Supplementary Appendix

Supplement to: Sharif S, Greer A, Skorupski C, Hao Q, Johnstone J, Dionne J, Lau V, Manzanares W, Eltorki M, Duan E, Lauzier F, Marshall J, Heels-Ansdell D, Thabane L, Cook DJ, Rochwerg B. Probiotics in Critical Illness: A Systematic Review and Meta-analysis of Randomized Controlled Trials.

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Appendix 1. EMBASE, MEDLINE Search Strategy

1 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. (582068)
2 Randomized Controlled Trial/ (1065923)
3 exp Randomized Controlled Trials as Topic/ (299499)
4 "Randomized Controlled Trial (topic)"/ (170030)
5 Controlled Clinical Trial/ (558919)
6 exp Controlled Clinical Trials as Topic/ (311573)
7 "Controlled Clinical Trial (topic)"/ (10466)
8 Randomization/ (185218)
9 Random Allocation/ (181481)
10 Double-Blind Method/ (287236)
11 Double Blind Procedure/ (167007)

12 Double-Blind Studies/ (278151)
13 Single-Blind Method/ (62354)
14 Single Blind Procedure/ (36904)
15 Single-Blind Studies/ (64297)
16 Placebos/ (321341)
17 Placebo/ (343777)
18 Control Groups/ (112449)
19 Control Group/ (112449)
20 (random* or sham or placebo*).ti,ab,hw,kw. (3387712)
21 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw. (524482)
22 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw. (2121)
23 (control* adj3 (study or studies or trial* or group*)).ti,ab,kw. (2231696)
24 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kw. (94063)
25 allocated.ti,ab,hw. (142238)
26 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kw. (92003)
27 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kw. (18644)
28 (pragmatic study or pragmatic studies).ti,ab,hw,kw. (898)
29 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kw. (9193)
30 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kw. (17961)
31 (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kw. (111280)
32 or/1-31 (4985261)
33 exp animals/ (47409466)
34 exp animal experimentation/ or exp animal experiment/ (2467488)
35 exp models animal/ (1863095)
36 nonhuman/ (5977264)
37 exp vertebrate/ or exp vertebrates/ (46125295)
38 33 or 34 or 35 or 36 or 37 (49209166)
39 exp humans/ (38252593)
40 exp human experimentation/ or exp human experiment/ (483117)
41 39 or 40 (38254712)
42 38 not 41 (10956003)
43 32 not 42 (4218506)
44 exp bacillus subtilis/ (66829)
45 exp bifidobacterium/ (18021)
46 exp enterococcus/ (66153)
47 exp fermented foods/ (29489)
48 exp gluconacetobacter/ (1505)
49 Inulin/ (14093)
50 exp leuconostocaceae/ (5688)
51 exp lactobacillaceae/ (72161)
52 exp lactobacillus/ (69702)
53 exp lactococcus/ (12597)
54 Leuconostoc/ (3715)
55 Oenococcus/ (417)
56 exp pediococcus/ (2679)
57 exp polyphenols/ (35417)
58 probiotics/ (49036)
59 exp saccharomyces/ (205756)
60 exp Streptococcus/ (200594)
61 synbiotics/ (2023)
62 (probiotic? or synbiotic?).ti,kw,ab. (52972)
63 Microbial dietary supplement*.ti,kw,ab. (13)

64 (Bacillus laterosporus or bacillus subtilis or Bifidobacter* or Bifidus* or bulgarian bacillus or Fructooligosaccharides or galactooligosaccharides or Gluconacetobacter or inulin or Lactis or lactic acid bacter* or lactobacil* or lactococc* or Leuconostoc* or oenococcus or Pediococus or polyphenol* or Saccharomyc* or Streptococc* or Weissella).ti,kw,ab. (591069)
65 (acidophilus milk or cr?me fraiche or cultured milk or fermented milk or kiselo mlyako or mishti doi or sour cream or acidophiline or airag or aludttej or amabere amarurano or amasi or ariani or ayran or blaand or boruga or buttermilk or byaslag or calpis or chaas or chalap or cheese or clabber or crema espesa or dadiah or dahi or dhai or dichmilch or doogh or filmjolk or ghara or graddfil or grietine or jocoque or joghurt or kaernemaelk or karnemelk or kashk or kaymak or kefir or kefiri or kefyras or kermaviili or khuruud or kimiz or kisela pavlaka or kiselo mleko or kiselo vrhnje or kishk or kislo mleko or kivuguto or kule maoto or kulturmelk or kumis or laezh-ribod or lakto or langfil or lapte acru or lapte batut or lassi or leben or leche agria or mabisi or mastaw or matsoni or mattha or matzoon or maziwa lala or milersam or mursik or paninas or piima or prostokvasha or qatiq or qatyq or qurt or romme or rugpienis or ruguspiens or ryazhenka or sana or sauermilch or shrikhand or skabais krejums or skyr or smantana or smetana or soured milk or sour cream or surmelk or surmjolk or suzma or syrour rjomi or tarag or tejfol or tjukkmjolk or tvorog or twarog or tykmaelk or urubu or varenets or viili or xinogala or xinogalo or yakult or ymer or yoghourt or yoghurt or yogourt).ti,kw,ab. (31117)
66 (amazake or appam or atchara or bagoong or banh cuon or beer or belacan or boza or brem or burong or chakuli pitha or chicha or cincalok or cocoa or curtido or dhokla or doenjang or dosa or doubanjiang or douchi or douzhi or enduri pitha or ganjang or garri or garum or gejang or gochujang or gundruk or hakari or hongeohoe or idli or iguanq or injera or iru or jeotgal or jogijeot or kapusta or katsuobushi or kaymak or kenkey or ketchup or khonom chin or kimchi or kiviak or kombucha or koumiss or kusaya or kuzhi or kvass or lufu or mageu or meigan or miso mixian or mohnyin or murri or myeolchijeot or nata de coco or natto or nem chua or ngapi or ogi or ogiri or oncom or palappam or pesaha appam or peuyeum or pickles or podpiwek or poi or pon ye gyi or pimenta moida or pulque or puto or rakfisk or saeujeot or salami or sauerkraut or salgam or shark meat or shiokara or sinki or smantana or som moo or sour cabbage or sowans or soy sauce or ssamjang suan cai or sumbala or surstomming or taba ng talangka or tabasco sauce or tapai or tarhana or tempeh or tesguino or tianmianjiang or tibicos or tofu or tsukemono or tuong or tungrymbai or vinegar or wine or worcestershire sauce or yongfeng chili sauce or zha cai or zincica).ti,ab,kw. (73562)
67 or/44-66 (937933)
68 nutritional assessment/ (41098)
69 nutritional requirement/ (35770)
70 nutritional support/ (24445)
71 exp parenteral nutrition/ (70779)
72 enteral nutrition/ (45947)
73 (Nutrition* or feed* or enteral or parenteral or total).ti,ab. (6143282)
74 or/68-73 (6201145)
75 (Microbiome* or microbiotica or microbial antagonism or bacterial interference).ti,ab. (44669)
76 exp microbiota/ or antibiosis/ (140370)
77 75 or 76 (154978)
78 exp microflora/ or (flora or microbiota or microflora).ti,ab. (220839)
79 intestines/ or digestive system/ or (gut or intestinal).ti,ab. (854205)
80 78 and 79 (92961)
81 77 or 80 (187503)
82 74 and 81 (38774)
83 67 or 82 (963055)
84 43 and 83 (57900)
85 exp Sepsis/ (369730)
86 exp Shock, Septic/ (70340)
87 exp *Intensive Care Units/ (77383)
88 exp *Critical Care/ (283896)
89 *Critical Illness/ (25746)
90 *Critical Care Nursing/ (2123)
91 exp *Emergency Service, Hospital/ (44144)

92 (bacter?emi* or blood poisoning* or fungemia or py?emia* or pyohemia* or sepsis or sept#c?emia* or septic or (endotoxic adj shock) or (toxic adj shock) or tox?emi*).ti,ab. (421747)
93 (((acute* or critical* or serious* or severe*) adj2 (ill* or injur* or wound*)) or trauma*).ti,ab. (1125121)
94 ((intensive* or critical* or neurointensive* or neurocritical*) adj3 (care or therap* or treatment*)).ti. (136311)
95 (critical* or intensive* or trauma*).jn. (169750)
96 (ICU or MICU or CICU or CVICU or CCU or SICU or POCCU or ITU or HDU).ti. (26031)
97 (high dependency or coronary care unit* or emergency department*).ti. (74753)
98 mechanical ventilator/ (11628)
99 (CPAP or nCPAP or APRV).mp. (26117)
100 airway pressure release ventilat*.mp. (778)
101 intermittent positive pressure.mp. (8199)
102 (IPPB or IPPV).mp. (2387)
103 ((artificial* or controlled or mechanical*) adj3 (respirat* or ventilator? or ventilation or vent support)).mp. (229672)
104 respirator.mp. (8230)
105 pulmonary ventilat*.mp. (17793)
106 interactive ventilatory support*.mp. (396)
107 exp Respiration, Artificial/ (264722)
108 or/85-107 (2296725)
109 84 and 108 (4566)
110 109 use ppez (1401)
111 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. (582068)
112 Randomized Controlled Trial/ (1065923)
113 exp Randomized Controlled Trials as Topic/ (299499)
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124 Single Blind Procedure/ (36904)
125 Single-Blind Studies/ (64297)
126 Placebos/ (321341)
127 Placebo/ (343777)
128 Control Groups/ (112449)
129 Control Group/ (112449)
130 (random* or sham or placebo*).ti,ab,hw,kw. (3387712)
131 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw. (524482)
132 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw. (2121)
133 (control* adj3 (study or studies or trial* or group*)).ti,ab,kw. (2231696)
134 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kw. (94063)
135 allocated.ti,ab,hw. (142238)
136 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kw. (92003)
137 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kw. (18644)
138 (pragmatic study or pragmatic studies).ti,ab,hw,kw. (898)
139 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kw. (9193)

140 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kw. (17961)
141 (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kw. (111280)
142 or/111-141 (4985261)
143 exp animals/ (47409466)
144 exp animal experimentation/ or exp animal experiment/ (2467488)
145 exp models animal/ (1863095)
146 nonhuman/ (5977264)
147 exp vertebrate/ or exp vertebrates/ (46125295)
148 143 or 144 or 145 or 146 or 147 (49209166)
149 exp humans/ (38252593)
150 exp human experimentation/ or exp human experiment/ (483117)
151 149 or 150 (38254712)
152 148 not 151 (10956003)
153 142 not 152 (4218506)
154 exp bacillus subtilis/ (66829)
155 exp bifidobacterium/ (18021)
156 exp enterococcus/ (66153)
157 exp fermented product/ (2693)
158 exp gluconacetobacter/ (1505)
159 exp leuconostocaceae/ (5688)
160 exp lactobacillaceae/ (72161)
161 exp lactobacillus/ (69702)
162 exp lactococcus/ (12597)
163 exp pediococcus/ (2679)
164 polyphenol/ (17126)
165 exp probiotic agent/ (33326)
166 exp saccharomyces/ (205756)
167 exp Streptococcus/ (200594)
168 synbiotic agent/ (1558)
169 (probiotic? or synbiotic?).ti,kw,ab. (52972)
170 Microbial dietary supplement*.ti,kw,ab. (13)
171 (Bacillus laterosporus or bacillus subtilis or Bifidobacter* or Bifidus* or bulgarian bacillus or Fructooligosaccharides or galactooligosaccharides or Gluconacetobacter or inulin or Lactis or lactic acid bacter* or lactobacil* or lactococc* or Leuconostoc* or oenococcus or Pediococus or polyphenol* or Saccharomyc* or Streptococc* or Weissella).ti,kw,ab. (591069)
Annotation: Pro- and synbiotic strains
172 (acidophilus milk or cr?me fraiche or cultured milk or fermented milk or kiselo mlyako or mishti doi or sour cream or acidophiline or airag or aludttej or amabere amarurano or amasi or ariani or ayran or blaand or boruga or buttermilk or byaslag or calpis or chaas or chalap or cheese or clabber or crema espesa or dadiah or dahi or dhai or dichmilch or doogh or filmjolk or ghara or graddfil or grietine or jocoque or joghurt or kaernemaelk or karnemelk or kashk or kaymak or kefir or kefiri or kefyras or kermaviili or khuruud or kimiz or kisela pavlaka or kiselo mleko or kiselo vrhnje or kishk or kislo mleko or kivuguto or kule maoto or kulturmelk or kumis or laezh-ribod or lakto or langfil or lapte acru or lapte batut or lassi or leben or leche agria or mabisi or mastaw or matsoni or mattha or matzoon or maziwa lala or milersam or mursik or paninas or piima or prostokvasha or qatiq or qatyq or qurt or romme or rugpienis or ruguspiens or ryazhenka or sana or sauermilch or shrikhand or skabais krejums or skyr or smantana or smetana or soured milk or sour cream or surmelk or surmjolk or suzma or syrour rjomi or tarag or tejfol or tjukkmjolk or tvorog or twarog or tykmaelk or urubu or varenets or viili or xinogala or xinogalo or yakult or ymer or yoghourt or yoghurt or yogourt).ti,kw,ab. (31117)
173 (amazake or appam or atchara or bagoong or banh cuon or beer or belacan or boza or brem or burong or chakuli pitha or chicha or cincalok or cocoa or curtido or dhokla or doenjang or dosa or doubanjiang or douchi or douzhi or enduri pitha or ganjang or garri or garum or gejang or gochujang or gundruk or hakari or hongeohoe or idli or iguanq or injera or iru or jeotgal or jogijeot or kapusta or katsuobushi or kaymak or kenkey or ketchup or khonom chin or kimchi or kiviak or kombucha or koumiss or kusaya or kuzhi or kvass or lufu or mageu or meigan or

miso mixian or mohnyin or murri or myeolchijeot or nata de coco or natto or nem chua or ngapi or ogi or ogiri or oncom or palappam or pesaha appam or peuyeum or pickles or podpiwek or poi or pon ye gyi or pimenta moida or pulque or puto or rakfisk or saeujeot or salami or sauerkraut or salgam or shark meat or shiokara or sinki or smantana or som moo or sour cabbage or sowans or soy sauce or ssamjang suan cai or sumbala or surstomming or taba ng talangka or tabasco sauce or tapai or tarhana or tempeh or tesguino or tianmianjiang or tibicos or tofu or tsukemono or tuong or tungrymbai or vinegar or wine or worcestershire sauce or yongfeng chili sauce or zha cai or zincica).ti,ab,kw. (73562)

174 or/154-173 (918198)

175 nutritional assessment/ (41098)

176 nutritional requirement/ (35770)

177 nutritional support/ (24445)

178 exp parenteral nutrition/ (70779)

179 enteric feeding/ (30340)

180 (Nutrition* or feed* or enteral or parenteral or total).ti,ab. (6143282)

181 or/175-180 (6198572)

182 (Microbiome* or microbiotica or microbial antagonism or bacterial interference).ti,ab. (44669)

183 exp microbiome/ or antibiosis/ (49389)

184 182 or 183 (73254)

185 exp microflora/ or (flora or microbiota or microflora).ti,ab. (220839)

186 intestine/ or digestive system/ or (gut or intestinal).ti,ab. (859718)

187 185 and 186 (93067)

188 184 or 187 (140908)

189 181 and 188 (30488)

Annotation: Putting generic terms for feeding together with terms for gut/microbiome etc to prevent solely critically ill feeding results

190 174 or 189 (937512)

191 153 and 190 (56464)

192 exp Sepsis/ (369730)

193 exp Shock, Septic/ (70340)

194 exp *Intensive Care Units/ (77383)

195 exp *Critical Care/ (283896)

196 *Critical Illness/ (25746)

197 *Critical Care Nursing/ (2123)

198 exp *Emergency Service, Hospital/ (44144)

199 (bacter?emi* or blood poisoning* or fungemia or py?emia* or pyohemia* or sepsis or sept#c?emia* or septic or (endotoxic adj shock) or (toxic adj shock) or tox?emi*).ti,ab. (421747)

200 (((acute* or critical* or serious* or severe*) adj2 (ill* or injur* or wound*)) or trauma*).ti,ab. (1125121)

201 ((intensive* or critical* or neurointensive* or neurocritical*) adj3 (care or therap* or treatment*)).ti. (136311)

202 (critical* or intensive* or trauma*).jn. (169750)

203 (ICU or MICU or CICU or CVICU or CCU or SICU or POCCU or ITU or HDU).ti. (26031)

204 (high dependency or coronary care unit* or emergency department*).ti. (74753)

205 exp Systemic Inflammatory Response Syndrome/ (380254)

206 exp *Intensive Care/ (283896)

207 *Intensive Care Unit/ (55194)

208 *Coronary Care Unit/ (5274)

209 *Burn Unit/ (1421)

210 *Stroke Unit/ (1336)

211 *Critical Illness/ (25746)

212 *Emergency Ward/ (68183)

213 *Emergency Health Service/ (73587)

214 *Hospital Emergency Service/ (39694)

215 (wean or weaned or weaning).mp. (102741)

216 exp artificial ventilation/ (190696)
217 mechanical ventilator/ (11628)
218 (CPAP or nCPAP or APRV).mp. (26117)
219 airway pressure release ventilat*.mp. (778)
220 intermittent positive pressure.mp. (8199)
221 (IPPB or IPPV).mp. (2387)
222 ((artificial* or controlled or mechanical*) adj3 (respirat* or ventilator? or ventilation or vent support)).mp. (229672)
223 respirator.mp. (8230)
224 mechanical* ventilat*.mp. (127230)
225 pulmonary ventilat*.mp. (17793)
226 interactive ventilatory support*.mp. (396)
227 or/192-226 (2433972)
228 191 and 227 (4780)
229 228 use oemezd (3237)
230 110 or 229 (4638)
231 remove duplicates from 230 (3579)

Appendix 2. COCHRANE CENTRAL Search Strategy

Search Name: Probiotics in critically ill
Date Run: 10/12/2020 23:19:59
Comment:

