

Staphylococcus aureus hitchhiking from colonization to bacteremia via Candida within ICU infection prevention studies. A proof of concept modelling.

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Table S1: Observational studies (Benchmark groups) ^a

Author	Ref	Notes	MV	LOS	Patients n	VAP		Blood stream infection	
			%	d		v_sr_n	v_can_n	b_sr_n	b_can_n
A'court 1993	1	T	100	12	150	4		5	
Alvarez-Lerma 1996	2		93	7	6494	102			
Antonelli 1994	3	T	70	17	124	10	1		
Apostolopoulou 2003	4		100	16	175	9			
Arumugam 2018	5	T	100	7	332	16			
Azoulay noCandida 2006	6		100	17	589				4
AzoulayCandida 2006	6	crf	100	17	214				2
Bailly 2015	7		100	30	1491				11
Bekaert 2011	8		100	8	4479	133			
Bercault 2001	9		100	26	1144		2		
Bercault_IHT 2005	10		100	9	118	2			
Bercault_noINT 2005	10	I	100	11	118	2			
Berrouane_all 1998	11	T	83	13	565	71			
Blot >74 2014	12		100	8	516	17			
Blot 45_64 2014	12		100	8	670	27			
Blot 65_74 2014	12		100	8	549	22			
Bochicchio 2004	13	T	100	13	678	50			
Bonten'94 1994	14		100	25	64	3			
Boots 2008	15		100	13	412	32	0		
Bornstain 2004	16		100	12	747	17			
Borzotta 1999	17	T	85	10	459				7
Braun 1986	18	T	100		66	6			
Bregeon 1997	19		100		660	34	3		
Bronchard 2004	20	T	100	23	109	26			
Cade 1993	21		98	16	98	13	5	4	1
Cavalcanti 2006	22	T	100	10	190	18	6		
Cenderero 1999	23		100	7	123	9	0		
Chaari 2015	24	T	100	8	175	6			
Charles 2005	25	crf	97	21	56				1
Charles 2005	25		75	14	36				0
Chastre 1998	26		100	14	243	18	7		
Chevret 1993	27		100	5	255	23	4		
Combes 2000	28	T	100	18	104	4			
Cook_non-trauma 2010	29		100	13	2080	14	4		
Cook_trauma 2010	29	T	100	8	511	15	1		
Craven-medical 1988	30		100	6	277	9	1	4	
Craven-surgical 1988	30		100	6	521	12	5	10	

Table S1 (continued): Observational studies (Benchmark groups)

Author	Ref	Notes	MV	LOS	Patients	VAP		Blood stream infection	
			%	d		n	v_sr_n	v_can_n	b_sr_n
Daschner 1988	31		100	6	116	13	4		
De waele 2003	32	crf	79	16	46				0
de_Latorre 1995	33		100	15	80	3	2		
de_Santis 2000	34				713			13	
de_Santis 2013	34				1318			0	
El-Masri 2004	35	T		11	361			24	
Ensminger 2006	36	C	100	7	92	6			
Ertugrul 2006	37	T	100	10	100	12		9	
Esteve 2007	38		80	16	395				
Esteve 2007	38		78	17	404				
Evans 2010	39	T	100	8	416	40			
Ewig 1999	40	T	100	10	48	5	1		
Fabian_all 1993	41	T	100	11	278	32			
Fagon'89 1989	42		100	13	567	17			
Ferreira 2015	43		94	5	2527				
Gacouin 2009	44		100	11	361	21			
García-Garmendia 2001	45		46	5	2640			39	23
Garrouste-Orgeas 1997	46		100	11	86	13	1		
Garrouste-Orgeas 2006	47		75	11	3247			46	
George 1998	48		100	8	223	8	2		
Georges 2000	49		100	20	135	11			
Giamarellou-Bourboulis 2009	50	T	100	12	72		2	1	
Giard 2008	51		100	9	7236	193			
Gruson-97-98 2000	52	I	100		1029	54			
Gruson-95-96 2000	52		100		1004	67			
Gruson-99-01 2003	53		100		823	26			
Guérin 1997	54		100	19	260	3	0		
Gursel 2010	55		100	10	92	13	1		
Heyland 1999	56		100	7	1014	64	26		
Holzappel_93 1993	57		100	10	300	8		6	
Huang_1pre 2013	58			3	15816			77	38
Huang_1SC 2013	58			3	23480			128	49
Hugonnet 2007	59		100	6	936	55	40		
Hyllienmark 2007	60		100	4	221	2			
Hyllienmark 2013	61	T	42	3	135	11			
Ibáñez 2000	62		100	8	30	3			
Ibrahim'00 2000	63		100	5	1882	143	19		
Ibrahim'00 2000	64		69	11	4913			94	41
Ibrahim'01 2001	65		56	9	880	36			
Jacobs 1990	66		100	15	24	2			
Jaillette 2011	67		100	15	439	22			

Table S1 (continued): Observational studies (Benchmark groups)

Author	Ref	Notes	MV	LOS	Patients n	VAP		Blood stream infection	
			%	d		v_sr_n	v_can_n	b_sr_n	b_can_n
Jensen_HE 2015	68		66	6	604				24
Jensen_SOC 2015	68		67	5	596				13
Jimenez 1989	69		100	10	77	2			
Kallel 2020	70		93	26	2353			57	10
Kautzky 2014	71		37	17	35		1		0
Kautzky 2014	71	crf	57	24	30		1		2
Ko 2013	72		100	23	1453			16	
Kollef '93 1993	73		100	7	277	9			
Kollef '95 1995	74		100		300	22			
Kollef '95 1995	75		100	16	314	17			
Kollef '97 1997	76		100	8	521	25			
Kollef '97_pre 1997	77	C	90	4	353	5	1	5	5
Kollef '97_post 1997	77	C I	90	4	327	4	0	1	3
Koss- N 2001	78		100	14	87	3	10		
Koss- P 2001	78	I	100	11	66	4	3		
Kunac 2014	79		100		716	62		6	
Laggner 1989	80	T	100	11	32	0	0	1	0
Lambert 2011	81			5	119699			462	
Laupland 2002	82			5	1017			18	3
Laupland 2004	83		84	5	4473			45	19
León 2006	84	crf	95	21	1699				58
León 2009	85	crf	91	17	1107				37
León 2016	86	crf	84	15	233				11
Lepelletier 2010	87	T	100	18	161	34			
Li 2016	88		17	12	29		1		0
Li 2016	88	crf	40	25	82		10		3
Luna 2003	89		100	8	427	19	2		
Luyt 2005	90		100		290	12			
Magnason 2008	91		100	8	280	1	0	1	5
Mahul 1992	92		100	22	145	10	3		
Makris 2011	93	I	100	22	152	3			
Markowicz 2000	94		100	10	744	74			
Memish 2000	95		100	11	202	16	4		
Michel 2005	96		100	11	299	12			
Mitsogianni 2011	97			16	124			0	1
Mitsogianni 2010	97			16	143			1	0

Table S1 (continued): Observational studies (Benchmark groups)

Author	Ref	Notes	MV	LOS	Patients n	VAP		Blood stream infection	
			%	d		v_sr_n	v_can_n	b_sr_n	b_can_n
Moine 2002	98		80	14	764	19	2		
Montecalvo_J 1992	99		100	10	38			3	1
Myny 2005	100		100	4	385	27			
Nguile-Makao 2010	101		100	7	2873	89			
Nielsen 1992	102		100	5	242	5			
Nseir 2005	103		100	10	1241	15			
Nseir 2007	104	crf	100	24	102				3
Orsi 2007	105		98	36	1741			37	10
Orsi 2012	105		100	34	1165			4	4
Osmon 2003	106		72	8	893			29	26
Outcomerea 2019	107		100	8	7735	258			
Papazian 1996	108		100	10	586	20			
Petri 1997	109	crf	95	11	409				3
Potgieter 1987	110		78	9	250	23	5		
Prowle 2011	111		69	6	6339			88	51
Ramirez 2016	112		100	13	440	8	0		
Rello'91 1991	113		100	8	264	15	1		
Rello'92 1992	114	T	80	8	208	22			
Rello'92 1992	115		67	9	161	21			
Rello'94 1994	116		72		1650			16	4
Rello'02 2002	117		100	8	9080	143			
Rello'03 2003	118		100	20	99	2	0		
Resende 2013	119		100	22	126	5	0		
Reusser 1989	120		100	7	40	6		1	
Rincón-Ferrari 2004	121	T	100	10	310	27			
Rodrigues 2009	122		100	10	233	11	2		
Rodriguez 1991	123	T	100	14	294	37			
Ruiz-Santana 1987	124		100	7	1005	12	1		
Salata 1987	125		100	11	51	2	1		
Shahin 2013	126		100	10	267	6	3		
Sofianou 2000	127		100	36	198	13			
Stéphan 2006	128	T	100	16	175	43			
Tan 2016	129	crf	100	16	264	10			
Tan 2016	129		100	13	354	13			
Tejada-Artigas 2001	130	T	100	12	103	11			

