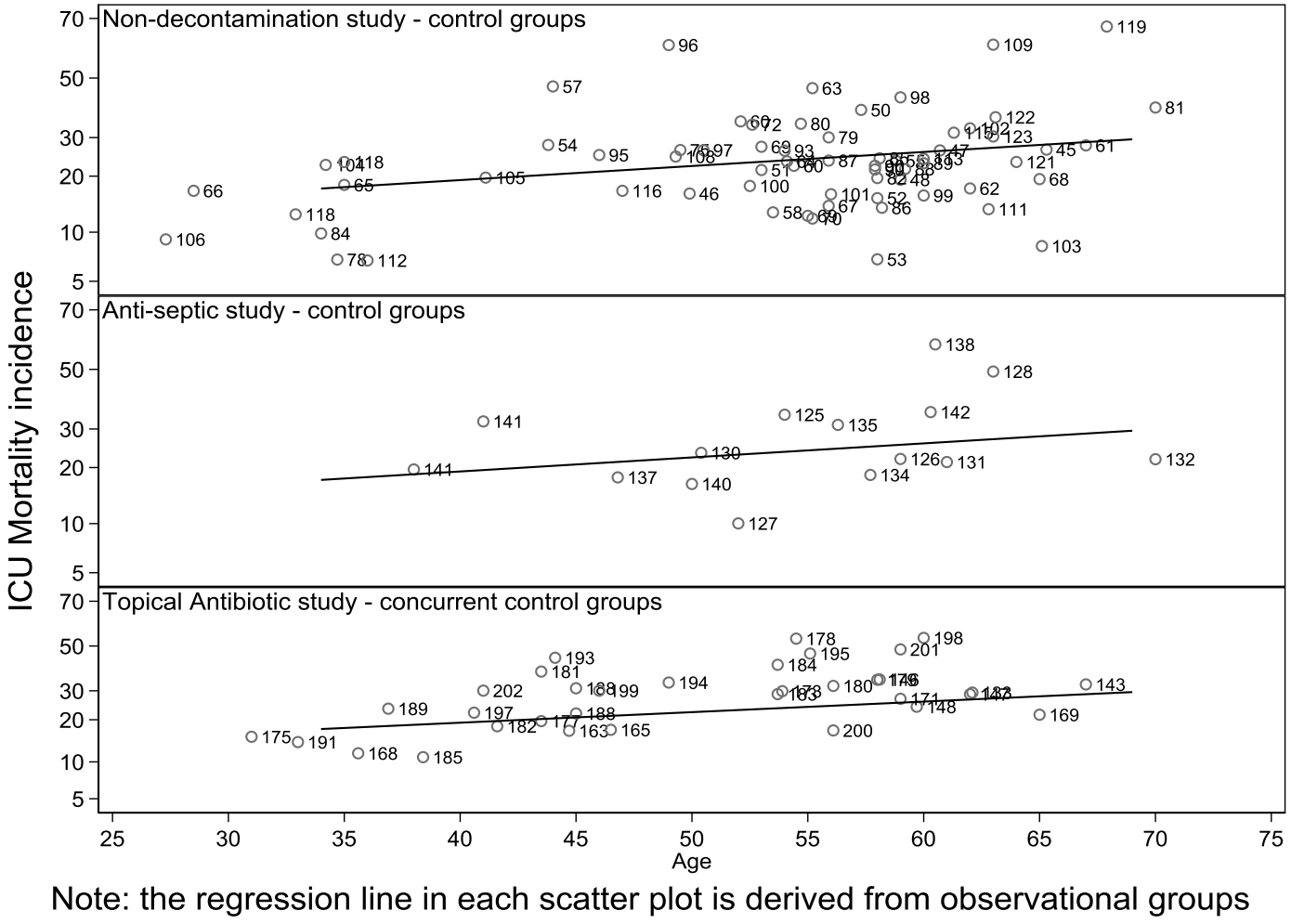
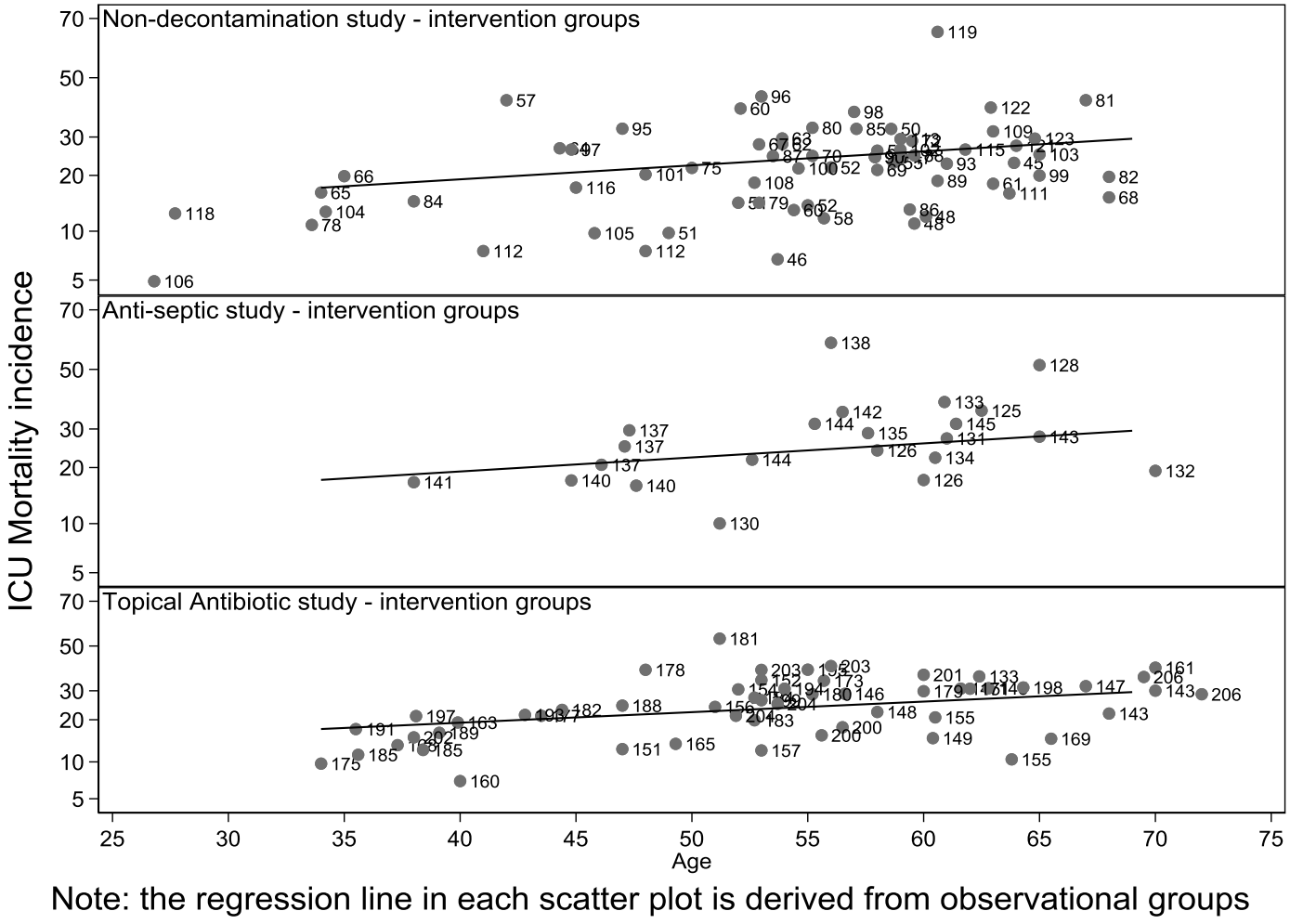


Fig S15 Mortality incidence among observational groups (grey shaded circles) together with associated linear regression line and ICU mortality incidence among groups from observational studies versus group mean age together with a linear regression line. This linear regression line serves as a reference line for Fig S16 (a-d).



Note: the regression line in each scatter plot is derived from observational groups

Fig S16 Mortality incidence among control groups from studies of non-decontamination (top), topical anti-septic (middle) and topical antibiotic (bottom) studies of VAP prevention (grey shaded circles) versus group mean age. The symbols id's are the study citation numbers. Also shown for reference is the linear regression line derived from ICU mortality incidence among groups from observational studies versus group mean age as derived in Fig S15.



Note: the regression line in each scatter plot is derived from observational groups

Fig S17 Mortality incidence among intervention groups from studies of non-decontamination (top), topical anti-septic (middle) and topical antibiotic (bottom) studies of VAP prevention (grey shaded circles) versus group mean age. The symbols id's are the study citation numbers. Also shown for reference is the linear regression line derived from ICU mortality incidence among groups from observational studies versus group mean age as derived in Fig S15.