ID	Search	Hits
#1	MeSH descriptor: [Bacillus subtilis] explode all trees	29
#2	MeSH descriptor: [Bifidobacterium] explode all trees	721
#3	MeSH descriptor: [Enterococcus] explode all trees	262
#4	MeSH descriptor: [Fermented Foods and Beverages] explode all trees	999
#5	MeSH descriptor: [Gluconacetobacter] explode all trees	0
#6	MeSH descriptor: [Inulin] explode all trees	236
#7	MeSH descriptor: [Leuconostocaceae] explode all trees	2
#8	MeSH descriptor: [Lactobacillaceae] explode all trees	1606
#9	MeSH descriptor: [Lactobacillus] explode all trees	1598
#10	MeSH descriptor: [Lactococcus] explode all trees	16
#11	MeSH descriptor: [Leuconostoc] explode all trees	2
#12	MeSH descriptor: [Oenococcus] explode all trees	0
#13	MeSH descriptor: [Pediococcus] explode all trees	8
#14	MeSH descriptor: [Polyphenols] explode all trees	726
#15	MeSH descriptor: [Probiotics] explode all trees	2035
#16	MeSH descriptor: [Saccharomyces] explode all trees	157
#17	MeSH descriptor: [Streptococcus] explode all trees	1784
#18	MeSH descriptor: [Synbiotics] explode all trees	146
#19	(probiotic? or synbiotic?):ti,ab	6906
#20	"Microbial dietary supplement?":ti,ab	1
#21	(Bacillus laterosporus or bacillus subtilis or Bifidobacter* or Bifidus* or bulgarian bacillus or Fructooligosaccharides or galactooligosaccharides or Gluconacetobacter or inulin or Lactis or lactic acid bacter* or lactobacil* or lactococc* or Leuconostoc* or oenococcus or Pediococus or polyphenol* or Saccharomyc* or Streptococc* or Weissella):ti,ab	13363
#22	(acidophilus milk or cr?me fraiche or cultured milk or fermented milk or kiselo mlyako or mishti doi or sour cream or acidophiline or airag or aludttej or amabere amarurano or amasi or ariani or ayran or blaand or	

boruga or buttermilk or byaslag or calpis or chaas or chalap or cheese or clabber or crema espesa or dadiah or dahi or dhai or dichmilch or doogh or filmjolk or ghara or graddfil or grietine or jocoque or joghurt or kaernemaelk or karnemelk or kashk or kaymak or kefir or kefiri or kefyras or kermaviili or khuruud or kimiz or kisela pavlaka or kiselo mleko or kiselo vrhnje or kishk or kislo mleko or kivuguto or kule maoto or kulturmelk or kumis or laezh-ribod or lakto or langfil or lapte acru or lapte batut or lassi or leben or leche agria or mabisi or mastaw or matsoni or mattha or matzoon or maziwa lala or milersam or mursik or paninas or piima or prostokvasha or qatiq or qatyq or qurt or romme or rugpienis or ruguspiens or ryazhenka or sana or sauermilch or shrikhand or skabais krejums or skyr or smantana or smetana or soured milk or sour cream or surmelk or surmjolk or suzma or syrour rjomi or tarag or tejfol or tjukkmjolk or tvorog or twarog or tykmaelk or urubu or varenets or viili or xinogala or xinogalo or yakult or ymer or yoghourt or yoghurt or yogourt):ti,ab 3304

#23 (amazake or appam or atchara or bagoong or banh cuon or beer or belacan or boza or brem or burong or chakuli pitha or chicha or cincalok or cocoa or curtido or dhokla or doenjang or dosa or doubanjiang or douchi or douzhi or enduri pitha or ganjang or garri or garum or gejang or gochujang or gundruk or hakari or hongeohoe or idli or iguanq or injera or iru or jeotgal or jogijeot or kapusta or katsuobushi or kaymak or kenkey or ketchup or khonom chin or kimchi or kiviak or kombucha or koumiss or kusaya or kuzhi or kvass or lufu or mageu or meigan or miso mixian or mohnyin or murri or myeolchijeot or nata de coco or natto or nem chua or ngapi or ogi or ogiri or oncom or palappam or pesaha appam or peuyeum or pickles or podpiwek or poi or pon ye gyi or pimenta moida or pulque or puto or rakfisk or saeujeot or salami or sauerkraut or salgam or shark meat or shiokara or sinki or smantana or som moo or sour cabbage or sowans or soy sauce or ssamjang suan cai or sumbala or surstomming or taba ng talangka or tabasco sauce or tapai or tarhana or tempeh or tesguino or tianmianjiang or tibicos or tofu or tsukemono or tuong or tungrymbai or vinegar or wine or worcestershire sauce or yongfeng chili sauce or zha cai or zincica):ti,ab 3020

#24 #1 or #2 or #3 of #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 22163

#25 MeSH descriptor: [Nutrition Assessment] explode all trees 680

#26 MeSH descriptor: [Nutritional Requirements] this term only 577

#27 MeSH descriptor: [Nutritional Support] this term only 244

#28 MeSH descriptor: [Parenteral Nutrition] explode all trees 1660

#29 MeSH descriptor: [Enteral Nutrition] this term only 1844

#30 (Nutrition* or feed* or enteral or parenteral or total):ti,ab 334435

#31 #25 or #26 or #27 or #28 or #29 or #30 335004

#32 (Microbiome* or microbiotica or microbial antagonism or bacterial interference):ti,ab 2165

#33 MeSH descriptor: [Microbiota] explode all trees 710

#34 MeSH descriptor: [Antibiosis] this term only 28

#35 #32 or #33 or #342689

#36 (flora or microbiota or microflora):ti,ab 7823

#37 MeSH descriptor: [Intestines] explode all trees 6343

#38 MeSH descriptor: [Digestive System] explode all trees 16630

#39 (gut or intestinal):ti,ab 19479

#40 #37 or #38 or #3933801

#41 #36 and #40 4550

#42 #35 or #41 6265

#43 #31 and #42 2154

#44 #24 and #43 1092

#45 MeSH descriptor: [Sepsis] explode all trees 4557

#46 MeSH descriptor: [Shock, Septic] explode all trees 973

#47 MeSH descriptor: [Intensive Care Units] explode all trees 3621

#48 MeSH descriptor: [Critical Care] explode all trees 2070

#49 MeSH descriptor: [Critical Illness] explode all trees 2289

#50 MeSH descriptor: [Emergency Service, Hospital] explode all trees 2400

#51 (bacter?emi* or blood poisoning* or fungemia or py?emia* or pyohemia* or sepsis or septec?emia* or septic or (endotoxic shock) or (toxic shock) or tox?emi*):ti,ab 13542

#52 (((acute* or critical* or serious* or severe*) adj2 (ill* or injur* or wound*)) or trauma*):ti,ab 23378

#53	(ICU or MICU or CICU or CVICU or CCU or SICU or POCCU or ITU or HDU):ti	1838
#54	(high dependency or coronary care unit* or emergency department*):ti	3534
#55	MeSH descriptor: [Respiration, Artificial] explode all trees 6233	
#56	#45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 #53 or #54 or #55	30496
#57	#44 and #56 42	

39 clinical trials (CCTR)
3 reviews (CDSR)

Appendix 3. Clinical Trials.gov Search Strategy

Advanced search, no date limit applied

Condition or disease: sepsis OR septicemia OR bacteremia or septic OR fungemia OR pyohemia OR toxemia OR “blood poisoning” OR “toxic shock” OR “endotoxic shock” OR "critical illness" OR "ICU" OR "critical care" OR "intensive care"

AND

Other terms: probiotic*OR symbiotic* OR Bifidobacterium or bacillus OR enterococcus OR fermented OR gluconacetobacter OR leuconostocaceae OR lactobacillaceae OR lactobacillus OR lactococcus OR leuconostoc OR pediococcus OR saccharomyces OR streptococcus

68 studies

Appendix 4. WHO International Clinical Trials Registry Platform (ICTRP) Search Strategy

Advanced search

Condition: "sepsis" OR "septicemia" OR "bacteremia" OR "septic shock" OR “septic” OR “Fungemia” OR “pyohemia” OR “toxemia” or “blood poisoning” OR “toxic shock” or “endotoxic shock” (without synonyms box unchecked)

AND

Intervention (256 character max): “probiotic*OR symbiotic* OR Bifidobacterium or bacillus OR enterococcus OR fermented OR gluconacetobacter OR leuconostocaceae OR lactobacillaceae OR lactobacillus OR lactococcus OR leuconostoc OR pediococcus OR saccharomyces OR streptococcus” (without synonyms box unchecked)

AND
Recruitment status: “all”

Phases: “all”

62 records for 51 studies

Appendix 5. LILACS Search Strategy

Advanced search

Title, abstract, subject: sepsis OR septicemia OR bacteremia or septic OR fungemia OR pyohemia OR toxemia OR “blood poisoning” OR “toxic shock” OR “endotoxic shock” OR "critical illness" OR "ICU" OR "critical care" OR "intensive care"

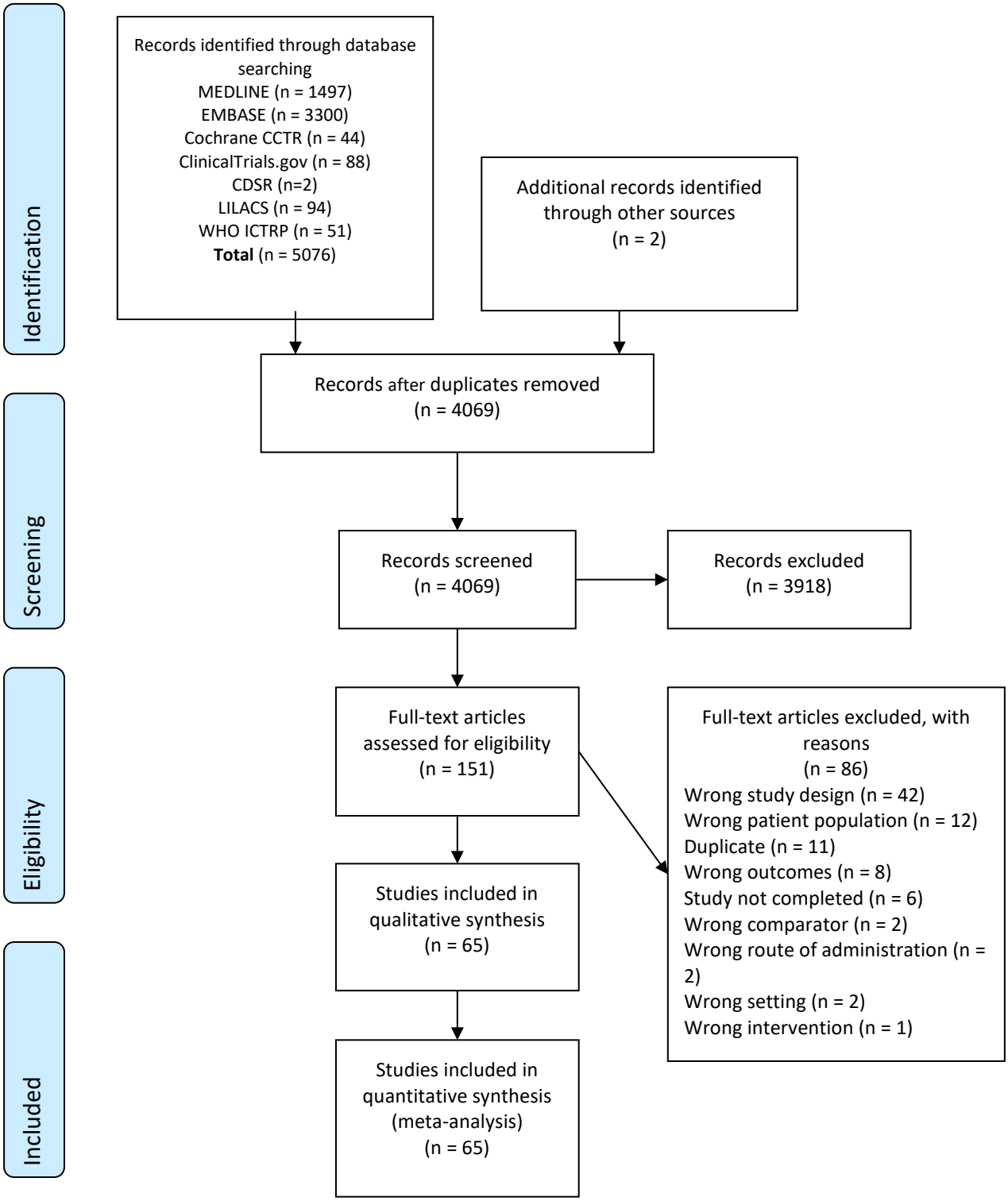
AND

Title, abstract, subject: probiotic OR probiotics OR synbiotic OR synbiotics OR Bifidobacterium or bacillus OR enterococcus OR fermented OR gluconacetobacter OR inulin OR leuconostocaceae OR lactobacillaceae OR lactobacillus OR lactococcus OR leuconostoc OR oenococcus OR pediococcus OR polyphenols OR saccharomyces OR streptococcus

Filtered to controlled clinical trial and all databases other than Medline

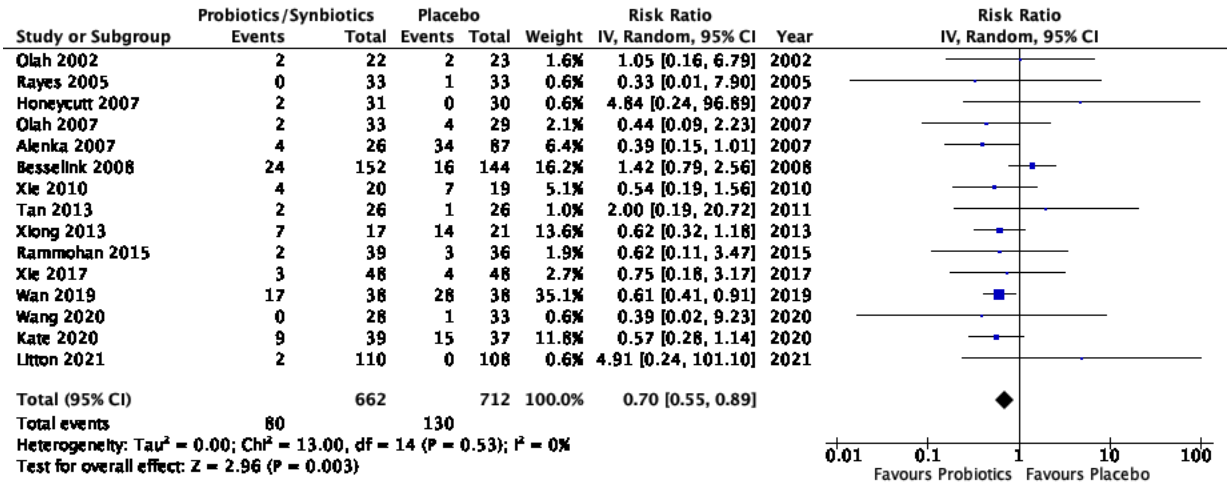
93 studies

Appendix 6. Supplement Figure 1. Study Flow Chart.

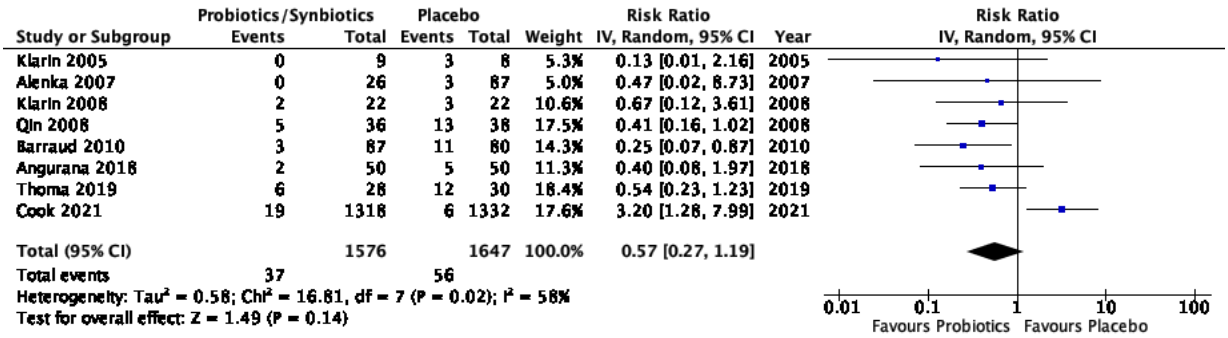


Appendix 7. Forest Plots for All Outcomes, Including Subgroup and Sensitivity Analyses

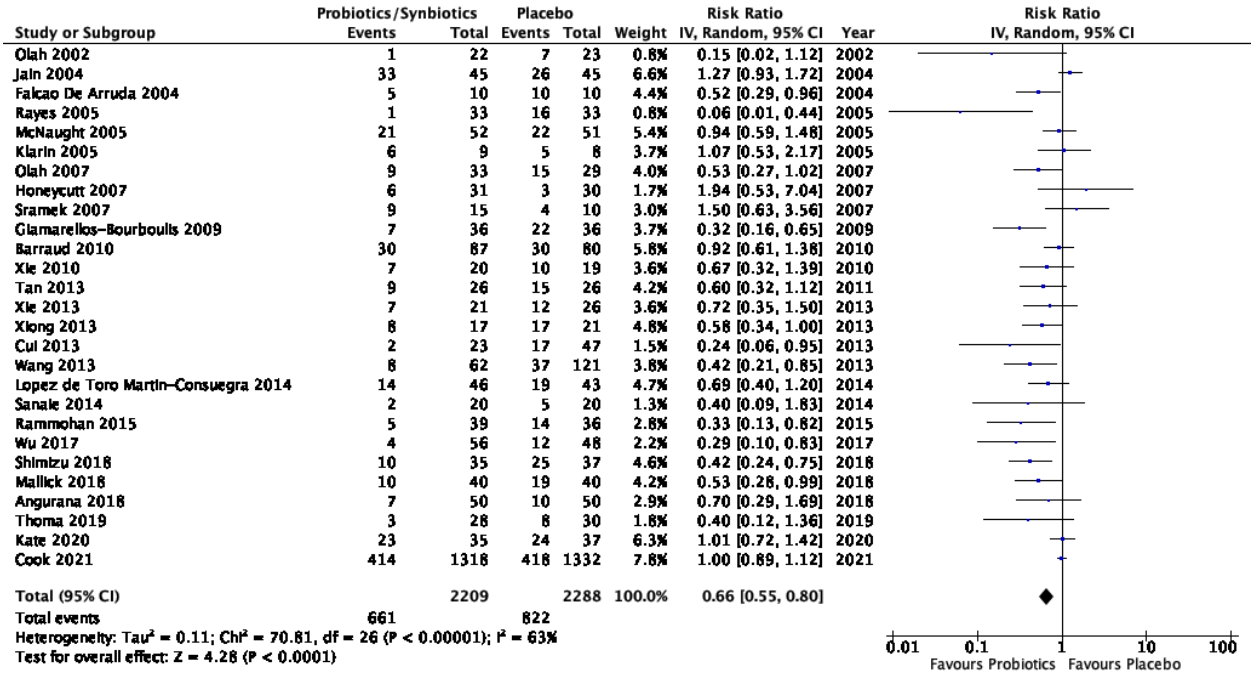
Supplement Figure 2. Forest plot. Healthcare Associated Pneumonia (HAP):
Comparing probiotics/synbiotics and placebo for the outcome of healthcare associated pneumonia; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