Table S1 (continued): Observational studies (Benchmark groups)

Author	Ref	Notes	MV	LOS	Patients n	VAP		Blood stream infection	
			%	d		v_sr_n	v_can_n	b_sr_n	b_can_n
Thompson 2008	131			6	4270			74	24
Timsit 1996	132		100	19	387	18			
Torres 1990	133		100	3	322	2			
Trouillet 1998	134		100		498	52			
Urli 2002	135		95	21	178	40	1	12	4
Valles 2007	136		100	22	60	9			
Vanhems 2011	137		100	6	3387	137			
Verhamme 2007	138		84	8	4000	56	6		
Violan 1998	139		100	16	314	26			
Warren 2001	140		28	4	3163			3	4
Woske 2001	141		100	19	103	29			
Xie 2011	142		100	7	4155	92	88		
Xie 2020	143		67	25	8474			45	45
Zahar 2009	144		100	10	1233	51			

Table S1 footnotes

Notes: T = Data originating from a study for which the majority of ICU admission were for trauma; C = cardio-thoracic ICU; I = Infection control intervention to entire ICU; crf = group wide candidemia risk factor

MV = percentage of group receiving mechanical ventilation; NS – Not stated; LOS is mean or median length of ICU stay; ICU-LOS is the ICU length of stay.

v_sr_n is the count of *Staphylococcus aureus* VAP; and v_can_n is the count of *Candida* isolates from patients with VAP.

b_sr_n is the count of *Staphylococcus aureus* bacteremia; b_can_n is the count of Candidemia;

Several (n = 43) of these studies were cited in the following source systematic reviews.

- Melsen WG, Rovers MM, Bonten MJM: Ventilator-associated pneumonia and mortality: A systematic review of observational studies. *Crit Care Med* 2009, 37:2709–2718.
- Safdar N, Dezfulian C, Collard HR, Saint S: Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med* 2005, 33:2184–93.
- Agrafiotis M, Siempos II, Ntaidou TK, Falagas ME. Attributable mortality of ventilator-associated pneumonia: a meta-analysis. *Intern J Tub Lung Dis.* 2011;15(9):1154-1163.

Table S2: Groups of non decontamination studies ^a

Author	Ref	Notes	MV	LOS	Patients n	VAP		Blood stream infection	
			%	d		v_sr_n	v_can_n	b_sr_n	b_can_n
Acosta-escribano 2010	145	T	100	18	54	4	1		
Acosta-escribano 2010	145	T	100	16	50	8	0		
Bonten 1995	146		100	17	67	4			0
Bonten 1995	146		100	19	74	7			0
Cook 1998	147		100	9	596	44	19		
Cook 1998	147		100	9	604	36	11		
Daumal 1999	148		100	6	174	7	2		
Daumal 1999	148		100	7	187	9	6		
Djedaini 1995	149		100	10	61	0	0		
Djedaini 1995	149		100	9	68	2	1		
Drakulovic 1999	150		100	10	47	4	0		
Drakulovic 1999	150		100	9	39	0	0		
Dreyfuss 1991	151		100	10	35	2			
Dreyfuss 1991	151		100	13	28	1			
Dreyfuss 1995	152		100	10	70	2			
Dreyfuss 1995	152		100	13	61	0			
Driks 1987	153		100	14	69	4	0		
Driks 1987	153		100	11	61	0	0		
Forestier 2008	154	T	100	13	106	11			
Forestier 2008	154	T	100	13	102	12			
Heyland 1999	155		100	12	46	0	0		
Heyland 1999	155		100	13	49	1	0		
Holzapfel_C 1999	156		100	15	200	21	3	2	1
Holzapfel_I 1999	156		100	17	199	7	1	2	1
Kappstein 1991	157	T	100	5	55	9	7		
Kappstein 1991	157	T	100	5	49	11	3		
Kirschenbaum 2002	158		100	20	20	1			
Kirschenbaum 2002	158		100	21	17	0			
Kirton 1997	159	T	100		140	6			
Kirton 1997	159	T	100		140	6			
Knight 2009	160		100	7	129	1	0		
Knight 2009	160		100	6	130	0	0		
Kollef 2008	161		100	4	743	16	7		
Kollef_silverETT 2008	161		100	4	766	9	5		
Lacherade 2005	162		100	25	184	16	2		
Lacherade 2005	162		100	21	185	18	0		

Table S2 (continued): Groups of non decontamination studies ^a

Author	Ref	Notes	MV	LOS	Patients n	VAP		Blood stream infection	
			%	d		v_sr_n	v_can_n	b_sr_n	b_can_n
Lacherade 2010	163		100	11	164	8			
Lacherade 2010	163		100	11	169	2			
Laueny 2014	164	T	100	17	91	6	0		
Laueny 2014	164	T	100	11	98	17	0		
Lorente 2003	165		100	18	116	8	3		
Lorente 2003	165		100	16	114	7	4		
Lorente 2004	166		100	16	143	6	3		
Lorente 2004	166		100	20	161	14	2		
Lorente2006	167		100	13	233	11	1		
Lorente 2006	167		100	13	210	10	2		
Lorente'06a 2005	168		100	10	221	8	1		
Lorente'06a 2005	168		100	10	236	8	1		
Lorente 2006	169		100	21	51	5	0		
Lorente 2006	169		100	20	53	2	0		
Lorente 2007	170		100	16	140	8	0		
Lorente 2007	170		100	14	140	2	0		
Lorente 2014	171		100	16	150	5			
Lorente 2014	171		100	15	134	1			
Manzano 2008	172		100	12	63	9			
Manzano 2008	172		100	9	64	4			
Martin 1993	173		100	10	66	1	0		
Martin 1993	173		100	10	65	0	1		
Morrow 2010	174		100	15	73	14	1		
Morrow 2010	174		100	15	73	8	0		
Nseir 2011	175		100	10	61	3			
Nseir 2011	175		100	12	61	1			
Pickworth 1993	176	T	100	7	44	1	0		
Pneumatikos 2006	177	T	100	16	40	4	0		
Pneumatikos 2006	177	T	100	15	39	2	0		
Prod'hom_A 1994	178		100	6	81	5			
Prod'hom_S 1994	178		100	5	83	2			
Prod'hom_R 1994	178		100	5	80	4			
Reigneir 2013	179		100	10	222	17			
Reigneir 2013	179		100	10	227	10			
Rumbak 2004	180		100	5	60	5			
Rumbak 2004	180		100	16	60	1			

Table S2 (continued): Groups of non decontamination studies ^a

Author	Ref	Notes	MV	LOS	Patients		VAP		Blood stream infection	
					d	n	v_sr_n	v_can_n	b_sr_n	b_can_n
Ryan_C 1993	181			100	5	56	1			
Ryan_S 1993	181			100	6	58	2			
Smulders 2002	182			100	14	75	3	1		
Smulders 2002	182			100	12	75	1	0		
Staudinger 2010	183			100	14	75	2	2		
Staudinger 2010	183			100	8	75	2	0		
Thomachot 1998	184			100	12	66	7	0		
Thomachot 1998	184			100	12	70	8	0		
Thomachot 1999	185	T		100	11	77	8	0		
Thomachot 1999	185	T		100	12	63	7	0		
Thomachot 2002	186	T		100	9	84	7			
Thomachot 2002	186	T		100	9	71	5			
Valencia 2007	187			100	13	69	2			
Valencia 2007	187			100	13	73	2			
Walaszek 2017	188			100	5	804	4	5		
Walaszek 2017	188			100	5	1003	2	1		
Zeng 2016	189			100	22	117	16	4		
Zeng 2016	189			100	18	118	12	2		

Table S2 footnotes

Notes; T = Data originating from a study for which the majority of ICU admission were for trauma; C = cardio-thoracic ICU; crf = group wide candidemia risk factor;

MV = percentage of group receiving mechanical ventilation; NS – Not stated; LOS is mean or median length of ICU stay; ICU-LOS is the ICU length of stay.

v_sr_n is the count of *Staphylococcus aureus* VAP; and v_can_n is the count of *Candida* isolates from patients with VAP.

b_sr_n is the count of *Staphylococcus aureus* bacteremia; b_can_n is the count of Candidemia;

Several (n = 47) of these studies were cited in the following source systematic reviews.

- Messori A, Trippoli S, Vaiani M, Gorini M, Corrado A: Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials. *BMJ* 2000, 321:1103–1106.
- Huang J, Cao Y, Liao C, Wu L, Gao F: Effect of histamine-2-receptor antagonists versus sucralfate on stress ulcer prophylaxis in mechanically ventilated patients: a meta-analysis of 10 randomized controlled trials. *Crit Care* 2010, 14:R194.
- Alhazzani W, Almasoud A, Jaeschke R, Lo BW, Sindi A, Altayyar S, Fox-Robichaud A: Small bowel feeding and risk of pneumonia in adult critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care* 2013, 17:R127.

- Melsen WG, Rovers MM, Bonten MJM: Ventilator-associated pneumonia and mortality: A systematic review of observational studies. *Crit Care Med* 2009, 37:2709–2718.
- Safdar N, Dezfulian C, Collard HR, Saint S: Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med* 2005, 33:2184–93.
- Han J, Liu Y. Effect of ventilator circuit changes on ventilator-associated pneumonia: a systematic review and meta-analysis. *Respiratory care*, 2010; 55: 467-474.
- Subirana M, Solà I, Benito S: Closed tracheal suction systems versus open tracheal suction systems for mechanically ventilated adult patients. *Cochrane Database Syst Rev* 2007, 4: CD004581;
- Siempos II, Vardakas KZ, Kopterides P, Falagas ME. Impact of passive humidification on clinical outcomes of mechanically ventilated patients: A meta-analysis of randomized controlled trials. *Crit Care Med* 2007; 35: 2843-51;
- Muscedere J, Rewa O, McKechnie K, Jiang X, Laporta D, Heyland DK. Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: a systematic review and meta-analysis. *Crit Care Med* 2011; 39:1985–1991.
- Delaney A, Gray H, Laupland KB, Zuege DJ. Kinetic bed therapy to prevent nosocomial pneumonia in mechanically ventilated patients: a systematic review and meta-analysis. *Crit Care* 2006; 10:R70;
- Sud S, Friedrich JO, Taccone P, Polli F, Adhikari NK, Latini R, Gattinoni L. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Inten Care Med* 2010; 36(4); 585-599.
- Siempos II, Vardakas KZ, Falagas ME. Closed tracheal suction systems for prevention of ventilator-associated pneumonia. *Brit J Anaesthesia*, 2008; 100(3): 299-306.

Table S3: Groups of anti-septic studies ^a

Author & regimen	Ref	Notes	MV	LOS	Patients n	VAP		Blood stream infection	
			%	d		v_sr_n	v_can_n	b_sr_n	b_can_n
Bellissimo-Rodrigues 2014	190		76	11	127		1		
Bellissimo-Rodrigues 2014_Chlx	190		77	11	127		0		
Bleasdale 2007	191		35	3	445			1	2
Bleasdale 2007_Chlx	191		36	3	391			0	2
Cabov 2010	192		57	6	30	2		2	
Cabov 2010_Chlx	192		77	6	30	0		0	
Caruso 2009	193		100	17	132	5	3		
Caruso 2009_Saline	193		100	17	130	1	0		
Climo_NC 2013	194			6	1398			8	16
Climo 2013_Chlx	194			6	1410			9	7
Fourrier 2000	195		100	24	30	3	1	1	0
Fourrier 2000_Chlx	195		100	18	30	0	0	0	0
Fourrier 2005	196		100	13	114	2	0	0	0
Fourrier 2005_Chlx	196		100	14	114	1	0	1	0
Huang_2pre 2013	58			3	15218			70	56
Huang_3pre 2013	58			3	17356			80	59
Huang_3UD 2013_Chlx	58			3	26024			92	62
Huang_2TD 2013_Chlx	58			3	24752			106	63
Koeman 2006	197		100	13	130	5	1		
Koeman 2006_Chlx	197		100	14	127	2	3		
Koeman 2006_ChlxC	197		100	13	128	5	4		
Kollef 2006	198		100	14	347	25	6		
Kollef 2006_Iseganin	198		100	14	362	17	0		
Lorente 2012	199		100	9	219	4	0		
Lorente 2012_Chlx	199		100	10	217	4	0		
Milstone 2013	200	P		3	1326			4	6
Milstone 2013_Chlx	200	P		3	667			3	3
Mori H 2006	201		100	7	414	5	2		
Mori 2006-PVI	201		100	8	1248	7	1		
Noto_pre 2015	202			3	4852			15	6
Noto_post 2015_Chlx	202			3	4488			16	2
Seguin – SC 2006	203	T	100	14	31	7			
Seguin – CC 2006	203	T	100	19	31	7			
Seguin 2006-PVI	203	T	100	15	36	3			

Table S3 (continued): Groups of anti-septic studies ^a

Author & regimen	Ref	Notes	MV	LOS	Patients n	VAP		Blood stream infection	
			%	d		v_sr_n	v_can_n	b_sr_n	b_can_n
Seguin 2014	204	T	100	16	72	11			
Seguin 2014-PVI	204	T	100	15	78	14			
Swan 2016	205		57	7	164	2	1	0	
Swan 2016_Chlx	205		69	7	161	1	0	0	
Wittekamp 2018	206		100	10	2251			13	15
Wittekamp 2018_Chlx	206		100	10	2108			25	22

Table S3: Footnotes

Notes; T = Data originating from a study for which the majority of ICU admission were for trauma; P = paediatric ICU; I = Infection control intervention to entire ICU; crf = group wide candidemia risk factor;

MV = percentage of group receiving mechanical ventilation; NS – Not stated; LOS is mean or median length of ICU stay; ICU-LOS is the ICU length of stay.

v_sr_n is the count of *Staphylococcus aureus* VAP; and v_can_n is the count of *Candida* isolates from patients with VAP.

b_sr_n is the count of *Staphylococcus aureus* bacteremia; b_can_n is the count of Candidemia;

Several (n = 5) of these studies were cited in the following source meta-analyses.

- 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, 334:889–900.
- Labeau SO, Van de Vyver K, Brusselaers N, Vogelaers D, Blot SI: Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis. *Lancet Infect Dis* 2011, 11:845-854.
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- Price R, MacLennan G, Glen J. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. *BMJ*. 2014; **348**: g2197.
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Intervention regimens abbreviations

Chlx = chlorhexidine; Chlx BW = chlorhexidine body wash; ChC = chlorhexidine and colistin; TD = targeted decolonization; UD = universal decolonization; PVI = povidone iodine; CC = concurrent control; SC = saline control; iseganan, is a synthetic variant of a porcine protegrin, which is a natural antibiotic peptide released by neutrophils in response to invasion by microbes [Kollef 2006].