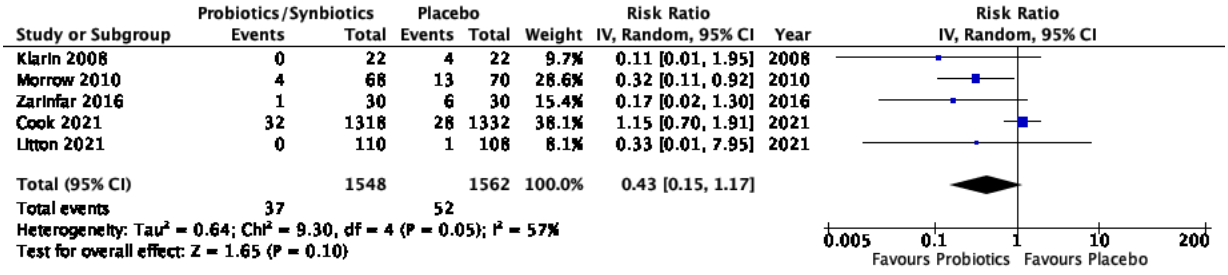
Supplement Figure 3. Forest plot. Catheter related bloodstream infections (CRBSI):
Comparing probiotics/synbiotics and placebo for the outcome of catheter related bloodstream infections; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



Supplement Figure 4. Forest plot. Other Healthcare Associated Infections:
Comparing probiotics/synbiotics and placebo for the outcome of other healthcare associated infections; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



Supplement Figure 5. Forest plot. *Clostridium difficile* Infection:
Comparing probiotics/synbiotics and placebo for the outcome of *Clostridium difficile* infection; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

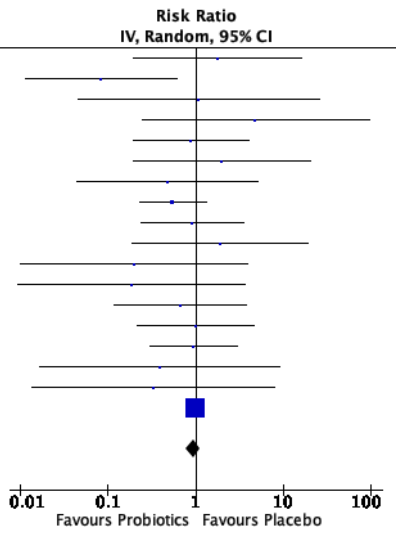


Supplement Figure 6. Forest plot. Urinary Tract Infection:

Comparing probiotics/synbiotics and placebo for the outcome of Urinary Tract Infection; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

Study or Subgroup	Probiotics/Synbiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Klarin 2005	2	9	1	8	0.7%	1.78 [0.20, 16.10]	2005
Rayes 2005	1	33	12	33	0.8%	0.08 [0.01, 0.60]	2005
Alenka 2007	0	26	1	87	0.3%	1.09 [0.05, 25.90]	2007
Honeycutt 2007	2	31	0	30	0.4%	4.84 [0.24, 96.89]	2007
Olah 2007	3	33	3	29	1.4%	0.88 [0.19, 4.02]	2007
Klarin 2008	2	22	1	22	0.6%	2.00 [0.20, 20.49]	2008
Besselink 2008	1	152	2	144	0.6%	0.47 [0.04, 5.17]	2008
Giamarellos-Bourboulis 2009	6	36	11	36	4.1%	0.55 [0.23, 1.32]	2009
Barraud 2010	4	87	4	80	1.8%	0.92 [0.24, 3.56]	2010
Xie 2010	2	20	1	19	0.6%	1.90 [0.19, 19.27]	2010
Tan 2013	0	26	2	26	0.4%	0.20 [0.01, 3.97]	2011
Rammohan 2015	0	39	2	36	0.4%	0.18 [0.01, 3.73]	2015
Angurana 2018	2	50	3	50	1.1%	0.67 [0.12, 3.82]	2018
Mallick 2018	3	40	3	40	1.4%	1.00 [0.21, 4.66]	2018
Kate 2020	5	39	5	37	2.4%	0.95 [0.30, 3.01]	2020
Wang 2020	0	28	1	33	0.3%	0.39 [0.02, 9.23]	2020
Litton 2021	0	110	1	108	0.3%	0.33 [0.01, 7.95]	2021
Cook 2021	171	1318	174	1332	82.7%	0.99 [0.82, 1.21]	2021
Total (95% CI)		2099		2150	100.0%	0.94 [0.78, 1.12]	
Total events	204		227				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 13.10$, df = 17 (P = 0.73); $I^2 = 0\%$
Test for overall effect: Z = 0.71 (P = 0.48)

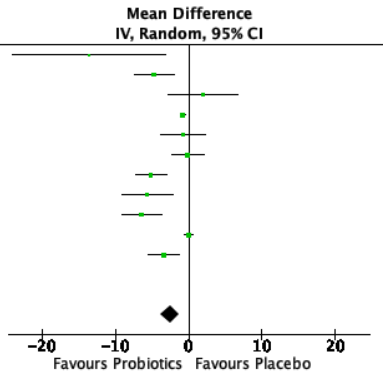


Supplement Figure 7. Forest plot. Duration of Invasive Mechanical Ventilation:

Comparing probiotics/synbiotics and placebo for the outcome of duration of Invasive Mechanical Ventilation; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

Study or Subgroup	Probiotics/Synbiotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Falcao De Arruda 2004	7.5	4.5	10	21	16.2	10	1.3%	−13.50 [−23.92, −3.08]	2004
Klarin 2008	4.3	4.1	22	9	5.1	22	8.7%	−4.70 [−7.43, −1.97]	2008
Forestier 2008	28.8	17.8	102	26.8	17.3	106	4.6%	2.00 [−2.77, 6.77]	2008
Knight 2009	5.2	1.4	130	6	1.5	129	15.4%	−0.80 [−1.15, −0.45]	2009
Frohmader 2010	6	5.2	20	6.7	5.2	25	7.9%	−0.70 [−3.76, 2.36]	2010
Morrow 2010	9.5	6.3	68	9.6	7.2	70	10.2%	−0.10 [−2.36, 2.16]	2010
Banupriya 2015	5.24	3.24	75	10.35	8.71	75	10.6%	−5.11 [−7.21, −3.01]	2015
Malik 2016	8.4	3.5	24	14	8	25	7.0%	−5.60 [−9.03, −2.17]	2016
Zeng 2016	13.1	9.8	118	19.5	11.3	117	8.8%	−6.40 [−9.11, −3.69]	2016
Angurana 2018	7	1.48	50	7	1.48	50	15.1%	0.00 [−0.58, 0.58]	2018
Madmoodpoor 2019	8.75	4.8	56	12.1	7.1	64	10.5%	−3.35 [−5.50, −1.20]	2019
Litton 2021	0.33	0.75	110	0	0	108		Not estimable	2021
Total (95% CI)			785			801	100.0%	−2.53 [−3.74, −1.31]	

Heterogeneity: $Tau^2 = 2.47$; $Chi^2 = 67.89$, df = 10 (P < 0.00001); $I^2 = 85\%$
Test for overall effect: Z = 4.07 (P < 0.0001)

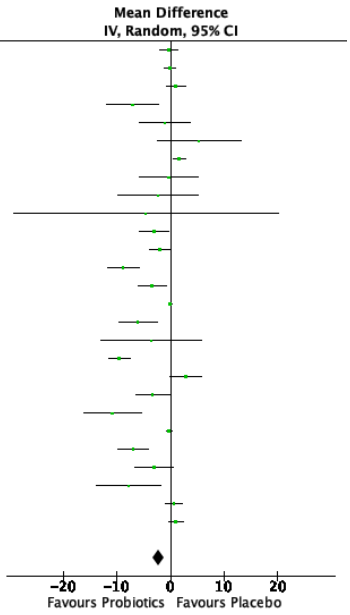


Supplement Figure 8. Forest plot. Hospital Length of Stay:

Comparing probiotics/synbiotics and placebo for the outcome of Hospital Length of Stay; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

Study or Subgroup	Probiotics/Synbiotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Jain 2004	16.2	3.9	45	16.5	4.5	45	5.0%	−0.30 [−2.04, 1.44]	2004
Rayes 2005	27.8	2.4	33	27.9	2.1	33	5.5%	−0.10 [−1.19, 0.99]	2005
McNaught 2005	5.35	5.34	52	4.35	3.81	51	5.0%	1.00 [−0.79, 2.79]	2005
Li 2007	42	5	14	49	6.8	11	2.6%	−7.00 [−11.80, −2.20]	2007
Forestier 2008	29.5	16.9	102	30.5	17.6	106	2.7%	−1.00 [−5.69, 3.69]	2008
Besselink 2008	28.9	41.5	152	23.5	25.9	144	1.3%	5.40 [−2.44, 13.24]	2008
Knight 2009	20.5	5.4	130	18.8	4.8	129	5.4%	1.70 [0.46, 2.94]	2009
Morrow 2010	21.4	14.9	68	21.7	17.4	70	2.3%	−0.30 [−5.70, 5.10]	2010
Barraud 2010	26.6	22.3	87	28.9	26.4	80	1.4%	−2.30 [−9.74, 5.14]	2010
Ferrie 2011	54.5	31.26	13	59.04	33.92	14	0.2%	−4.54 [−29.13, 20.05]	2011
Zhang 2012	42	5	33	45	6.1	33	4.2%	−3.00 [−5.69, −0.31]	2012
Zhuang 2012	13.17	3.79	42	15.18	4.39	38	5.0%	−2.01 [−3.82, −0.20]	2012
Cui 2013	10.4	3.9	23	19.2	8.5	47	4.0%	−8.80 [−11.71, −5.89]	2013
Lopez de Toro Martin-Consuegra 2014	20.8	5.9	46	24.2	6.4	43	4.3%	−3.40 [−5.96, −0.84]	2014
Mayes 2014	1.04	0.03	10	1.02	0.64	10	5.8%	0.02 [−0.38, 0.42]	2014
Banupriya 2015	13.13	7.71	75	19.17	13.51	75	3.5%	−6.04 [−9.56, −2.52]	2015
Rongrungruang 2015	24.6	21.7	75	28.2	35.1	75	1.0%	−3.60 [−12.94, 5.74]	2015
Rammohan 2015	8.4	2.9	39	17.9	5.2	36	4.9%	−9.50 [−11.43, −7.57]	2015
Zeng 2016	13.5	12.4	118	10.6	10.2	117	4.0%	2.90 [−0.00, 5.80]	2016
Zarinfar 2016	24.1	5.6	30	27.4	6.6	30	3.8%	−3.30 [−6.40, −0.20]	2016
Wu 2017	29.7	12.3	58	40.5	15.7	51	2.3%	−10.80 [−16.15, −5.45]	2017
Mallick 2018	18.7	1.2	40	18.9	1.2	40	5.8%	−0.20 [−0.73, 0.33]	2018
Madmoodpoor 2019	14.2	8.6	48	21.1	5.7	54	4.0%	−6.90 [−9.77, −4.03]	2019
Wang 2020	16.7	4.7	28	19.7	9.3	33	3.4%	−3.00 [−6.62, 0.62]	2020
Kate 2020	11.7	9.3	35	19.5	15.8	37	2.0%	−7.80 [−13.75, −1.85]	2020
Cook 2021	25.7	21.5	1318	25	20	1332	5.2%	0.70 [−0.88, 2.28]	2021
Litton 2021	10	5.26	110	9	5.26	108	5.3%	1.00 [−0.40, 2.40]	2021
Total (95% CI)			2824			2842	100.0%	−2.21 [−3.24, −1.18]	

Heterogeneity: Tau² = 4.71; Chi² = 224.42, df = 26 (P < 0.00001); I² = 88%
Test for overall effect: Z = 4.20 (P < 0.0001)

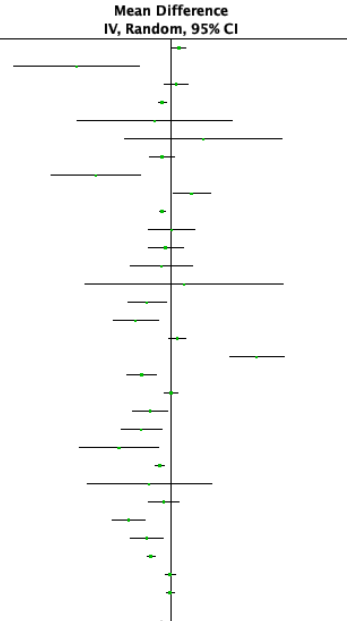


Supplement Figure 9. Forest plot. ICU Length of Stay:

Comparing probiotics/synbiotics and placebo for the outcome of ICU Length of Stay; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

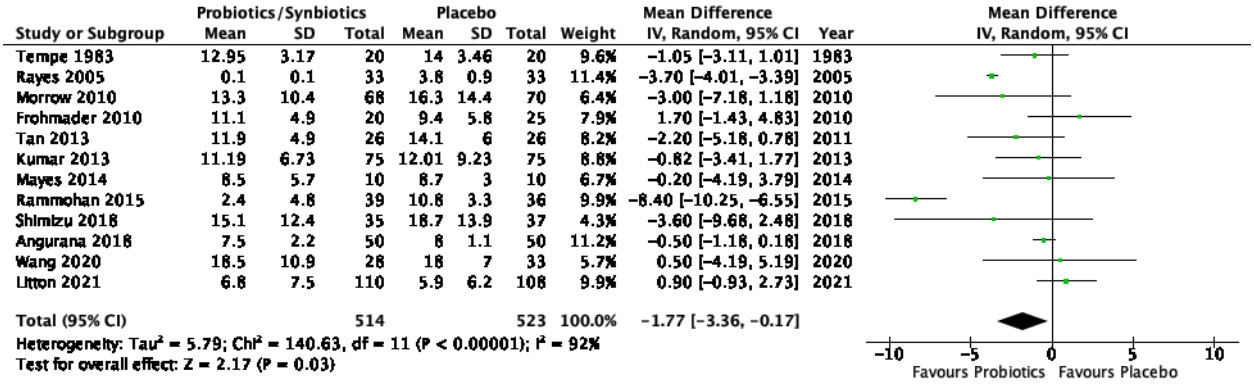
Study or Subgroup	Probiotics/Synbiotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Jain 2004	8.2	3	45	6.8	2.5	45	5.2%	1.40 [0.26, 2.54]	2004
Falcao De Arruda 2004	11.25	4.8	10	27	16.2	10	0.5%	−15.75 [−26.22, −5.28]	2004
McNaught 2005	5.3	5.3	52	4.3	5	51	4.3%	1.00 [−0.99, 2.99]	2005
Rayes 2005	8.8	0.9	33	10.2	1.8	33	5.6%	−1.40 [−2.09, −0.71]	2005
Klarin 2005	16.2	11	9	18.8	15.7	8	0.4%	−2.60 [−15.64, 10.44]	2005
Sramek 2007	16.2	18	15	10.7	15.5	10	0.4%	5.50 [−7.74, 18.74]	2007
Alenka 2007	13.4	3.7	26	14.8	4.2	26	4.1%	−1.40 [−3.55, 0.75]	2007
Klarin 2008	8.9	5.1	22	21.4	17.2	22	1.0%	−12.50 [−20.00, −5.00]	2008
Besselink 2008	6.6	17.1	152	3	9.3	144	3.1%	3.60 [0.49, 6.71]	2008
Knight 2009	6.5	1.5	130	7.8	2.1	129	5.7%	−1.30 [−1.74, −0.86]	2009
Morrow 2010	14.8	11.8	68	14.6	11.6	70	2.5%	0.20 [−3.71, 4.11]	2010
Frohmader 2010	7.3	5.7	20	8.1	4	25	3.3%	−0.80 [−3.75, 2.15]	2010
Barraud 2010	18.7	12.4	87	20.2	20.8	80	1.7%	−1.50 [−6.75, 3.75]	2010
Ferrie 2011	32.04	24.46	13	29.75	18.81	14	0.2%	2.29 [−14.26, 18.84]	2011
Tan 2013	6.8	3.8	26	10.7	7.3	26	3.1%	−3.90 [−7.06, −0.74]	2011
Xiong 2013	6.38	5.68	17	12.2	6.43	21	2.5%	−5.82 [−9.67, −1.97]	2013
Lopez de Toro Martin-Consuegra 2014	10	3.6	46	8.8	3.2	43	4.9%	1.20 [−0.21, 2.61]	2014
Rongrungruang 2015	33.3	19.6	75	18.8	5.2	75	2.0%	14.50 [9.91, 19.09]	2015
Banupriya 2015	7.7	4.6	75	12.54	9.91	75	3.8%	−4.84 [−7.31, −2.37]	2015
Rammohan 2015	4.3	3.1	39	4.2	2.2	36	5.1%	0.10 [−1.11, 1.31]	2015
Zarinfar 2016	14.2	4.7	30	17.6	6.5	30	3.4%	−3.40 [−6.27, −0.53]	2016
Malik 2016	10.9	3.9	24	15.8	7.8	25	2.8%	−4.90 [−8.33, −1.47]	2016
Zeng 2016	21.5	13.5	118	30.1	33.8	117	1.2%	−8.60 [−15.19, −2.01]	2016
Angurana 2018	7	2	50	8.8	1.4	50	5.6%	−1.80 [−2.48, −1.12]	2018
Shimizu 2018	26.6	23.2	35	30.1	21.6	37	0.6%	−3.50 [−13.87, 6.87]	2018
Mallick 2018	8.1	5.9	40	9.2	5.9	40	3.6%	−1.10 [−3.69, 1.49]	2018
Madmoodpoor 2019	11.6	8	48	18.6	6.3	54	3.4%	−7.00 [−9.82, −4.18]	2019
Wan 2019	10.32	5.31	38	14.24	6.79	38	3.5%	−3.92 [−6.66, −1.18]	2019
Kate 2020	5.58	1.73	35	8.8	1.5	37	5.5%	−3.22 [−3.97, −2.47]	2020
Litton 2021	2.25	3.3	110	2.25	3.3	108	5.4%	0.00 [−0.88, 0.88]	2021
Cook 2021	12.7	8.9	1318	12.7	7.4	1332	5.6%	0.00 [−0.62, 0.62]	2021
Total (95% CI)			2806			2811	100.0%	−1.38 [−2.19, −0.57]	