Table S4: Groups of antibiotic-based prophylaxis (=TAP±PPAP±antifungal) studies ^a

Author & regimen	Ref	Notes	MV	LOS	Patients n	VAP		Blood stream infection	
			%	d		v_sr_n	v_can_n	b_sr_n	b_can_n
Groups from NCC studies									
Bergmans NC 2001	207		100	12	61	5	1		
Bergmans CC 2001	207		100	15	78	6	3		
Bergmans 2001_PGV	207		100	13	87	3	1		
Bonten NC 1994	208		91	16	54	2			
Bonten CC 1994	208		86	9	21	0			
Bonten 1994_PTA	208		100	13	22	0			
Camus NC 2014	209		28	4	925	17	3	3	2
Camus 2014_PT	209		28	4	1022	0	1	2	1
De La Court 2021_PTA	210				722			7	4
De La Court 2021_PTA	210				1236			12	11
de Smet 2009	211		88	9	1990			22	16
de Smet SDD 2009_PTA	211		93	9	2045			9	8
de Smet SOD 2009_PTA	211		94	9	1904			9	14
Godard 1990	212		80	13	84	4			2
Godard 1990_PT	212		81	11	97	0			0
Gorensek 1993	213	crf		15	34			0	1
Gorensek 1993_NoNy	213	crf		15	17			0	0
Hartenauer 1990	214		100	14	101	8	0	3	0
Hartenauer 1990_PTA	214		100	13	99	3	1	4	3
Hjortrup 1997_CefTNy	215	crf	100		150	14	11	2	4
Konrad 1989	216		100		83	4			
Konrad 1989_PTA	216		100		82	2			
Landelle 2018	217		100	9	291	10			
Landelle 2018_PTNy	217		100	8	413	9			
Landelle 2018_PTNy	217		100	9	356	4			
Ledingham 1988	218		60	5	161	5			
Ledingham 1988_PTA	218		60	5	163	1			
Leone 2002_PTA	219	T	100	12	324	23			
Mathieu 2day 2020_PTA	220	T	100		199				0
Mathieu 3day 2020_PTA	220	T	100		248				1
Nardi 1990	221		100	13	50	3			
Nardi 1990_PTA	221		100	12	47	3			

Table S4 (continued): Groups of antibiotic-based prophylaxis (=TAP±PPAP±antifungal) studies ^a

Author & regimen	Ref	Notes	MV	LOS	Patients n	VAP		Blood stream infection	
			%	d		v_sr_n	v_can_n	b_sr_n	b_can_n
Groups from NCC studies									
Nardi 2001_PTAM	222	T	100	11	119	1	0	2	
Nardi 2001_PTA	222	T	100	12	104	9	1	2	
Ong 2015_PTA	223		87	10	3080			10	
Oostdijk SDD 2014_PTA	224		51	6	5483			13	
Oostdijk SOD 2014_PTA	224		52	6	5508			32	
Rouby 1994_P	225		100	12	347	21			
Rouby 1994_E	225		100	18	251	14			
Silvestri 1999_PTA	226	e	100	9	117	2	0	8	
Steffen 1994_PTNY	227	crf	100	14	127			1	
Stoutenbeek 1984	228	T	100	14	59	18	0	0	
Stoutenbeek 1984_PTA	228	T	100	11	63	0	0	0	
Stoutenbeek 1987	229	T	100	14	59	3	0	7	
Stoutenbeek SDD 1987_PTA	229	T	100	11	63	3	0	0	
Stoutenbeek ED 1987_PTA	229	T	100	18	42	9	0	3	
SuDDICU 2022	230		100	11	3191			46	
SuDDICU 2022	230		100	10	2791			27	
Valles 2013	231		100	15	58	1			
Valles 2013	231		100	10	71	2			
Veelo 2008_PTA	232		100	17	231	8			
Winter CC 1992	233		92	8	92	1	0		
Winter NC 1992	233		92	7	84	4	0		
Winter 1992_PTA	233		92	6	91	0	0		
Wittekamp 2018_PTNY	206		100	10	2224			12	23
Wittekamp 2018_PTNY	206		100	11	2082			17	18

Table S4 (continued): Groups of antibiotic-based prophylaxis (=TAP±PPAP±antifungal) studies ^a

Author & regimen	Ref	Notes	MV	LOS	Patients	VAP		Blood stream infection	
			%	d	n	v_sr_n	v_can_n	b_sr_n	b_can_n
Groups from CC studies									
Abele-Horn 1997	234	T	100	22	30	5			
Abele-Horn 1997_PTA	234	T	100	18	58	9			
Acquarolo 2005	235		100	13	19	6	0		
Acquarolo 2005_AmpSul	235		100	13	19	3	0		
Aerdts 1991	236		100	28	39	4	2		1
Aerdts 1991_PNoA	236		100	23	17	0	0		0
Bion 1991	237	crf	50	2	31		2	0	0
Bion 1991_PTA	237	crf	50	2	21		3	0	0
Blair 1991	238		93	8	130	7	1		0
Blair 1991_PTA	238		93	8	126	1	0		1
Blaise 1994	239	crf	33	7	45	4		3	
Blaise 1994_O	239	crf	37	7	46	1		4	
Bouza 2013	240	C	100	12	38	4	0		
Bouza 2013_Lnz_Mrp	240	C	100	10	40	2	0		
Camus 2005	241		100	13	126	8		1	
Camus 2005_MChlx	241		100	10	130	3		1	
Camus 2005_PT	241		100	12	130	6		3	
Camus 2005_PTMCh	241		100	11	129	1		2	
Cerra 1992	242	e		26	21	8	10		4
Cerra 1992_NoNy	242	e		18	25	5	6		1
Cockerill 1992	243		85	12	75				2
Cockerill 1992_PGNY	243		85	10	75				1
de la Cal 2005	244	T	80	34	54	10	0	6	0
de la Cal 2005_PTA	244	T	74	31	53	0	2	14	1
Ferrer 1994	245		100	14	41	2	2	2	0
Ferrer 1994_PTA	245		100	15	39	3	0	0	0
Flaherty 1990	246	C	40	4	56				0
Flaherty 1990_PGA	246	C	40	4	51	0			0
Francois	247		100	11	95	8	0		
Francois	247		100	11	99	3	3		
Garbino_EN 2004_PNeV	248		100	14	71		1		3
Garbino_TPN 2004_PNeV	248		100	14	29		0		2

Table S4 (continued): Groups of antibiotic-based prophylaxis (=TAP±PPAP±antifungal) studies ^a

Author & regimen	Ref	Notes	MV	LOS	Patients n	VAP		Blood stream infection	
			%	d		v_sr_n	v_can_n	b_sr_n	b_can_n
Gaussorgues 1991	249		100	17	59		1	2	15
Gaussorgues 1991_PGA	249		100	16	59		0	1	5
Georges 1994	250	T	100	7	33	1	0		0
Georges 1994_PNeA	250	T	100	7	31	0	0		0
Hammond 1994	251	T	100	14	33	3			
Hammond 1994_PTA	251	T	100	16	39	4			
Jacobs 1992	252		100	10	43	0	0	0	0
Jacobs 1992_PTA	252		100	9	36	0	0	0	0
Karvouniaris 2015	253		100	13	84	4			
Karvouniaris 2015_P	253		100	16	84	5			
Kerver 1988	254		100	20	47		0		0
Kerver 1988_PTA	254		100	17	49		0		0
Korinek 1993	255	T	100	27	60	16	0		
Korinek 1993_PTA	255	T	100	25	63	9	0		
Laggner 1994	256		100	20	34	0	0	0	0
Laggner 1994_PA	256		100	16	33	0	0	1	0
Langlois-Karaga 1995	257	T	100	11	50	15			
Langlois-Karaga 1995_PGA	257	T	100	11	47	5			
Mirateli 2019	258		100	46	42	3			
Mirateli 2019	258		100	33	42	2			
Palomar 1997	259		100	6	42	8	0		0
Palomar Ctx 1997	259		100	8	46	3			1
Palomar_1 1997	259		100	11	41	5	0		0
Quinio 1995	260	T	100	16	72	16	0	4	0
Quinio 1995_PGA	260	T	100	16	76	9	0	8	0
Rimola 1985	261	crf		10	72			5	
Rimola 1985_PGVNy	261	crf		11	68			2	
Rocha 1992	262	T	100	18	54	15		3	0
Rocha 1992_PTA	262	T	100	19	47	5		2	0
Rodríguez-Roldán 1990	263		100	12	15	1			
Rodríguez-Roldán 1990_PTNeA	263		100	10	13	0			

Table S4 (continued): Groups of antibiotic-based prophylaxis (=TAP±PPAP±antifungal) studies ^a

Author & regimen	Ref	Notes	MV	LOS	Patients n	VAP		Blood stream infection	
			%	d		v_sr_n	v_can_n	b_sr_n	b_can_n
Rolando 1996	264	crf	73		61	1	1	1	1
Rolando 1996_PTA	264	crf	73		47	2	1	0	0
Rolando 1993	265	crf	75	8	31	1	3	3	0
Rolando 1993_PTAM	265	crf	75	8	28	2	0	0	0
Rolando_infected 1993	265	crf	75	8	21	0	1	0	0
Rolando_infected 1993_PTAM	265	crf	75	7	21	1	1	0	0
Sanchez-Garcia 1998	266		100	20	140	7	0		
Sanchez-Garcia 1998_PTA	266		100	17	131	5	0		
Sirvent 1997	267	T	100	16	50	11	0		
Sirvent 1997	267	T	100	13	50	3	0		
Smith 1993	268	crf	100	8	18		1		1
Smith 1993_PTA	268	crf	100	7	18		0		0
Stoutenbeek 2007	269	T	100	12	200	40	21	5	0
Stoutenbeek 2007_PTA	269	T	100	13	201	18	6	8	1
Ulrich 1989	270		83	13	52	5	1		0
Ulrich 1989_PNoA	270		77	17	48	2	1		0
Unertl 1987	271		100	23	20	5	0		
Unertl 1987_PGA	271		100	18	19	1	0		
van Delden 2012	272		100	11	45				
van Delden 2012_Azith	272		100	10	47				
Verwaest 1997	273		100	19	185	9	0	3	4
Verwaest 1997_PTA	273		100	22	200	9	0	10	0
Verwaest 1997_OA	273		100	17	193	6	1	7	0
Wiener 1995	274		100	11	31	4	0		2
Wiener 1995_PGNy	274		100	11	30	1	0		0
Zobel 1991	275	P	100	13	25			0	1
Zobel 1991_PGA	275	P	100	14	25			0	0

Table S4: Footnotes

Notes; T = Data originating from a study for which the majority of ICU admission were for trauma; C = cardio-thoracic ICU; P = paediatric ICU; crf = group wide candidemia risk factor; e = number of episodes rather than patients

MV = percentage of group receiving mechanical ventilation; NS – Not stated; LOS is mean or median length of ICU stay; ICU-LOS is the ICU length of stay.

v_sr_n is the count of *Staphylococcus aureus* VAP; and v_can_n is the count of *Candida* isolates from patients with VAP.

b_sr_n is the count of *Staphylococcus aureus* bacteremia; b_can_n is the count of Candidemia;

The control group in one study by Stoutenbeek [1987] appears also as the control group in another study by this Author [1984] and is used only once in the analysis here.

Several (n = 24) of these studies were cited in the following source systematic reviews.

- 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 ventilation. *Cochrane Database Syst Rev* 2021, Issue 1. Art. No.: CD000022. DOI: 10.1002/14651858.CD000022.pub4.
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TAP intervention regimens abbreviations; PTA (=P, topical polymyxin; T, topical tobramycin; A, topical amphotericin); PTA-Ctx (=P, topical polymyxin; T, topical tobramycin; A, topical amphotericin; Ctx, parenteral cephalosporin); P (P = polymyxin either aerosolized or topical); PNeV (P = polymyxin; Ne = Neomycin; V = Vancomycin); PGA-Ctx (=P, topical polymyxin; G, topical gentamicin; A, topical amphotericin; Ctx, parenteral cephalosporin); PTAM (=P, topical polymyxin; T, topical tobramycin; A, topical amphotericin; topical mupirocin); E (=E, topical erythromycin); PNoA-Ctx (=P, topical polymyxin; No, topical norfloxacin; A, topical amphotericin; Ctx, parenteral cephalosporin); PGV (=P, topical polymyxin; G, topical gentamicin; V, topical vancomycin); PGNy-Ctx (=P, topical polymyxin; G, topical gentamicin; Ny, topical nystatin; Ctx, parenteral cephalosporin); P-Ctx (=P, topical polymyxin; Ctx, parenteral cephalosporin); PTAV (=P, topical polymyxin; T, topical tobramycin; A, topical amphotericin; V, topical vancomycin); PGA (=P, topical polymyxin; G, topical gentamicin; A, topical amphotericin); PTNeA (=P, topical polymyxin; T, topical tobramycin; Ne, topical Neomycin; A, topical amphotericin); PGNy (=P, topical polymyxin; G, topical gentamicin; Ny, topical nystatin); PTA-Cz (=P, topical polymyxin; T, topical tobramycin; A, topical amphotericin; Cz, parenteral Ceftazidime).

Table S5: Groups of studies of single drug antifungal (SAF) prophylaxis

Author & regimen	Ref	Notes	MV %	LOS d	Patients n	RT Candida v_can_n	Candidemia b_can_n
Ables 2000	276	crf	95	8	59		0
Ables 2000_Fluc	276	crf	95	8	60		0
Eggimann 1999	277	crf			20		2
Eggimann 1999_Fluc	277	crf			23		0
Garbino 2002	278		100	8	101	0	9
Garbino 2002_Fluc	278		100	9	103	2	1
Giglio 2012	279		100	15	50	0	0
Giglio 2012_Ny	279		100	15	49	0	0
Jacobs 2003	280			11	39		1
Jacobs 2003_Fluc	280			11	32		0
Lumbreras 1996_Ny	281	crf		28	67		0
Lumbreras 1996_Fluc	281	crf		28	76		1
Normand 2005	282		100	12	47	0	0
Normand 2005_Ny	282		100	12	51	0	0
Ostrosky-Zeichner 2014	283	crf	100	7	102		7
Ostrosky-Zeichner 2014_Casp	283	crf	100	7	117		1
Parizkova 2000	284		100		20		0
Parizkova 2000_Fluc	284		100		18		0
Pelz_2001	285	T	87	5	130		3
Pelz_2001_Fluc	285	T	88	5	130		1
Piarroux_2004	286			15	455		6
Piarroux_2004_Fluc	286			12	428		0
Savino 1994	287		31	16	72		0
Savino 1994_Clot	287		23	12	80		0
Savino 1994_Ket	287		33	8	65		0
Savino 1994_Ny	287		39	15	75		0
Savino 1994	287	crf	31	16	72		2
Savino 1994_Clot	287	crf	23	12	80		1
Savino 1994_Ket	287	crf	33	8	65		1
Savino 1994_Ny	287	crf	39	15	75		5
Schuster 2008	288	crf		12	127		2
Schuster 2008_Fluc	288	crf		12	122		0

Table S5: Footnotes

T = Data originating from a trauma ICU; crf = group wide candidemia risk factor; MV = percentage of group receiving mechanical ventilation; NS – Not stated; LOS is mean or median length of ICU stay; ICU-LOS is the ICU length of stay.

RT Candida is respiratory tract candida (v_can_n; the count of *Candida* isolates from patients with VAP); b_can_n is the count of Candidemia

Several (n = 24) of these studies were cited in the following source systematic reviews [286-296].