Heterogeneity: Tau² = 2.93; Chi² = 213.07, df = 30 (P < 0.00001); I² = 86%
Test for overall effect: Z = 3.34 (P = 0.0008)



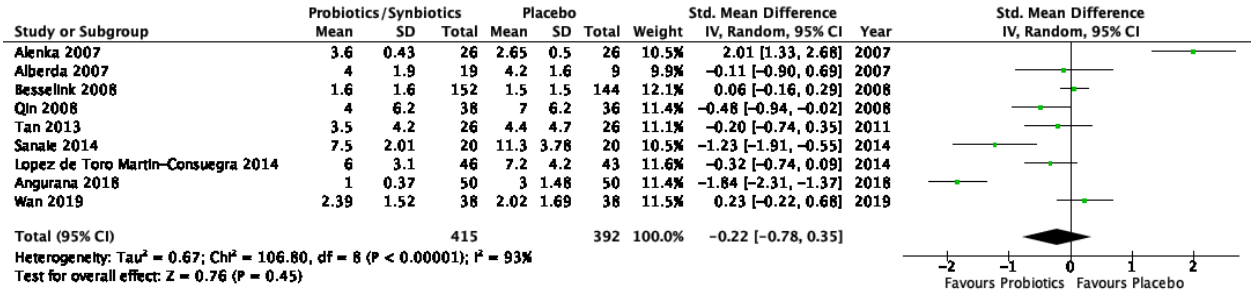
Supplement Figure 10. Forest plot. Antibiotic Duration:

Comparing probiotics/synbiotics and placebo for the outcome of antibiotic duration; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



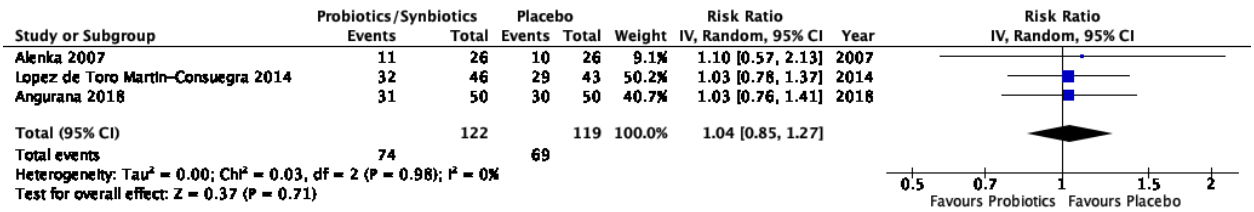
Supplement Figure 11. Forest plot. Organ Dysfunction:

Comparing probiotics/synbiotics and placebo for the outcome of organ dysfunction; results are shown by using the random-effects model with standardized mean difference and 95% confidence intervals (CI)

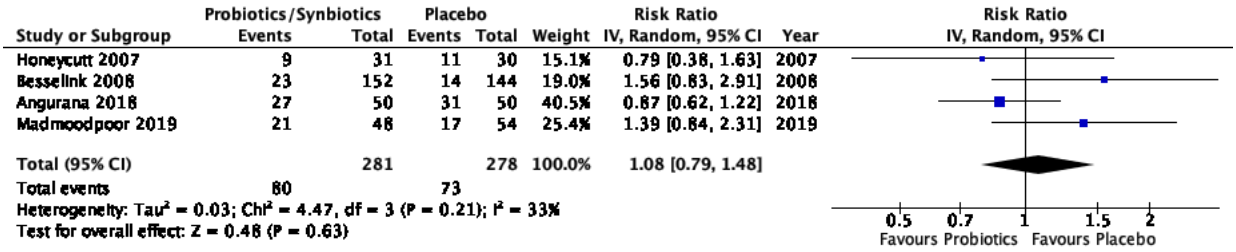


Supplement Figure 12. Forest plot. Incidence of Invasive Mechanical Ventilation:

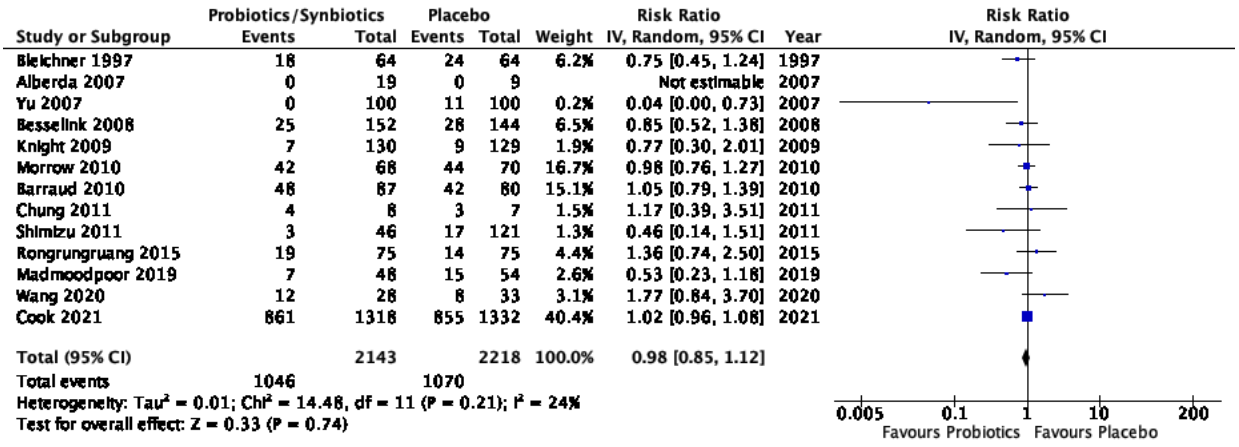
Comparing probiotics/synbiotics and placebo for the outcome of incidence of invasive mechanical ventilation; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



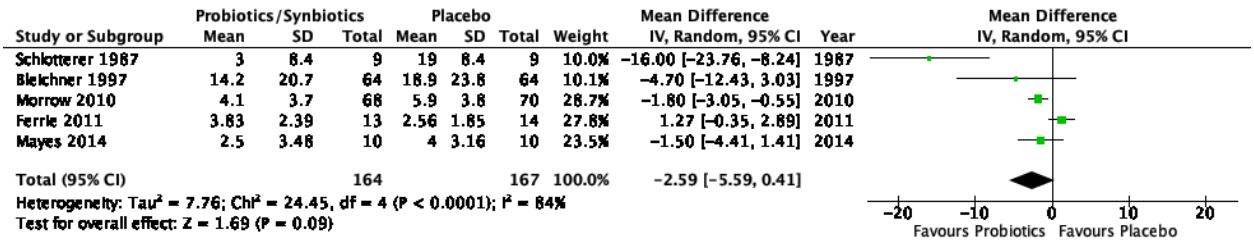
Supplement Figure 13. Forest plot. Receipt of inotropic/vasopressor therapy:
Comparing probiotics/synbiotics and placebo for the outcome of receipt of inotropic/vasopressor therapy; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



Supplement Figure 14. Forest plot. Incidence of diarrhea:
Comparing probiotics/synbiotics and placebo for the outcome of incidence of diarrhea; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

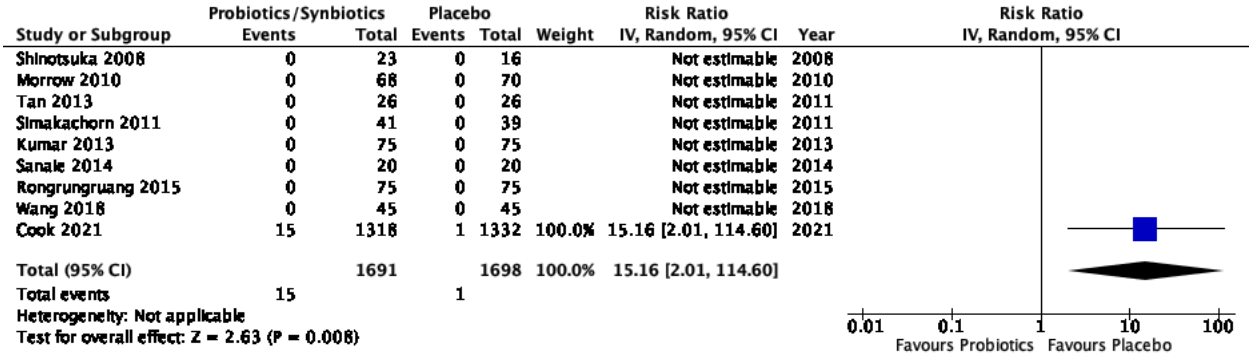


Supplement Figure 15. Forest plot. Duration of diarrhea:
Comparing probiotics/synbiotics and placebo for the outcome of duration diarrhea; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



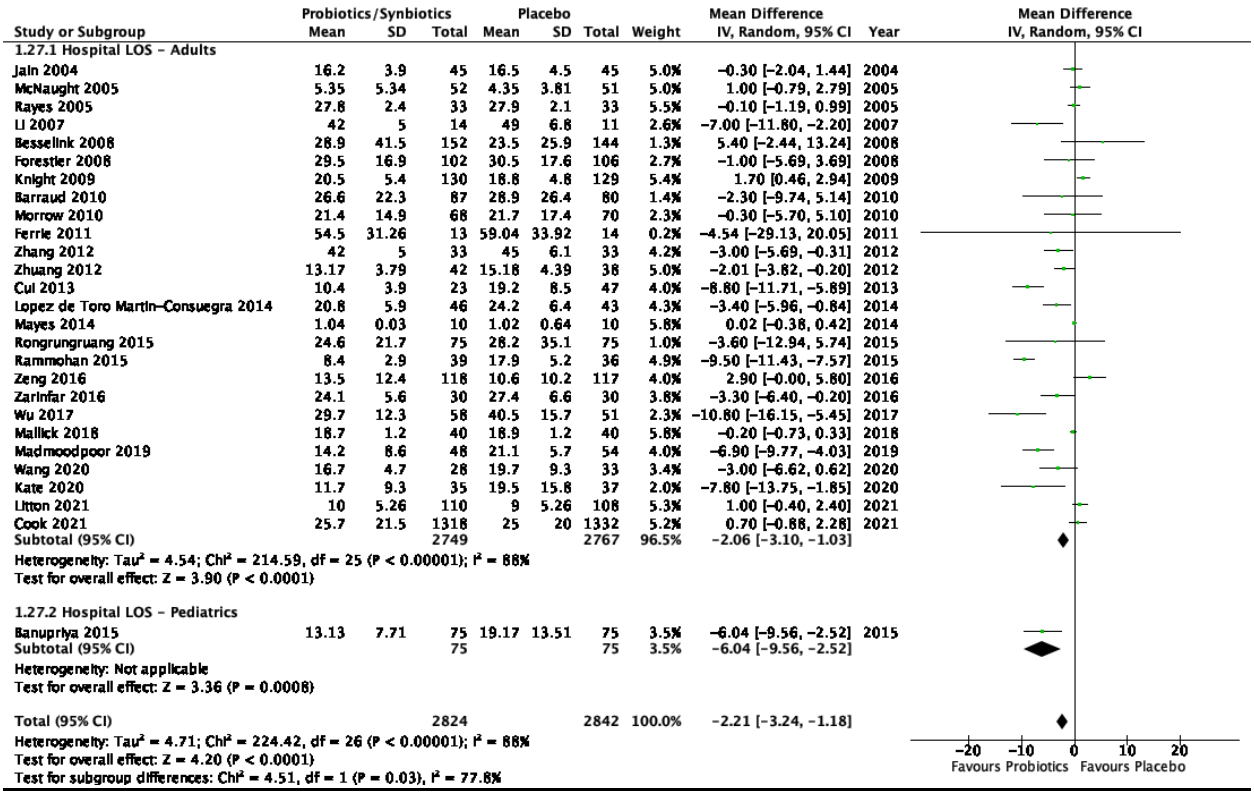
Supplement Figure 16. Forest plot. Invasive Probiotic Organism Isolation from a Sterile Site:

Comparing probiotics/synbiotics and placebo for the outcome of invasive probiotic organism isolation from a sterile site or as the role of predominant organism cultured from a non-sterile site; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

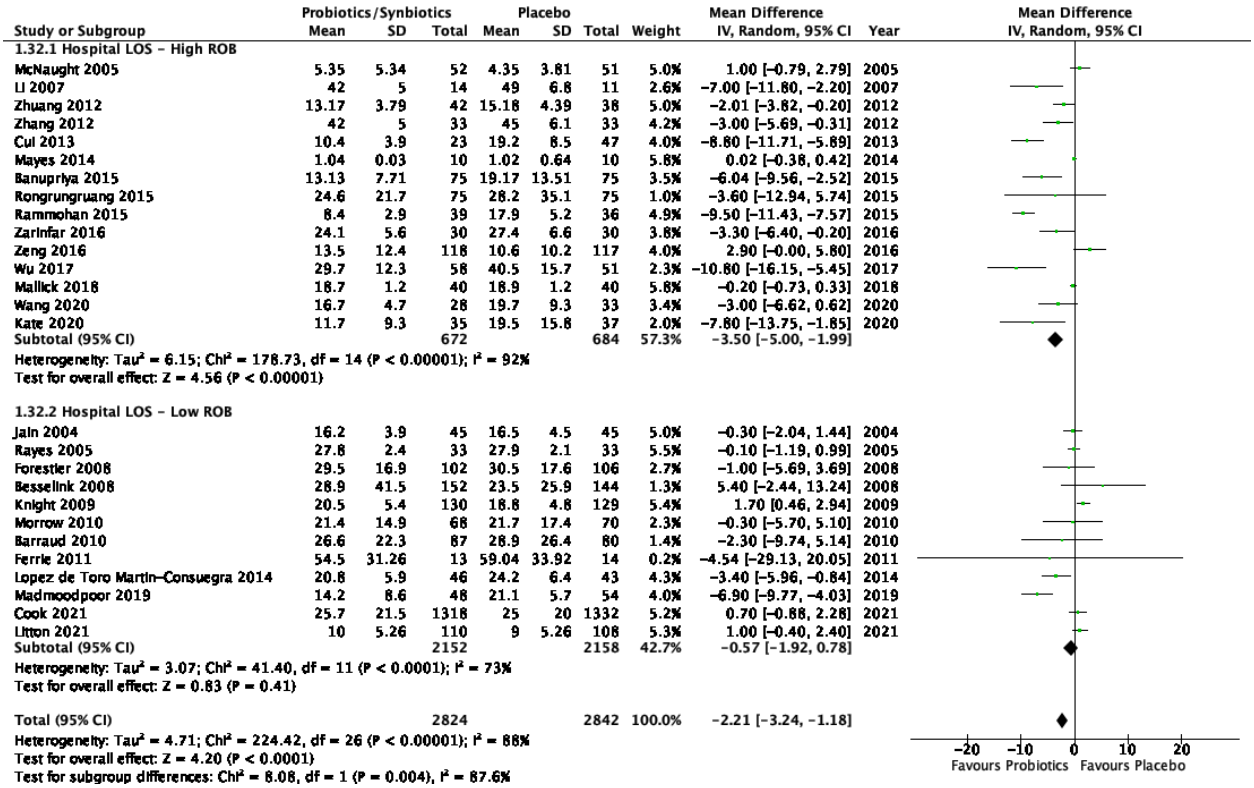


Supplement Figure 17. Forest plot. Hospital Length of Stay (LOS) by Adults vs Pediatrics:

Comparing probiotics/synbiotics and placebo for the outcome of hospital LOS by adults vs pediatrics; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

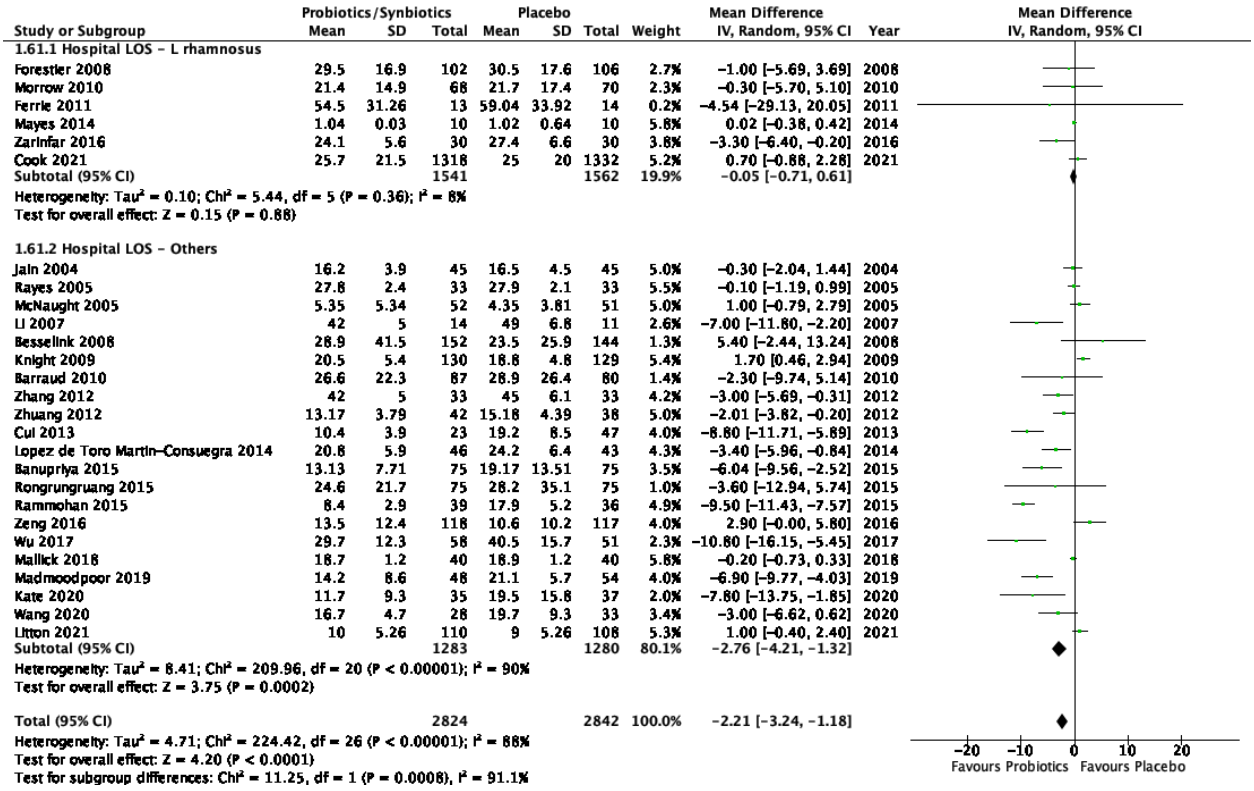


Supplement Figure 18. Forest plot. Hospital Length of Stay (LOS) by Quality of Study: Comparing probiotics/synbiotics and placebo for the outcome of hospital length of stay by quality of study; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