Table S6: Review of effect sizes in the literature ^{a, b}

	Effect size	95% CI	notes	Ref
Anti-septics				
Overall VAP				
	RR: 0.78	0.60 – 1.02 (13)	Excl cardiac surgery	290
	RR: 0.67	0.47 – 0.97 (13)	Chlorhexidine	291
	RR: 0.66	0.51 – 0.85 (22)	Nosocomial pneumonia	292
Overall bactremia				
	OR: 0.74	0.37 – 1.50 (5)	Chlorhexidine	293
Antibiotic based				
Overall VAP				
	OR: 0.35	0.30 – 0.42 (26)		294
	RR: 0.43	0.35 – 0.53 (18)	TAP + PPAP	295
	RR: 0.57	0.44 – 0.74 (19)	TAP alone (incl duplex)	295
	RR: 0.59	0.36 – 0.69 (13)	TAP alone (excl duplex)	295
Bacteraemia				
	OR: 0.48	0.37 – 0.64 (16)	Overall bacteraemia	294
	OR: 0.30	0.16 – 0.56 (8)	Gram Neg (TAP + PPAP)	296
	OR: 1.04	0.69 – 1.57 (8)	Gram Pos (TAP + PPAP)	296
	OR: 0.63	0.46 – 0.87 (16)	Overall bacteremia	296
Candida infections				
	OR: 0.39	0.21 – 0.72 (11)	Candidemia	297
	OR: 0.29	0.18 – 0.45 (15)	Invasive fungal infections	297
	OR: 0.32	0.18 – 0.57 (5)	(Overall fungal infections)	298
Single anti-fungal (SAF)				
Candidemia				
	OR: 0.32	0.12 – 0.82 (6)		297
Other candida infections				
	OR: 0.54	0.39 – 0.75 (10)	Invasive fungal infections	297
	OR: 0.69	0.37 – 1.79 (5)	superficial fungal infections	299
	OR: 0.57	0.39 – 0.83 (18)	Invasive fungal infections	299
	OR: 0.71	0.52 – 0.97 (12)	fungal colonization	299
	RR: 0.46	0.31 – 0.68 (9)	Invasive fungal infections	300

Table S6: Footnotes

OR = Odds ratio; RR = Risk ratio

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Figure S1. (Page 41) Search method, screening criteria and resulting classification of eligible studies and subsequent decant of component groups. The six steps are as follows;

- (1) An electronic search for systematic reviews or meta-analysis (SR/MA) 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 November 2021;*
- (2) The systematic reviews were then searched for studies of patient populations requiring prolonged (> 24 hours) ICU admission*
- (3) The studies were triaged from the systematic reviews into one of five 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, studies of antibiotic-based interventions, and studies of single drug antifungal (SAF) prophylaxis.*
- (4) All studies were reviewed for potentially eligible studies and screened against inclusion and exclusion criteria. Any duplicate or ineligible studies were removed and*
- (5) Studies identified outside of systematic reviews were included;*
- (6) The component groups were decanted from each study being control (rectangles), intervention (ovals) and observation (diamond) groups.*

Note; the total numbers do not tally as some systematic reviews provide studies in more than one category and some studies provide groups in more than one category and some studies have unequal numbers of control and interventions groups. TAP = Topical antibiotic prophylaxis