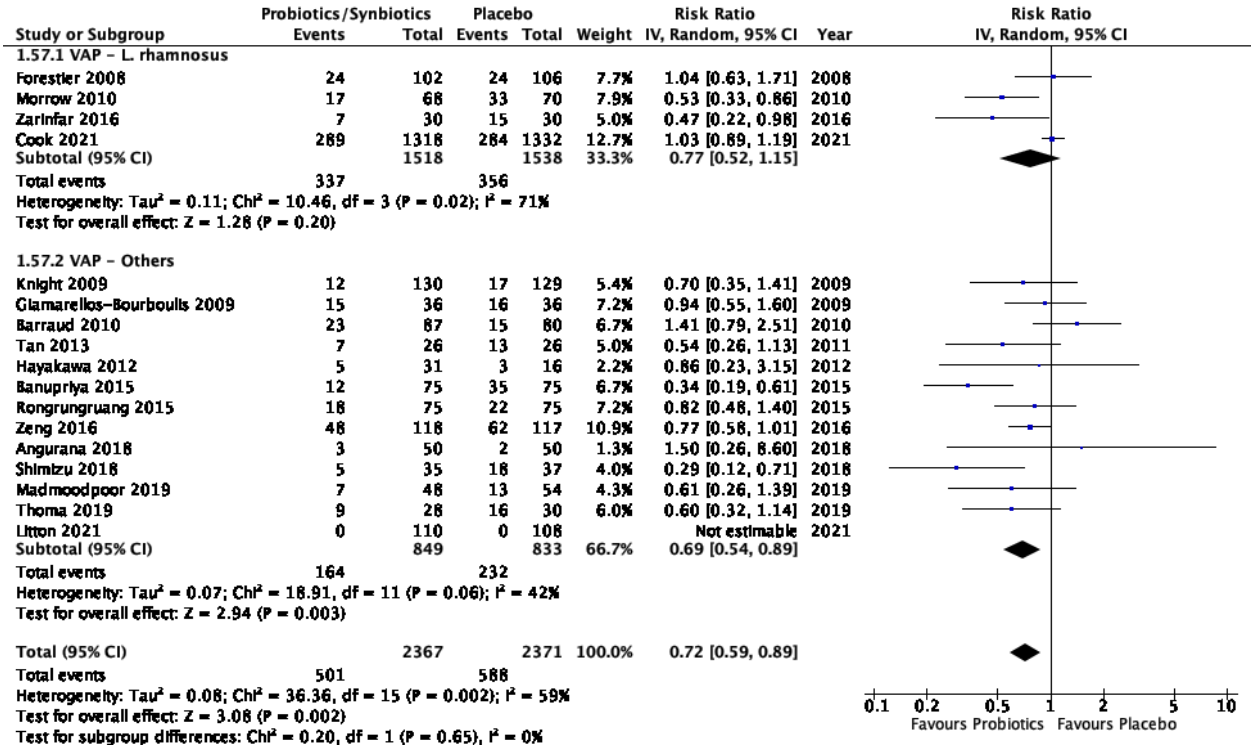
Supplement Figure 19. Forest plot. Hospital Length of Stay (LOS) by strain of Probiotic (*L. rhamnosus*):

Comparing probiotics/synbiotics and placebo for the outcome of hospital length of stay by strain of probiotic (*L. rhamnosus GG* vs all others); results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

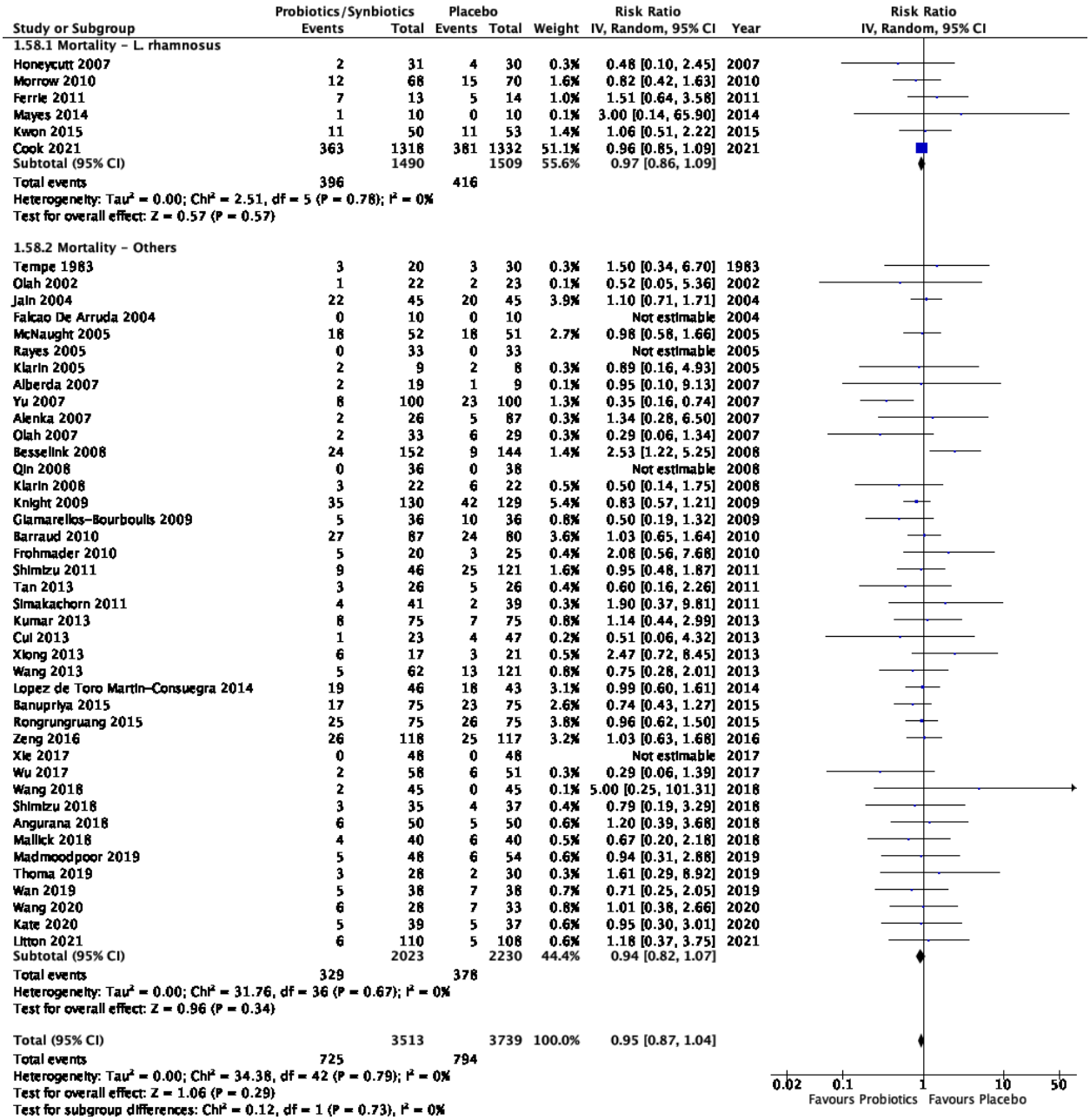


Supplement Figure 20. Forest plot. Ventilator Associated Pneumonia (VAP) by strain of Probiotic (*L. rhamnosus*):

Comparing probiotics/synbiotics and placebo for the outcome of VAP by strain of probiotic (*L. rhamnosus GG* vs all others); results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

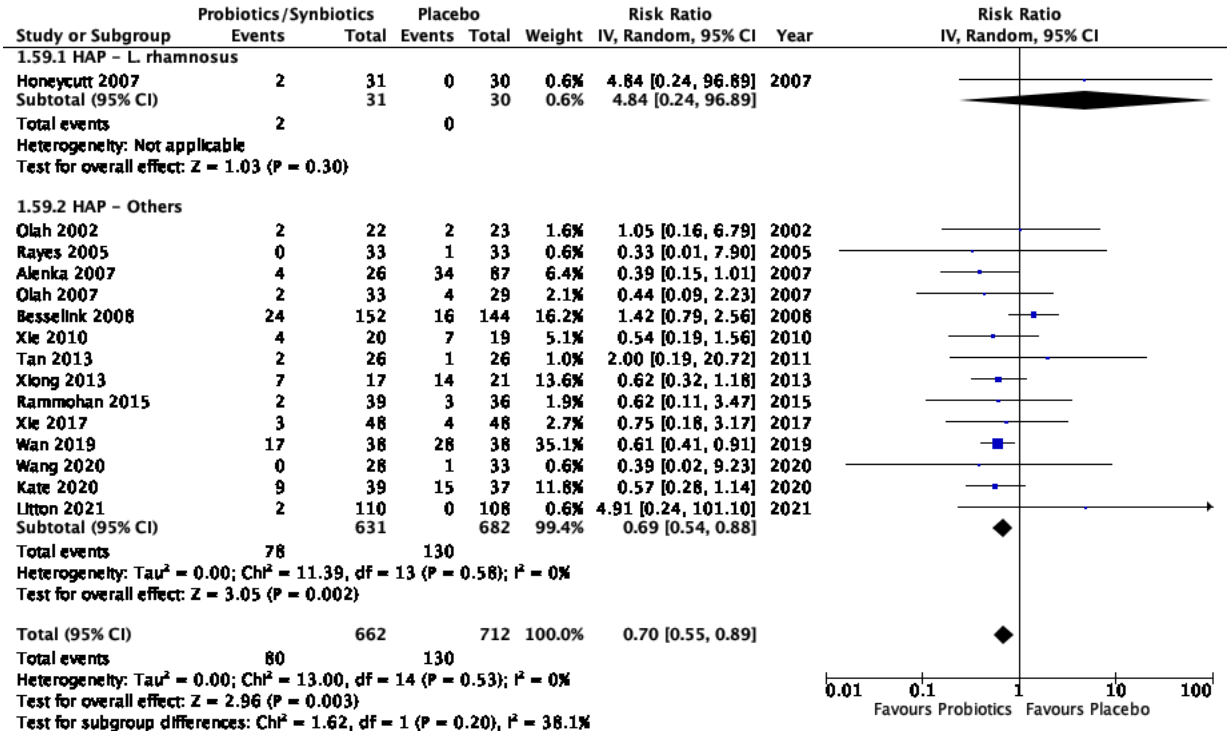


Supplement Figure 21. Forest plot. Mortality by strain of Probiotic (*L. rhamnosus*):
Comparing probiotics/synbiotics and placebo for the outcome of mortality by strain of probiotic (*L. rhamnosus GG* vs all others); results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



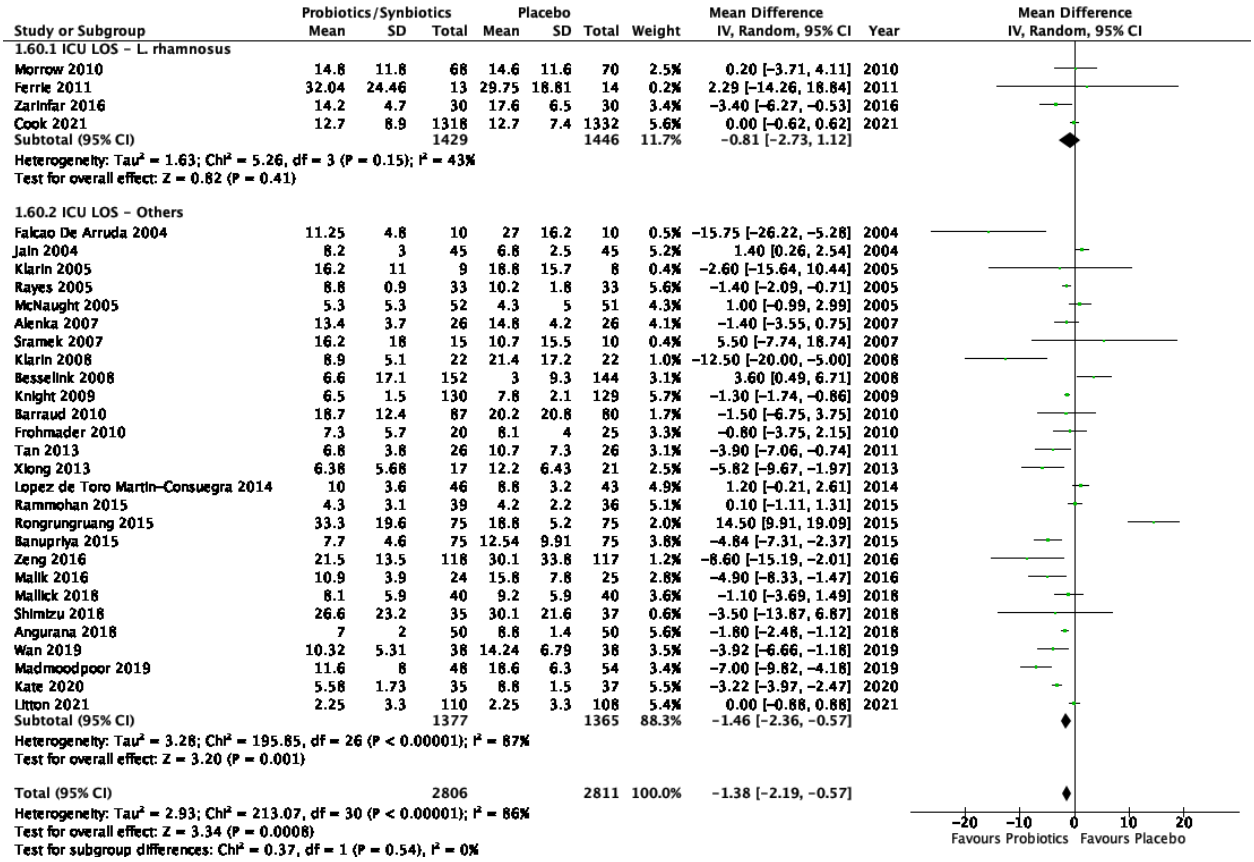
Supplement Figure 22. Forest plot. Healthcare-Associated Pneumonia (HAP) by strain of Probiotic (*L. rhamnosus*):

Comparing probiotics/synbiotics and placebo for the outcome of HAP by strain of probiotic (*L. rhamnosus GG* vs all others); results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



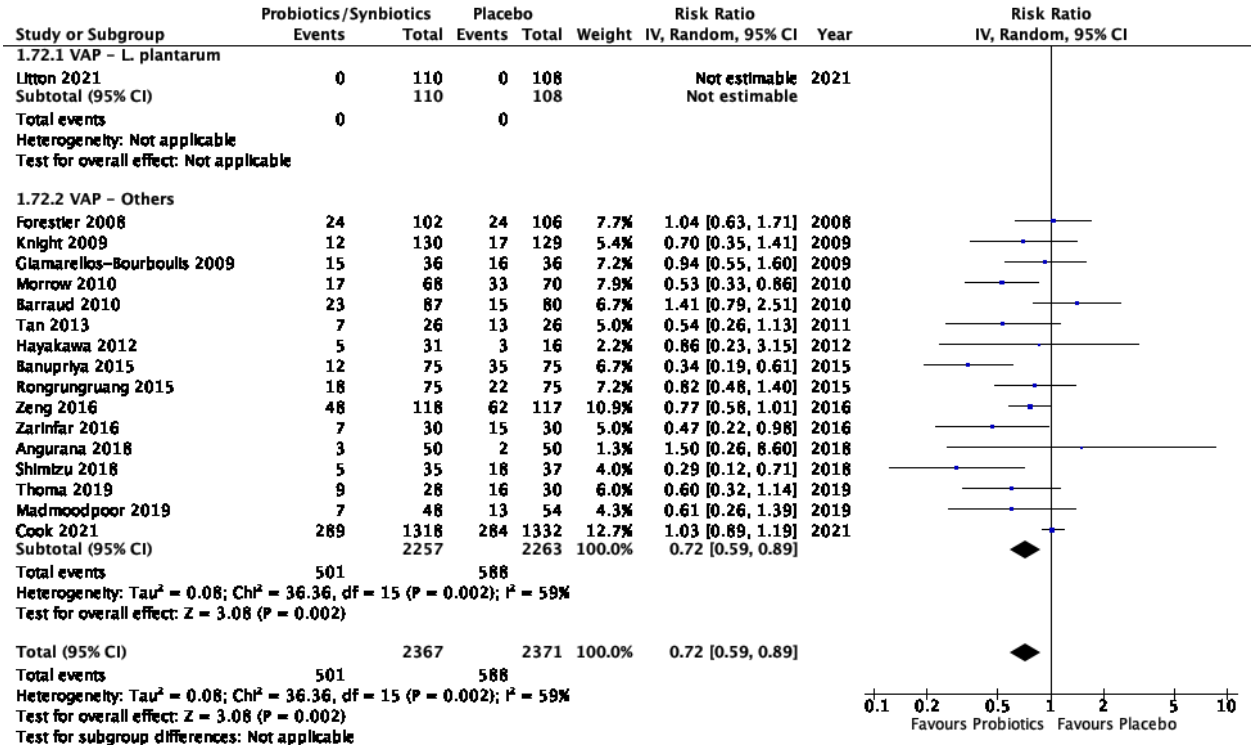
Supplement Figure 23. Forest plot. ICU Length of Stay (LOS) by strain of Probiotic (*L. rhamnosus*):