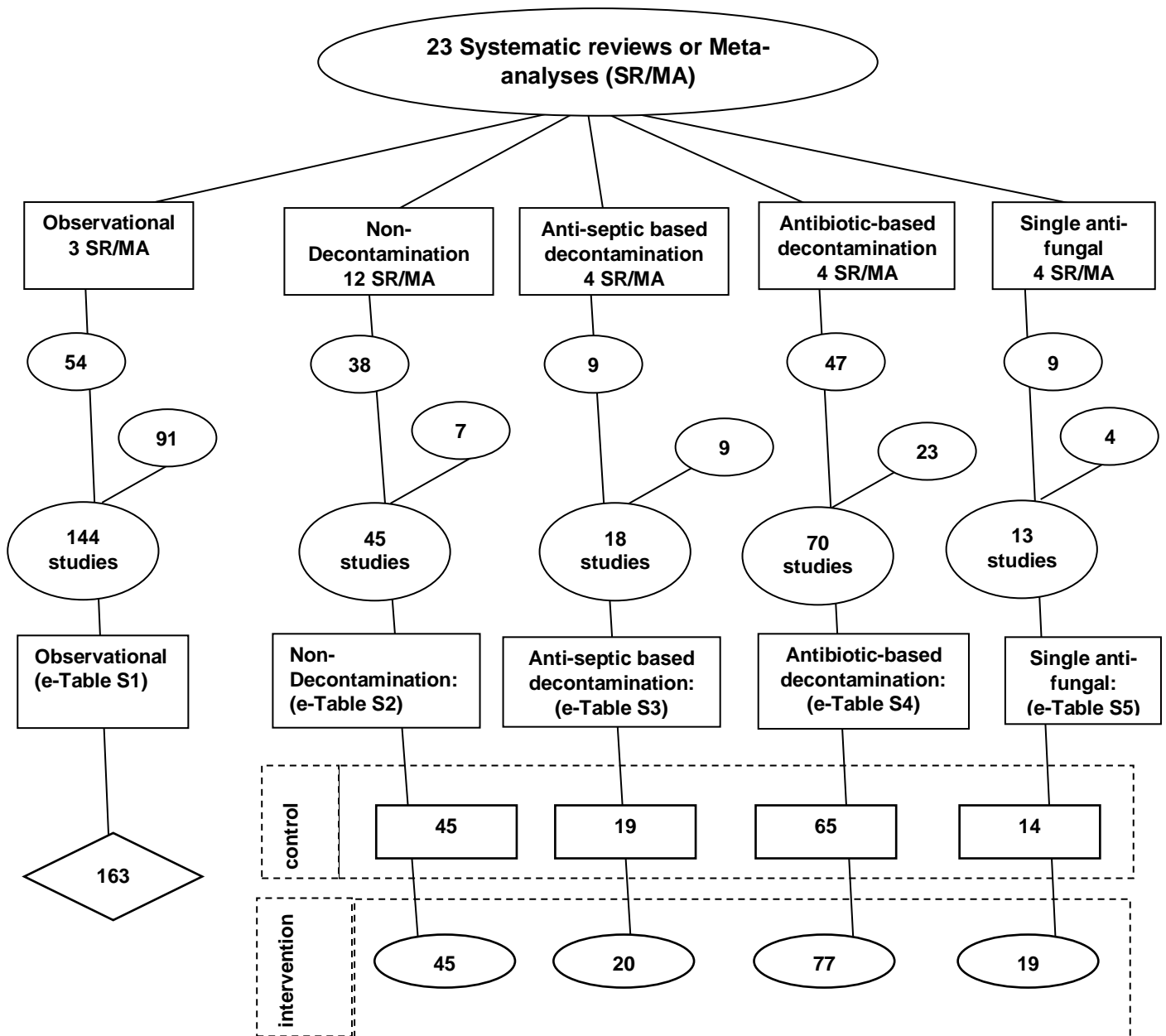
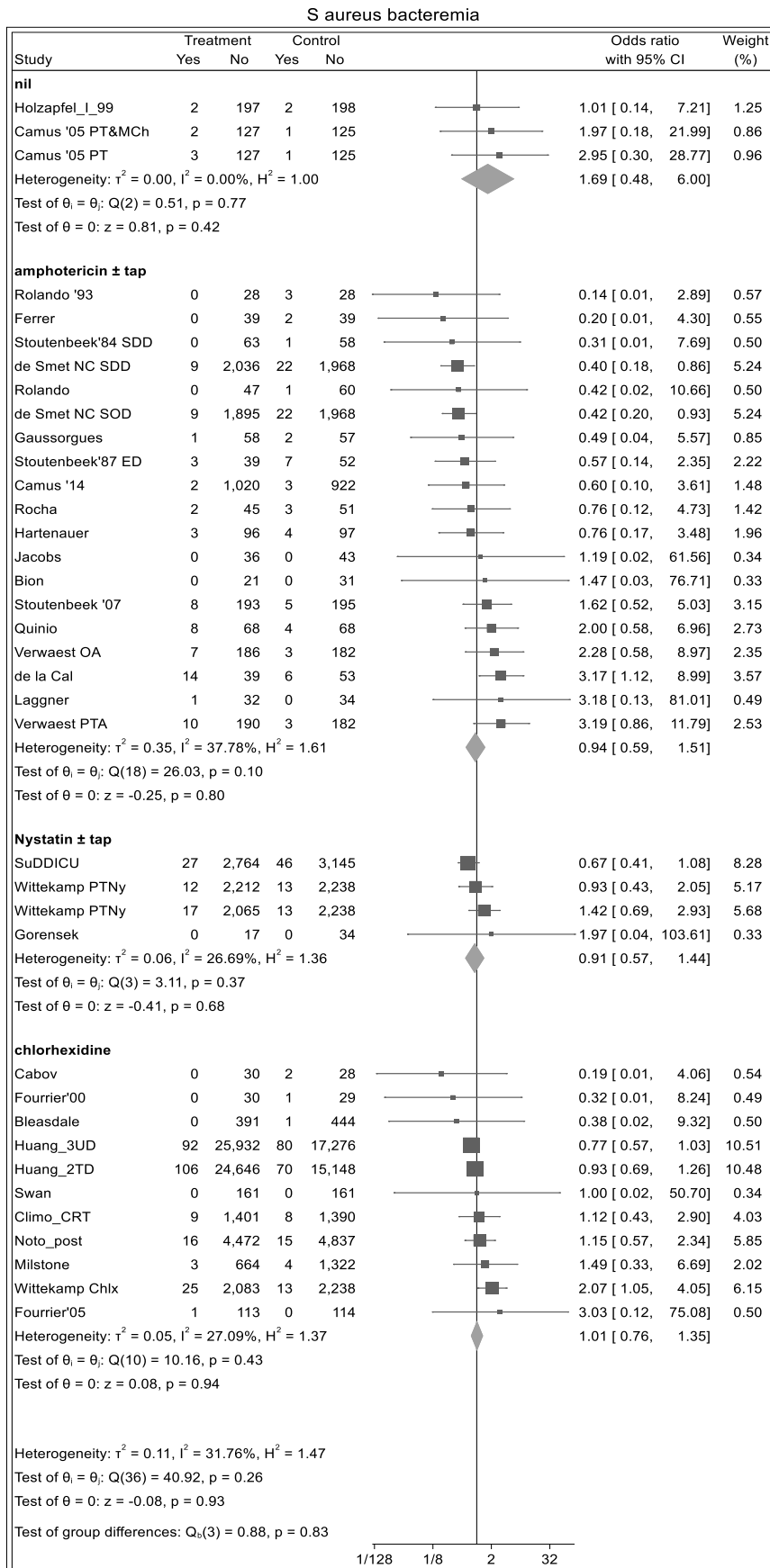
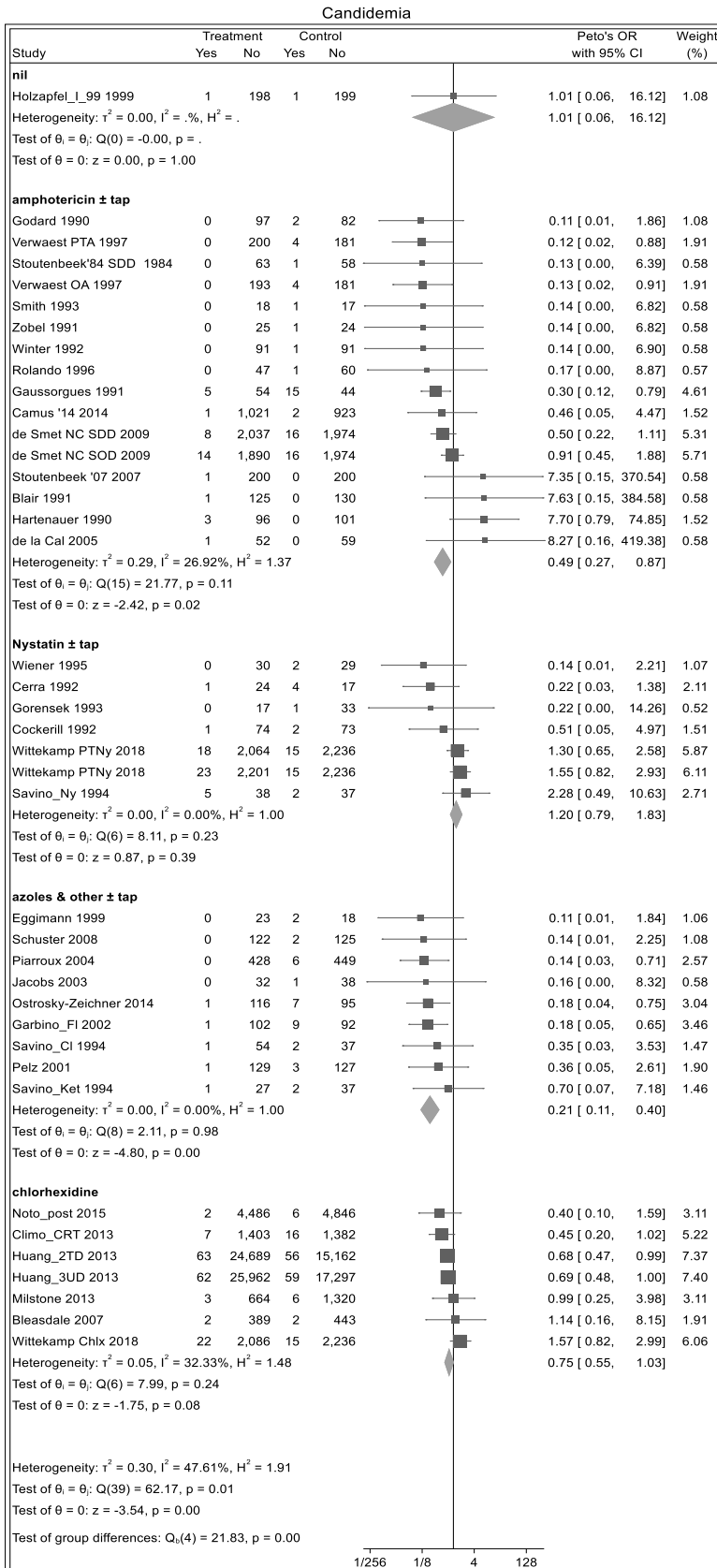


Figure s2 Effect size *Staph aureus* bacteremia



Random-effects REML model
Sorted by: _meta_es

Figure s3 Effect size Candidemia



Random-effects REML model
Sorted by: _meta_es

Figure s4. GSEM of the interaction model (Model C) in relation to Staphylococcus and Candida infection data. *Candida col* and *Staphylococcus col* (ovals) are latent variables representing *Candida* and *Staphylococcus* colonization, respectively. The variables in rectangles are binary predictor variables representing the group level exposure to the following; patient selection for candidemia risk factors (CRF); trauma ICU setting (trauma50), mean or median length of ICU stay ≥ 7 days (los7), exposure to a topical anti-septic (a_S), exposure to TAP (tap), concurrency of a control group with an antibiotic-based intervention group (CC), exposure to a non-decontamination based prevention method (non-D), greater than 90% use of mechanical ventilation (mvp90) or exposure to PPAP (ppap). Note that the model factorizes exposures from compound regimens (e.g. SDD and SOD, which combine TAP, an antifungal together with or without PPAP) into singleton TAP, PPAP and anti-fungal exposures. The circles contain error terms. The three part boxes represent the binomial data for *Candida* and *Staphylococcus* VAP (v_can_n, v_sr_n) and candidemia (b_can_n) or bacteremia (b_sr_n) counts with the number of patients as the denominator which is logit transformed using the logit link function in the generalized model.