Comparing probiotics/synbiotics and placebo for the outcome of ICU LOS by strain of probiotic (*L. rhamnosus GG* vs all others); results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

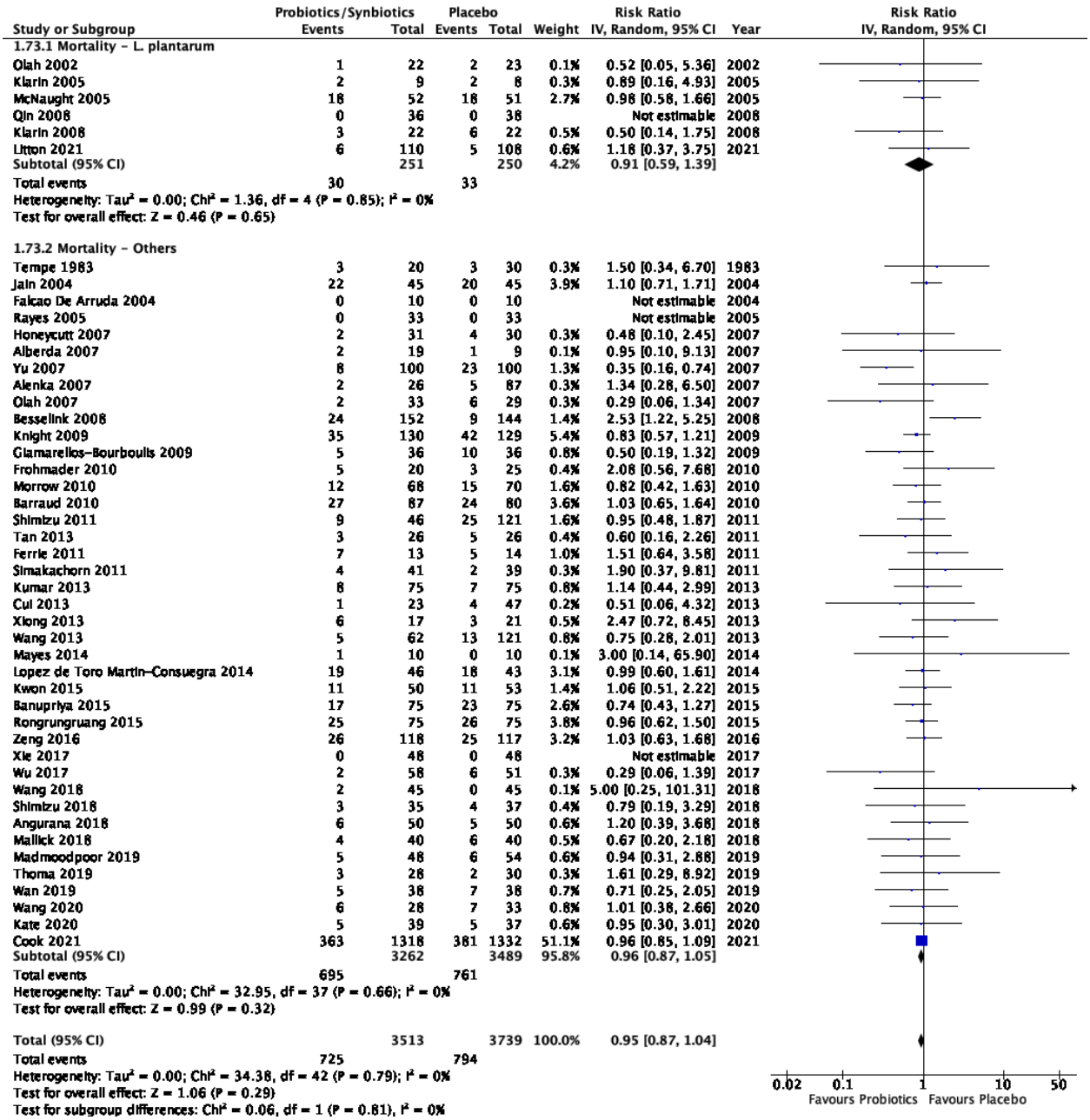


Supplement Figure 24. Forest plot. Ventilator-Associated Pneumonia (VAP) by strain of Probiotic (*L. plantarum*):

Comparing probiotics/synbiotics and placebo for the outcome of VAP by strain of probiotic (*L. plantarum* vs all others); results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

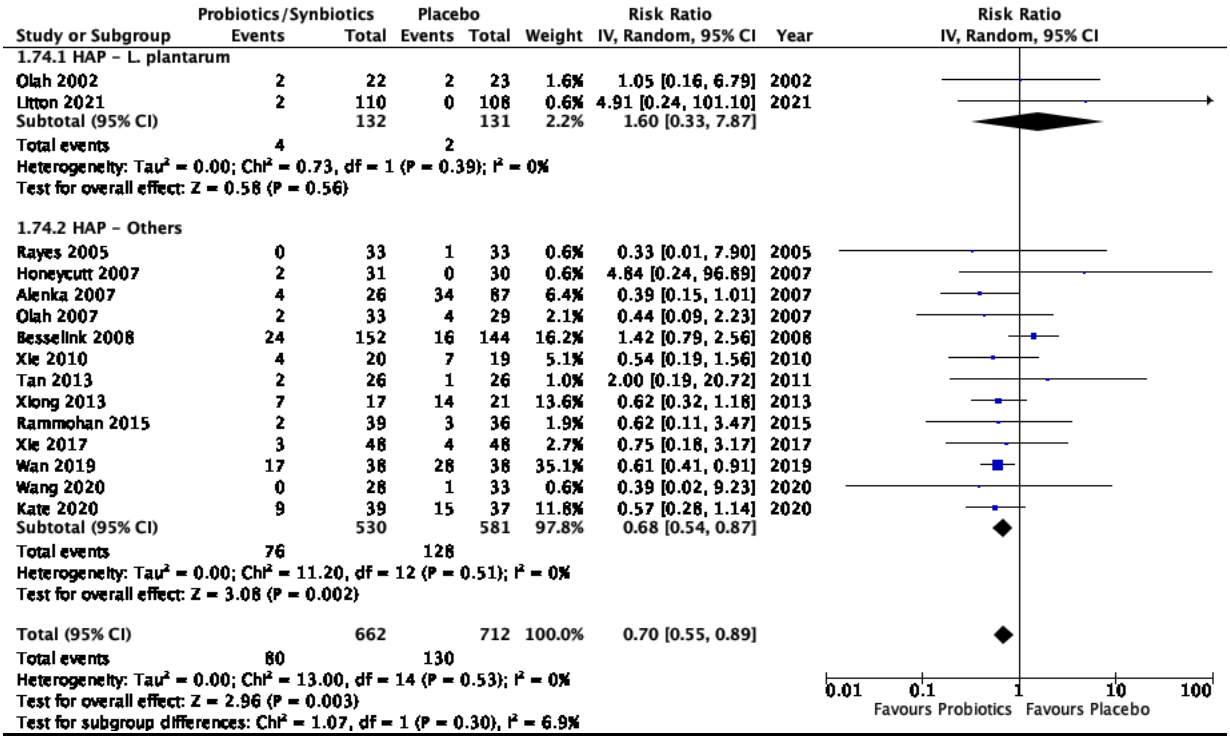


Supplement Figure 25. Forest plot. Mortality by strain of Probiotic (*L. plantarum*): Comparing probiotics/synbiotics and placebo for the outcome of mortality by strain of probiotic (*L. plantarum* vs all others); results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



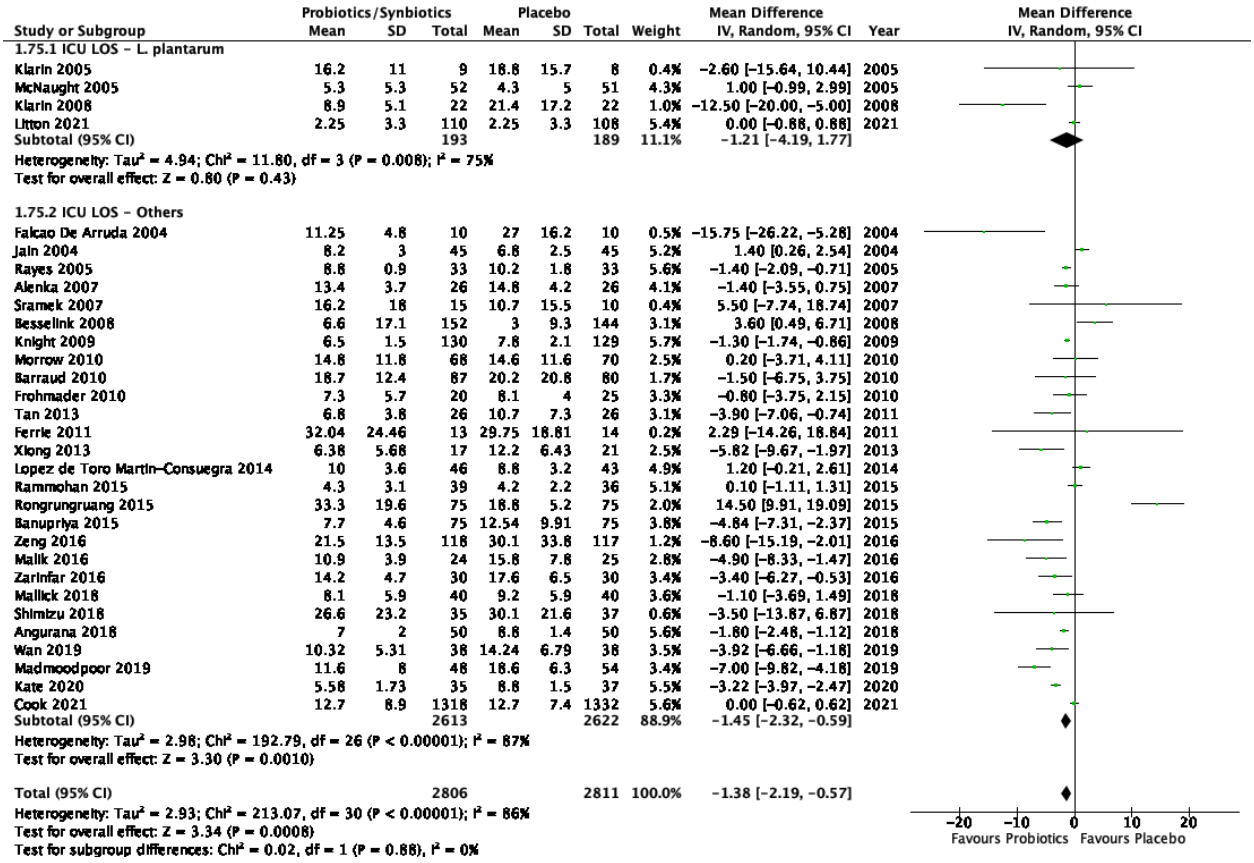
Supplement Figure 26. Forest plot. Healthcare-Associated Pneumonia (HAP) by strain of Probiotic (*L. plantarum*):

Comparing probiotics/synbiotics and placebo for the outcome of HAP by strain of probiotic (*L. plantarum* vs all others); results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



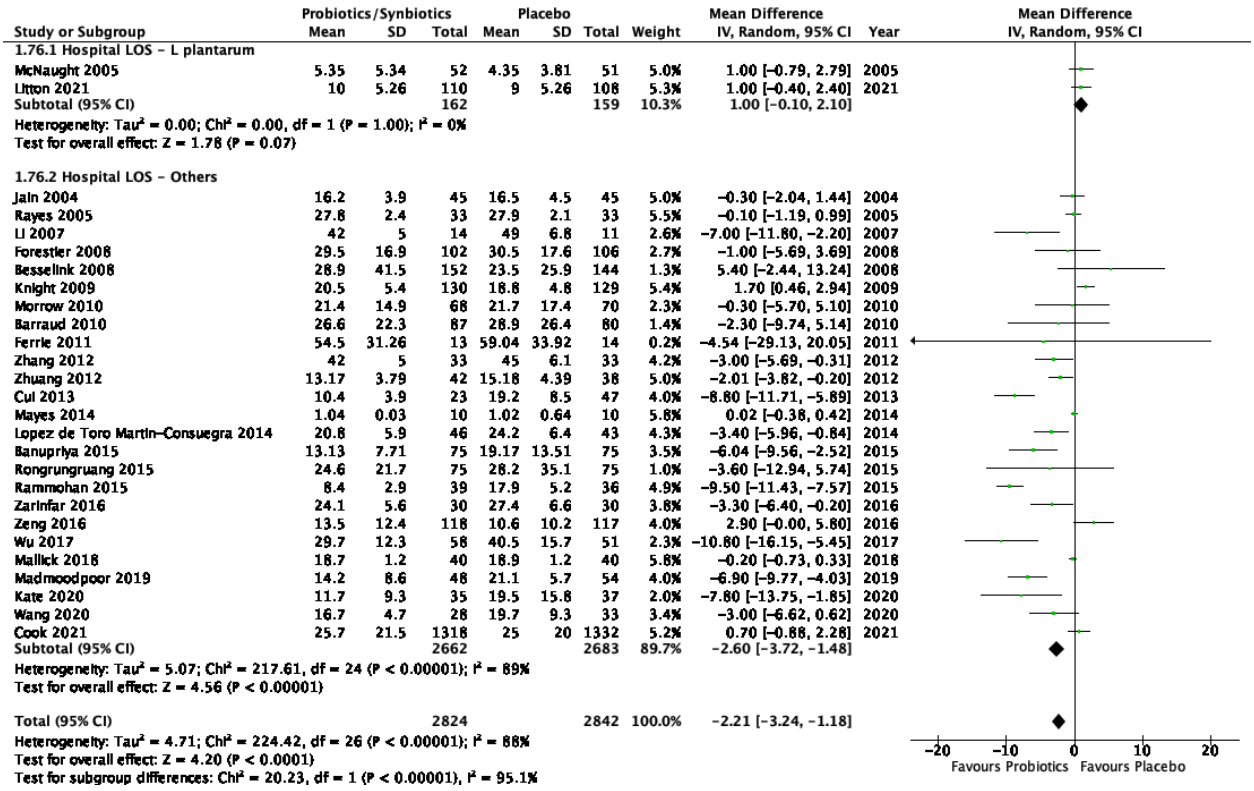
Supplement Figure 27. Forest plot. ICU Length of Stay (LOS) by strain of Probiotic (*L. plantarum*):

Comparing probiotics/synbiotics and placebo for the outcome of ICU LOS by strain of probiotic (*L. plantarum* vs all others); results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



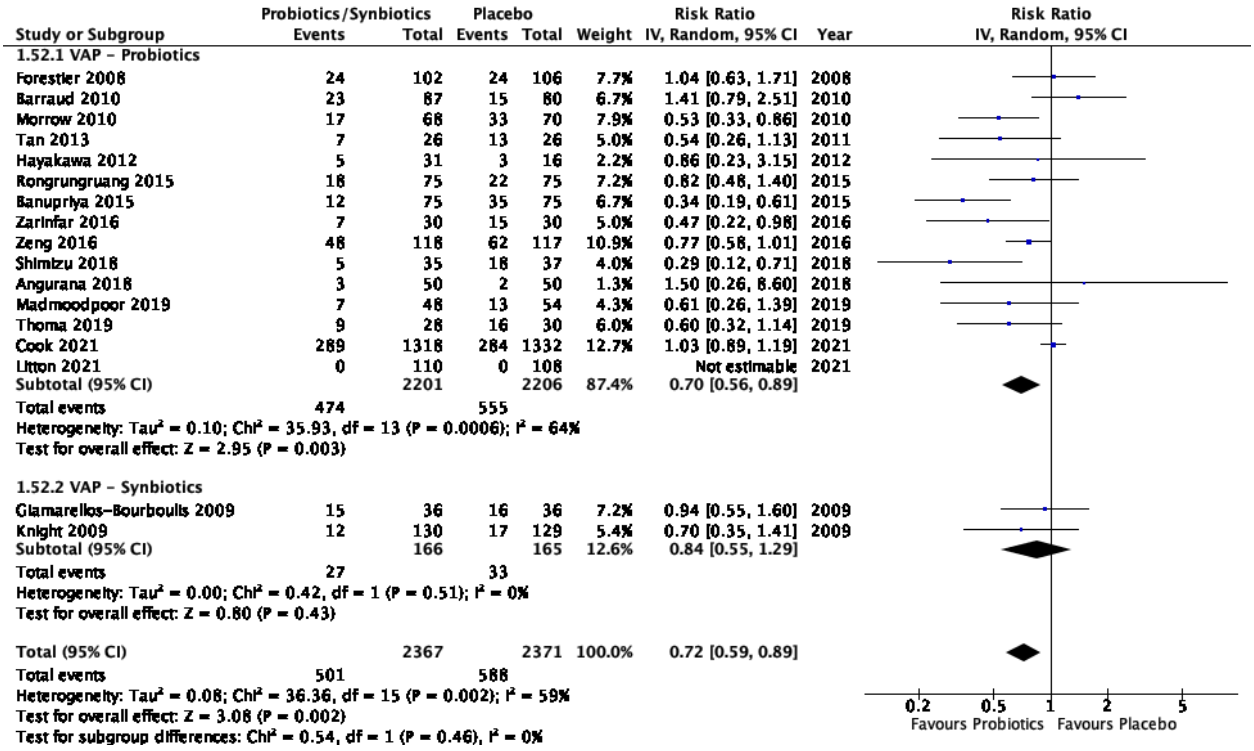
Supplement Figure 28. Forest plot. Hospital Length of Stay (LOS) by strain of Probiotic (*L. plantarum*):

Comparing probiotics/synbiotics and placebo for the outcome of Hospital LOS by strain of probiotic (*L. plantarum* vs all others); results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

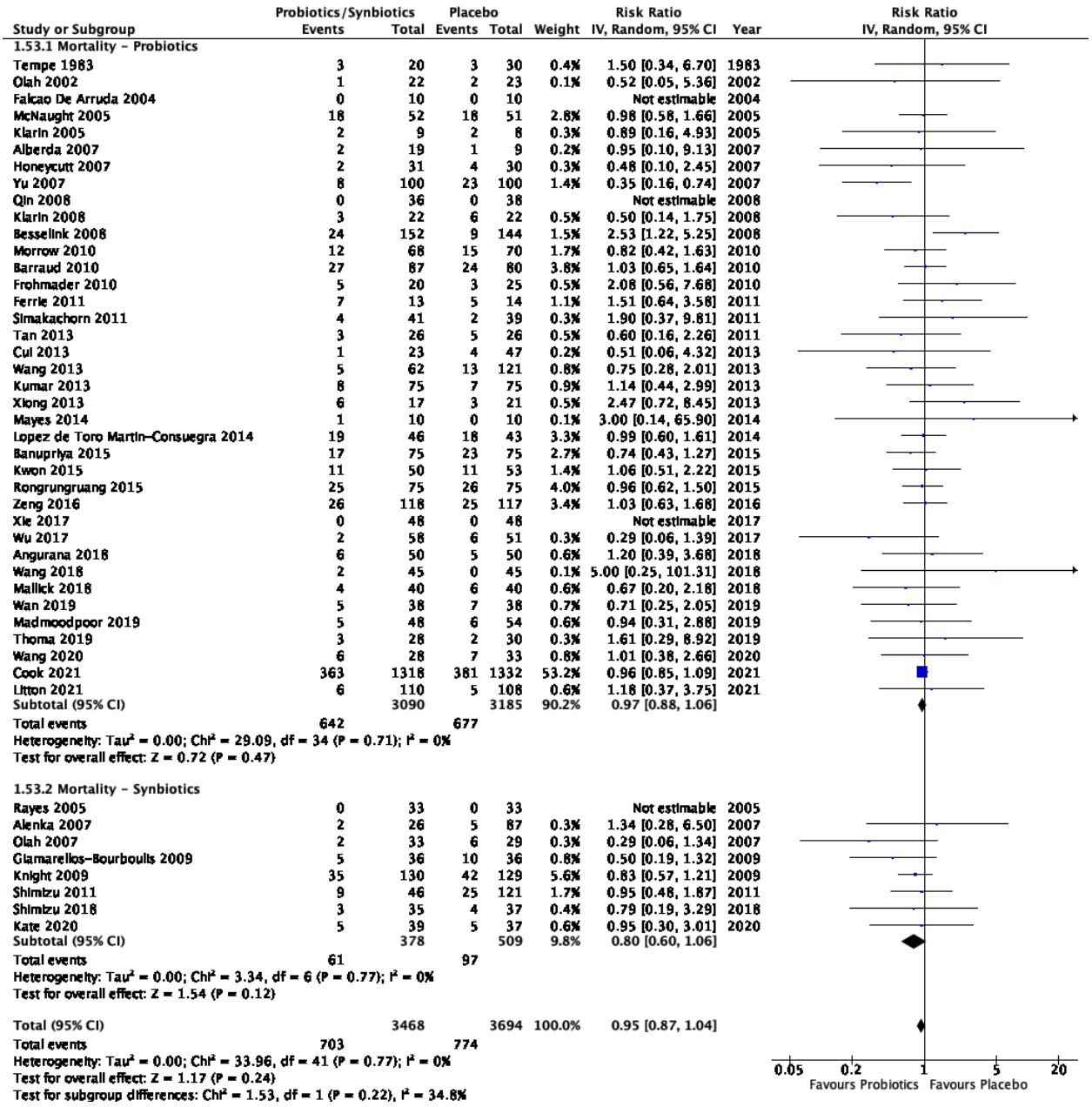


Supplement Figure 29. Forest plot. Ventilator-Associated Pneumonia (VAP) comparing Probiotics and Synbiotics:

Comparing probiotics and synbiotics for the outcome of VAP; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

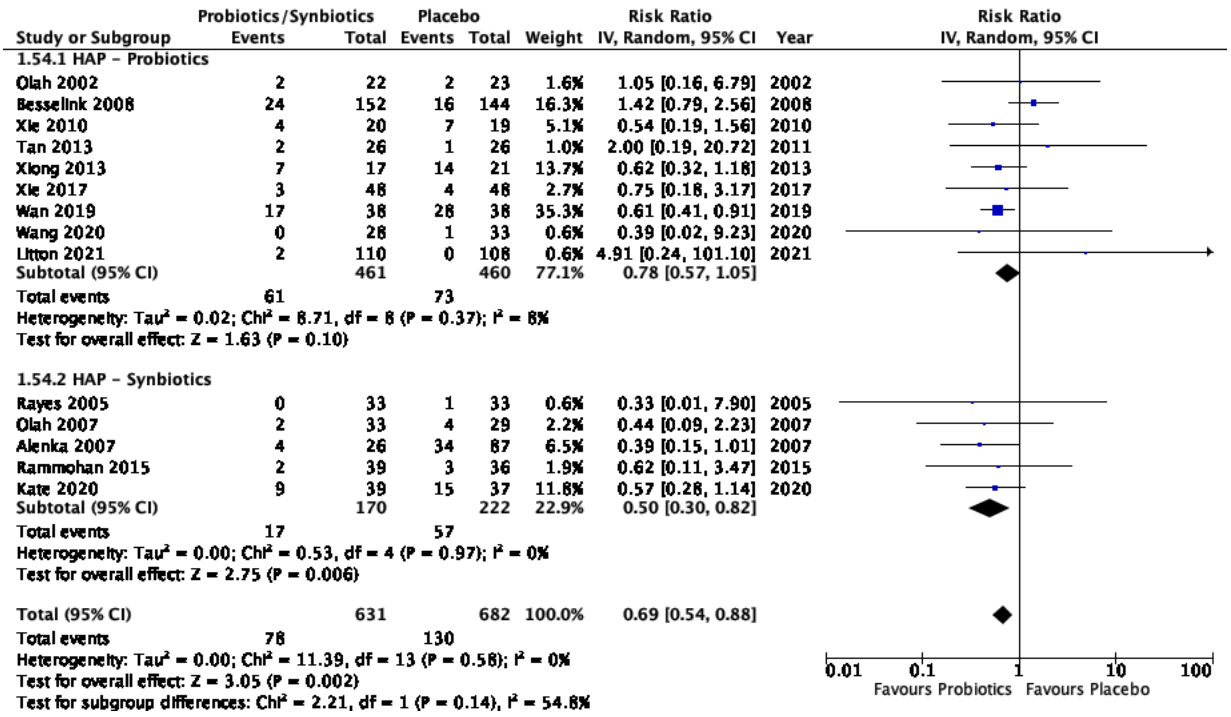


Supplement Figure 30. Forest plot. Mortality comparing Probiotics and Synbiotics: Comparing probiotics and synbiotics for the outcome of mortality; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



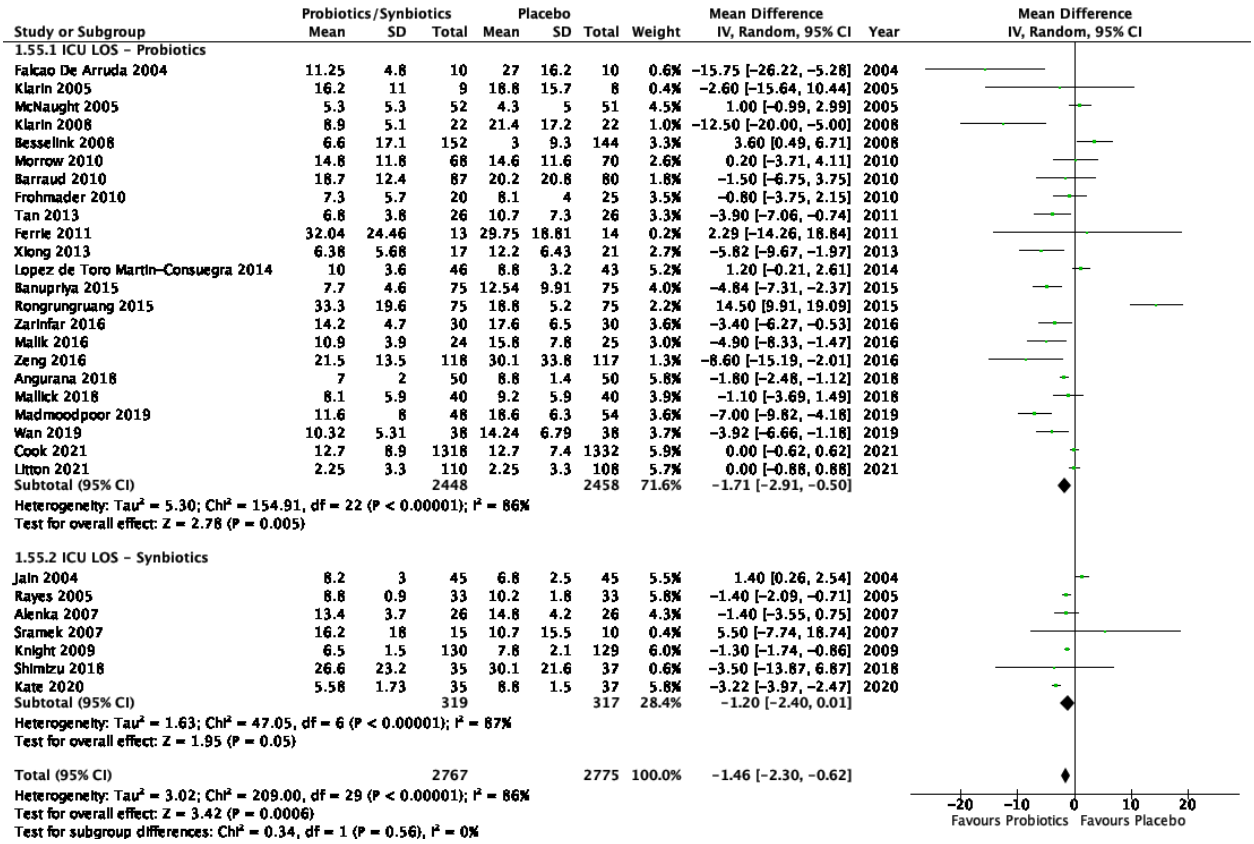
Supplement Figure 31. Forest plot. Healthcare-associated Pneumonia (HAP) comparing Probiotics and Synbiotics:

Comparing probiotics and synbiotics for the outcome of HAP; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



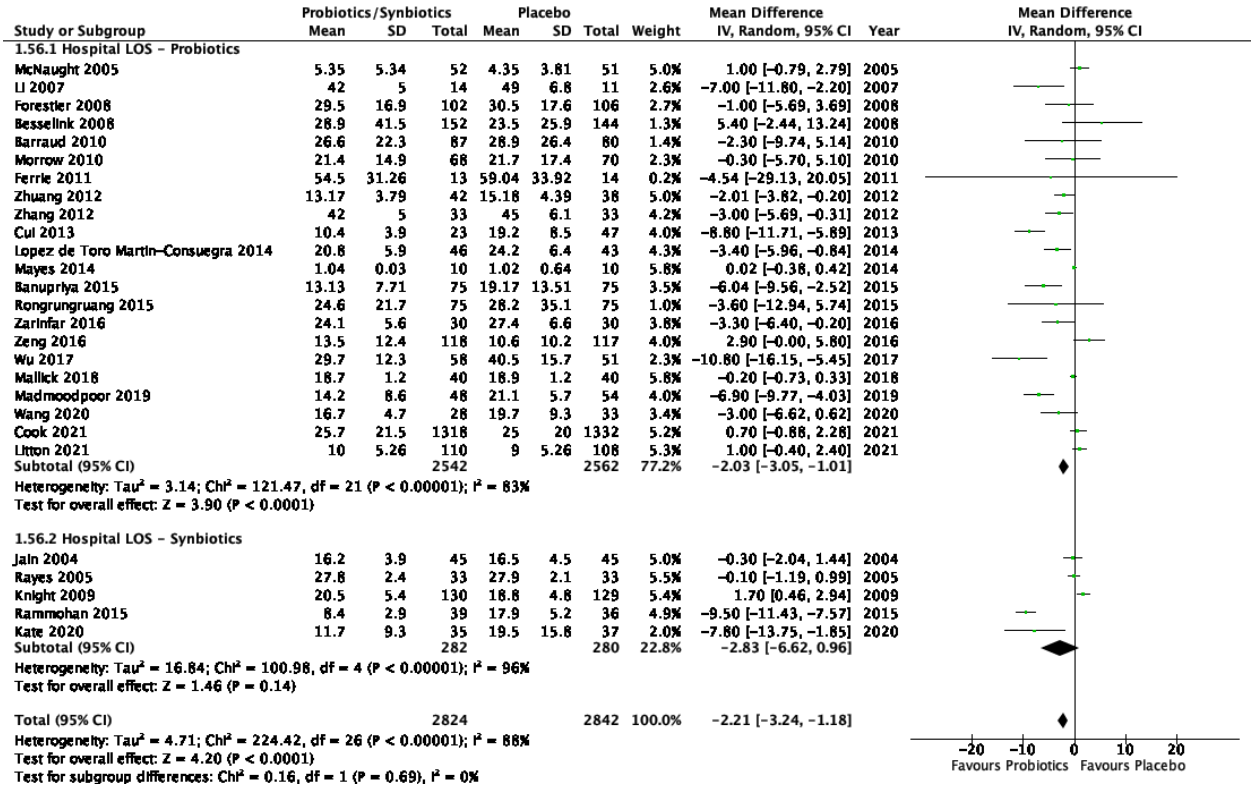
Supplement Figure 32. Forest plot. ICU Length of Stay (LOS) comparing Probiotics and Synbiotics:

Comparing probiotics and synbiotics for the outcome of ICU LOS; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



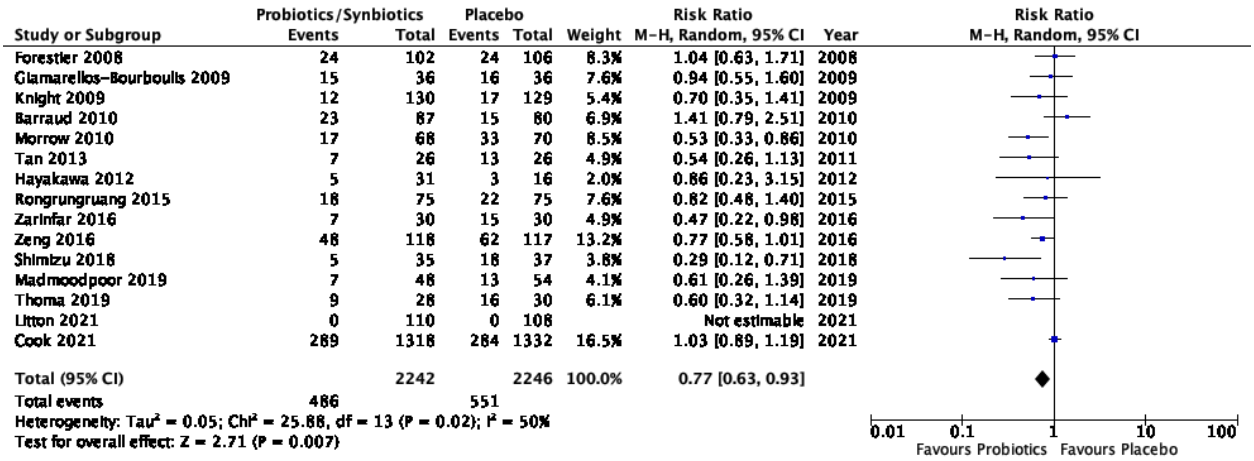
Supplement Figure 33. Forest plot. Hospital Length of Stay (LOS) comparing Probiotics and Synbiotics:

Comparing probiotics and synbiotics for the outcome of Hospital LOS; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

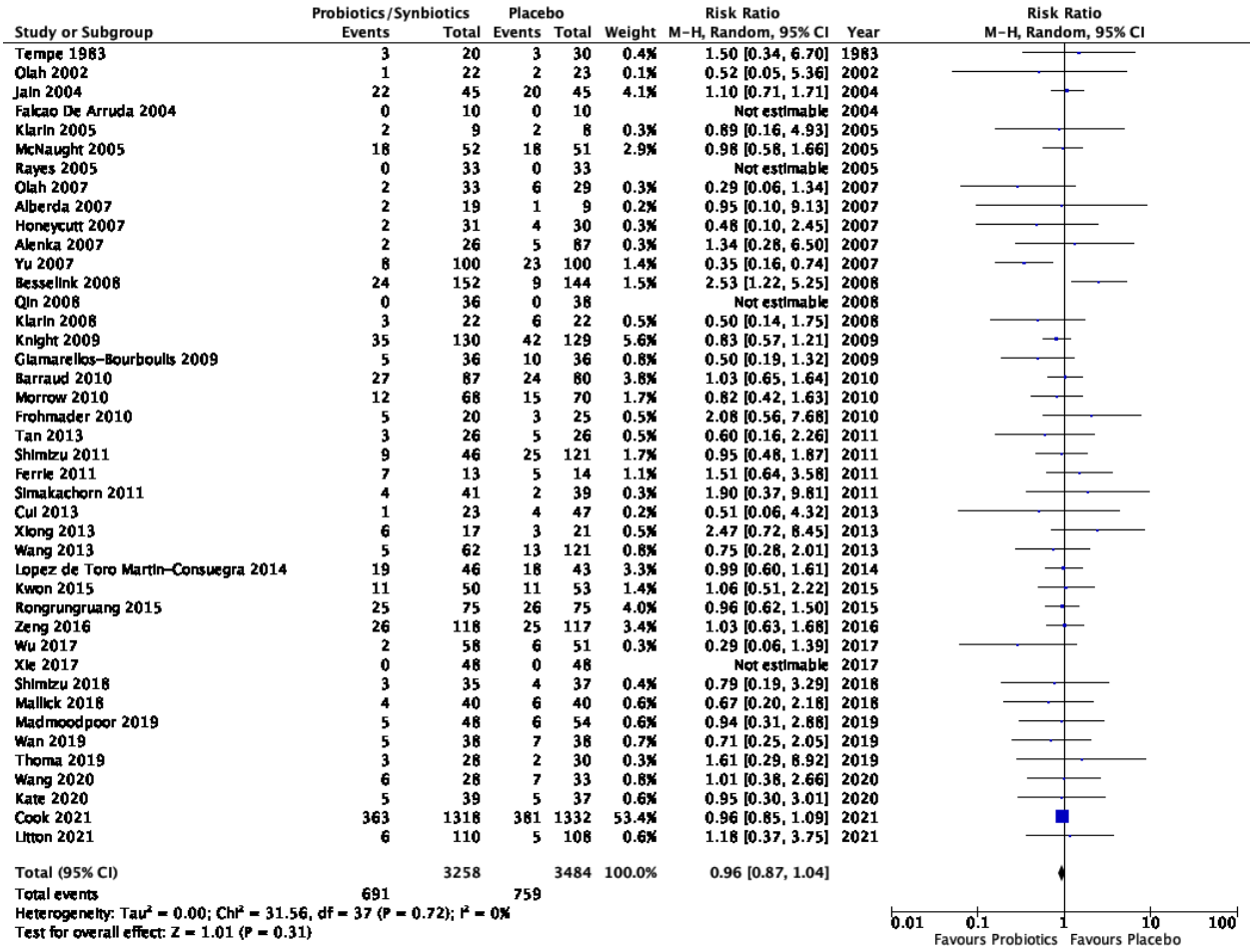


Supplement Figure 34. Forest plot. Ventilator-Associated Pneumonia in Adults Only (Sensitivity Analysis):