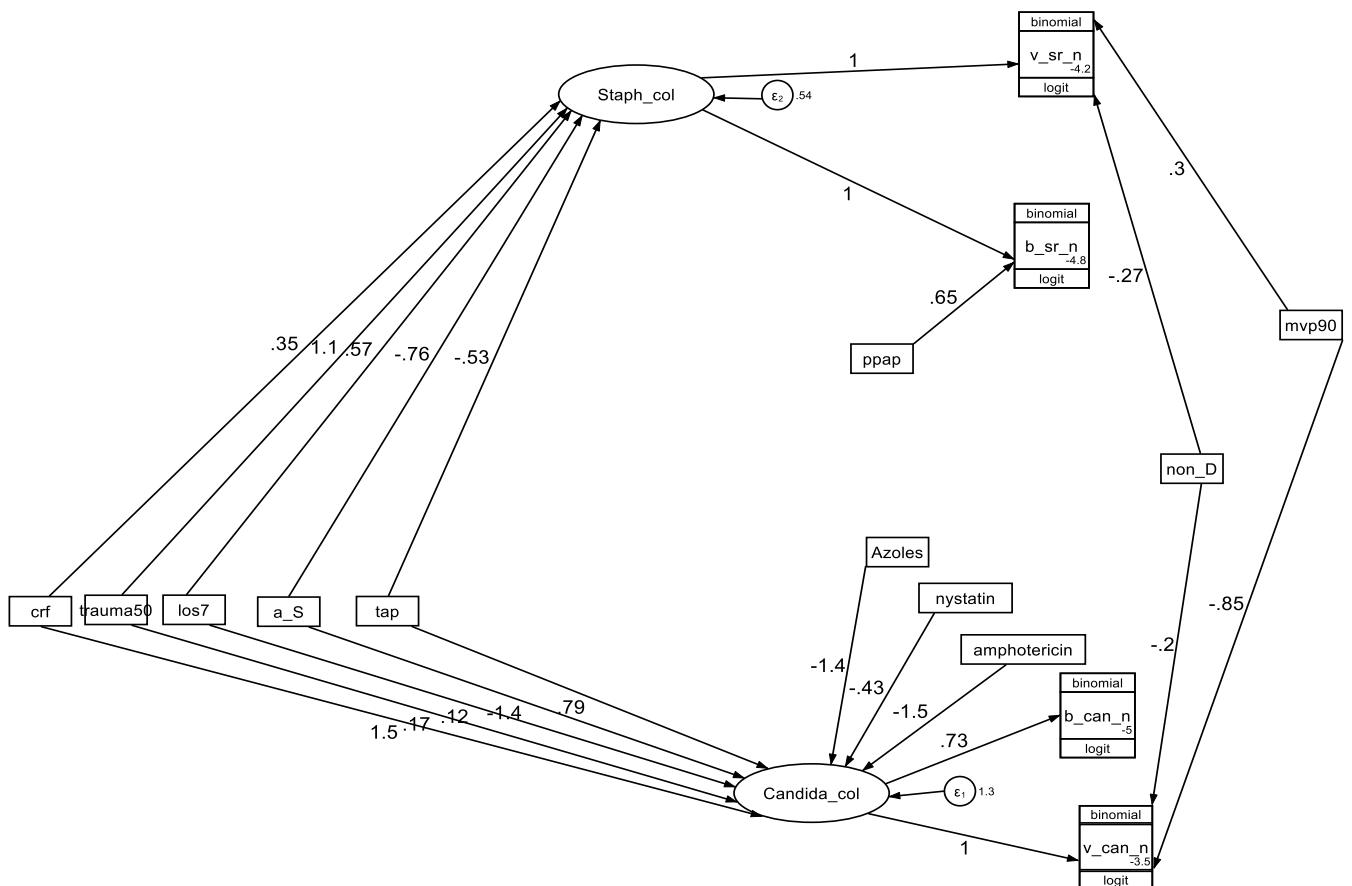


Figure s5. GSEM of the interaction model (Model B) in relation to *Staphylococcus* and *Candida* infection data. *Candida* col and *Staphylococcus* col (ovals) are latent variables representing *Candida* and *Staphylococcus* colonization, respectively. The variables in rectangles are binary predictor variables representing the group level exposure to the following; patient selection for candidemia risk factors (CRF); trauma ICU setting (trauma50), mean or median length of ICU stay ≥ 7 days (los7), exposure to a topical anti-septic (a_S), exposure to TAP (tap), concurrency of a control group with an antibiotic-based intervention group (CC), exposure to a non-decontamination based prevention method (non-D), greater than 90% use of mechanical ventilation (mvp90) or exposure to PPAP (ppap). Note that the model factorizes exposures from compound regimens (e.g. SDD and SOD, which combine TAP, an antifungal together with or without PPAP) into singleton TAP, PPAP and anti-fungal exposures. The circles contain error terms. The three part boxes represent the binomial data for *Candida* and *Staphylococcus* VAP (v_can_n, v_sr_n) and candidemia (b_can_n) or bacteremia (b_sr_n) counts with the number of patients as the denominator which is logit transformed using the logit link function in the generalized model.

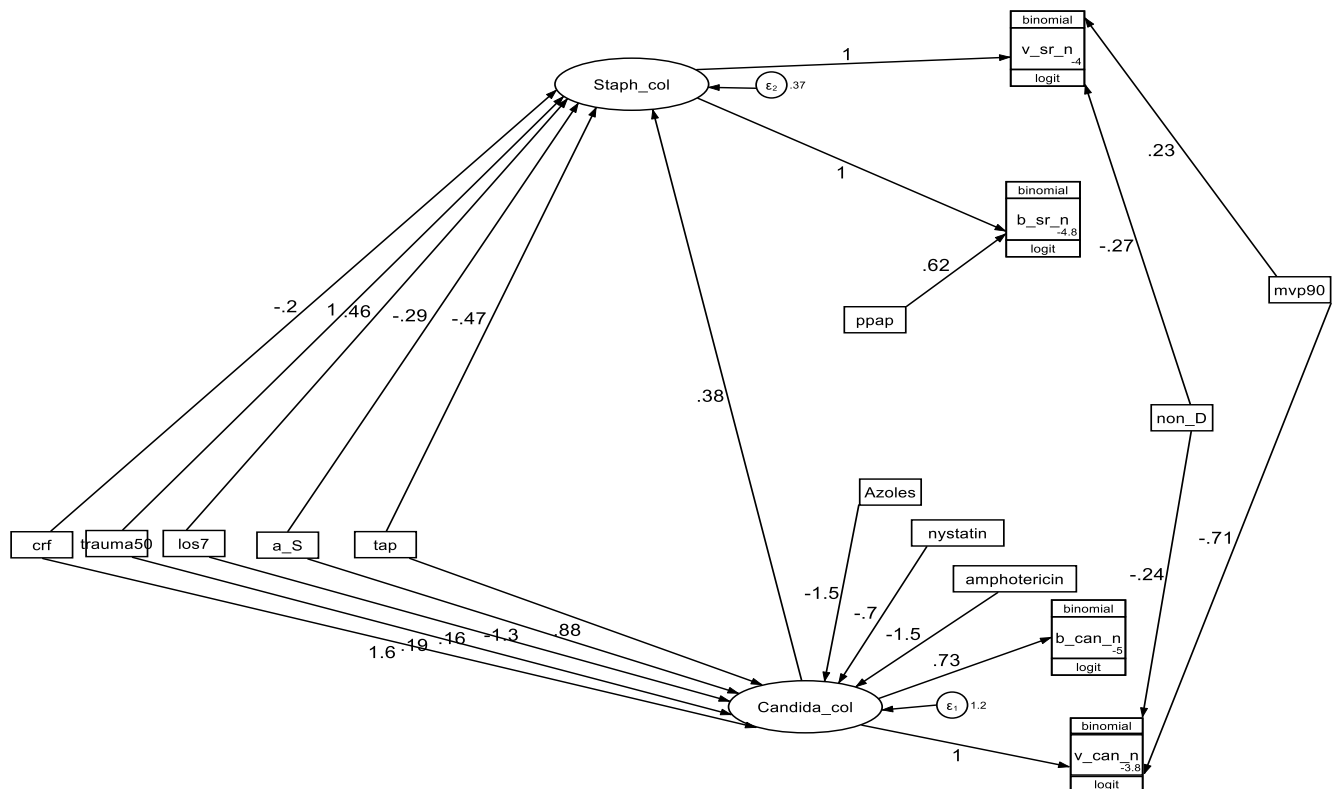


Figure s6. Model A projections for *Staphylococcus aureus* bacteremia (fig S8a) and Candidemia (Fig S8b) incidences among groups of patients from non-trauma ICU groups with mean LOS>7 days and not selected for candidemia risk factors (CRF). The benchmark incidence in each plot is the summary mean derived from the Non-concurrent control (NCC) projected mean (central vertical line). The projections are for control (top) or intervention (bottom panel) groups receiving prophylaxis with various singleton or combination interventions. non-D is non-decontamination, A_s is anti-septic, TAP is topical antibiotic