Comparing probiotics/synbiotics and placebo for the outcome of ventilator-associated pneumonia in the adult population; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

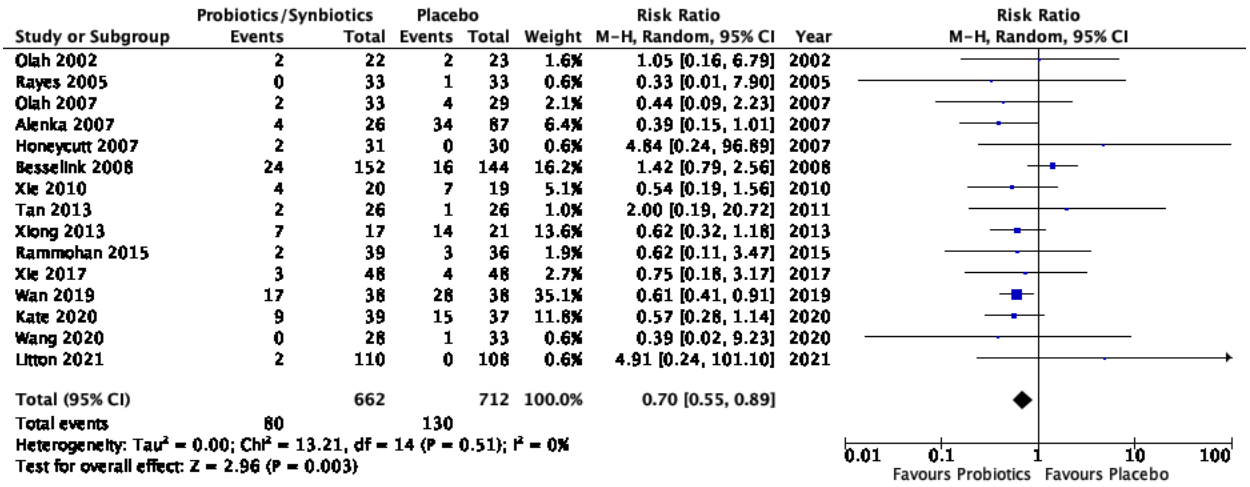


Supplement Figure 35. Forest plot. Mortality in Adults Only (Sensitivity Analysis): Comparing probiotics/synbiotics and placebo for the outcome of mortality in the adult population; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



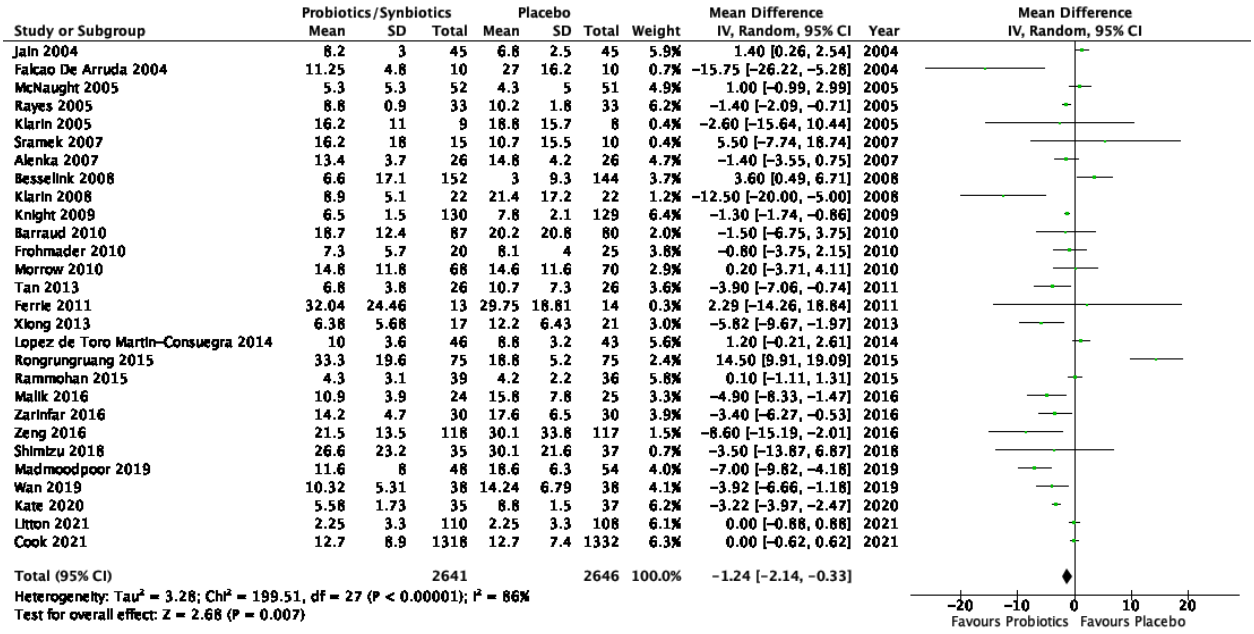
Supplement Figure 36. Forest plot. Healthcare-Associated Pneumonia in Adults Only (Sensitivity Analysis):

Comparing probiotics/synbiotics and placebo for the outcome of healthcare-associated pneumonia in the adult population; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



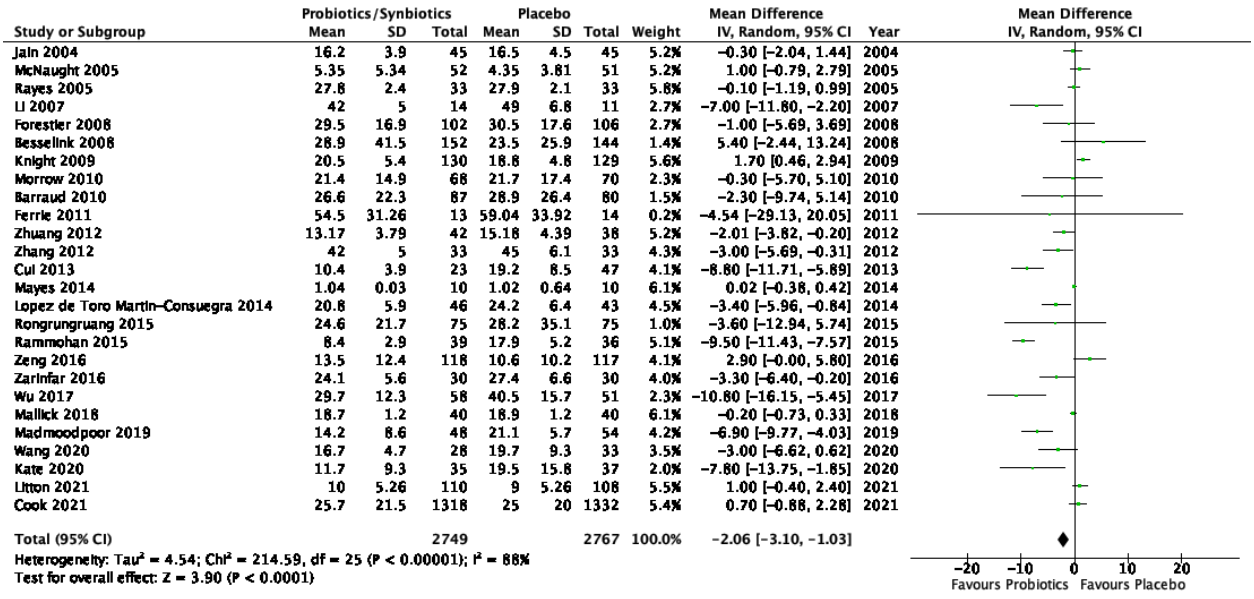
Supplement Figure 37. Forest plot. ICU Length of Stay (LOS) in Adults Only (Sensitivity Analysis):

Comparing probiotics/synbiotics and placebo for the outcome of ICU Length of Stay in the adult population; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



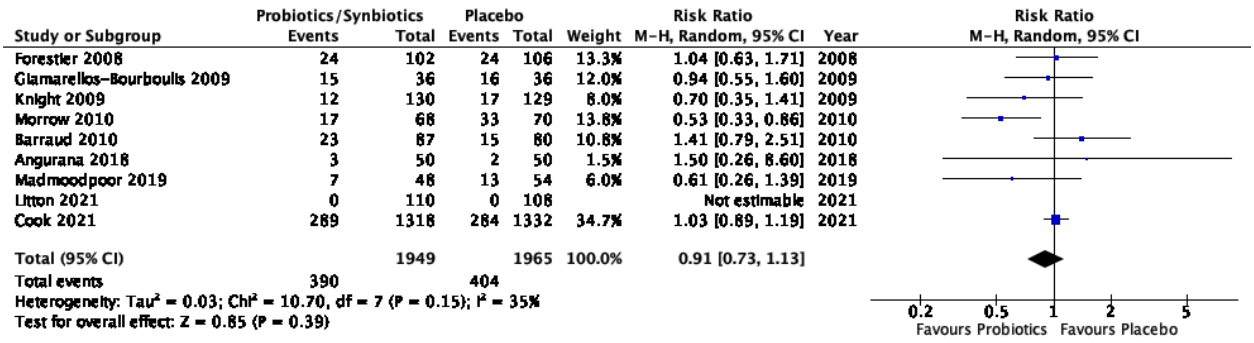
Supplement Figure 38. Forest plot. Hospital Length of Stay (LOS) in Adults Only (Sensitivity Analysis):

Comparing probiotics/synbiotics and placebo for the outcome of Hospital Length of Stay in the adult population; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



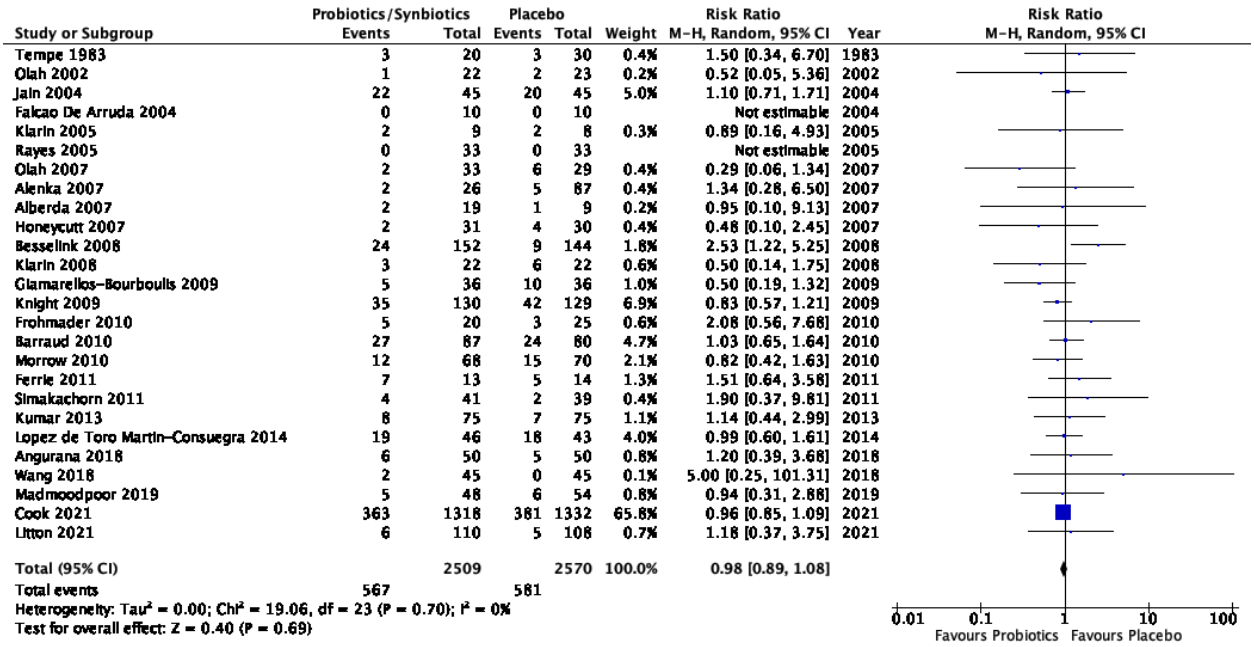
Supplement Figure 39. Forest plot. Ventilator-Associated Pneumonia in Low Risk of Bias Studies (Sensitivity Analysis):

Comparing probiotics/synbiotics and placebo for the outcome of ventilator-associated pneumonia in Low Risk of Bias studies; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



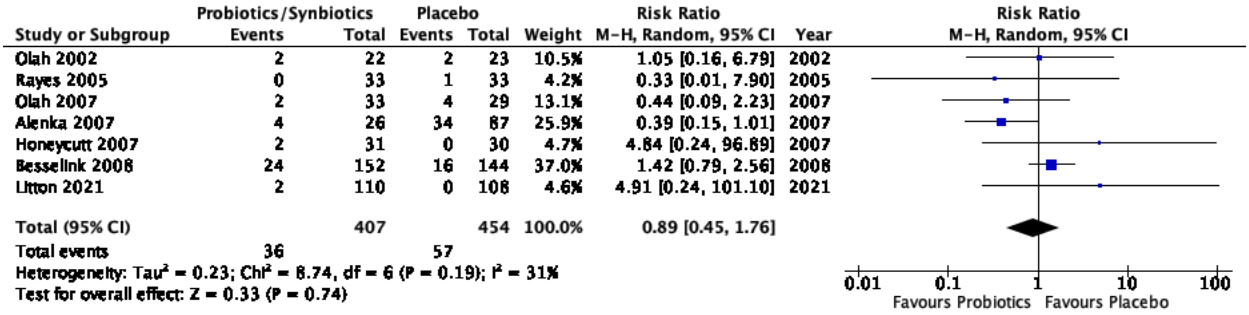
Supplement Figure 40. Forest plot. Mortality in Low Risk of Bias Studies (Sensitivity Analysis):

Comparing probiotics/synbiotics and placebo for the outcome of mortality in Low Risk of Bias studies; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



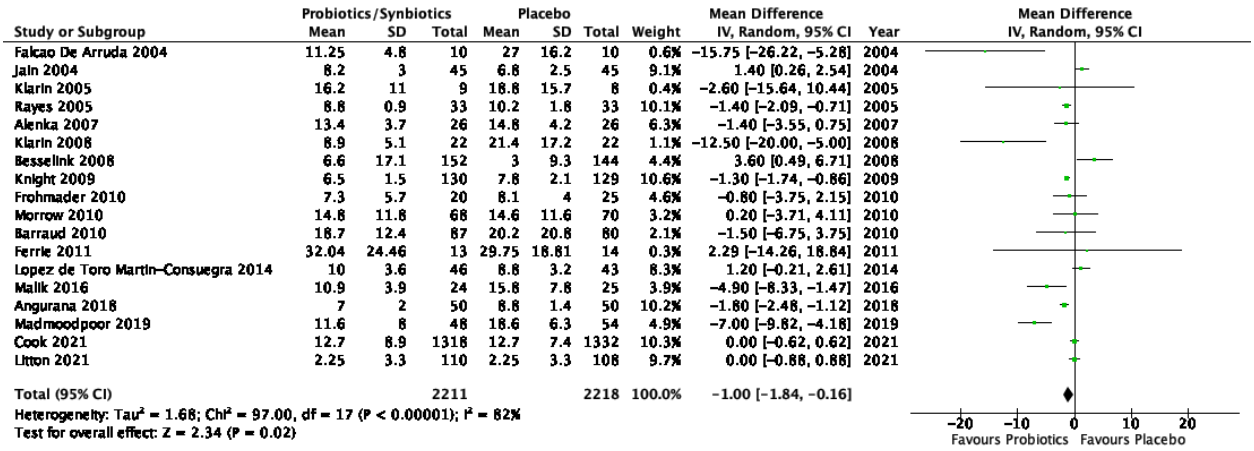
Supplement Figure 41. Forest plot. Healthcare-Associated Pneumonia in Low Risk of Bias Studies (Sensitivity Analysis):

Comparing probiotics/synbiotics and placebo for the outcome of healthcare-associated pneumonia in Low Risk of Bias studies; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



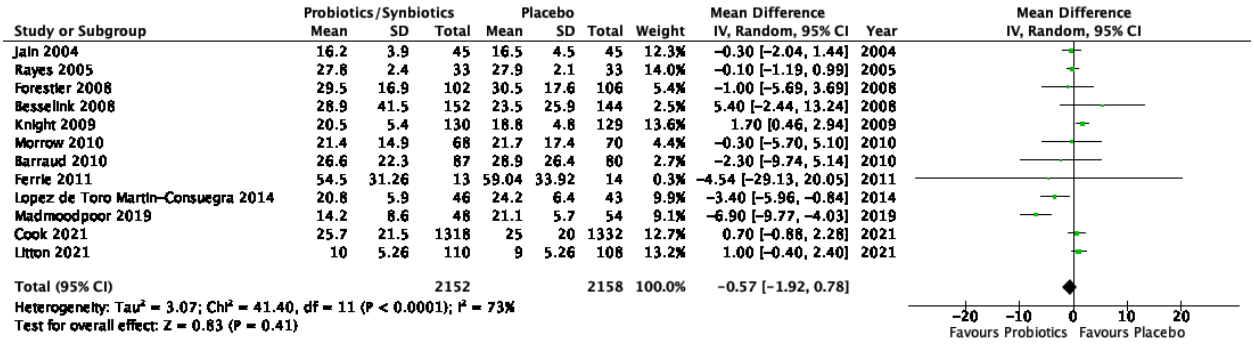
Supplement Figure 42. Forest plot. ICU Length of Stay (LOS) in Low Risk of Bias Studies (Sensitivity Analysis):

Comparing probiotics/synbiotics and placebo for the outcome of ICU Length of Stay in Low Risk of Bias studies; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



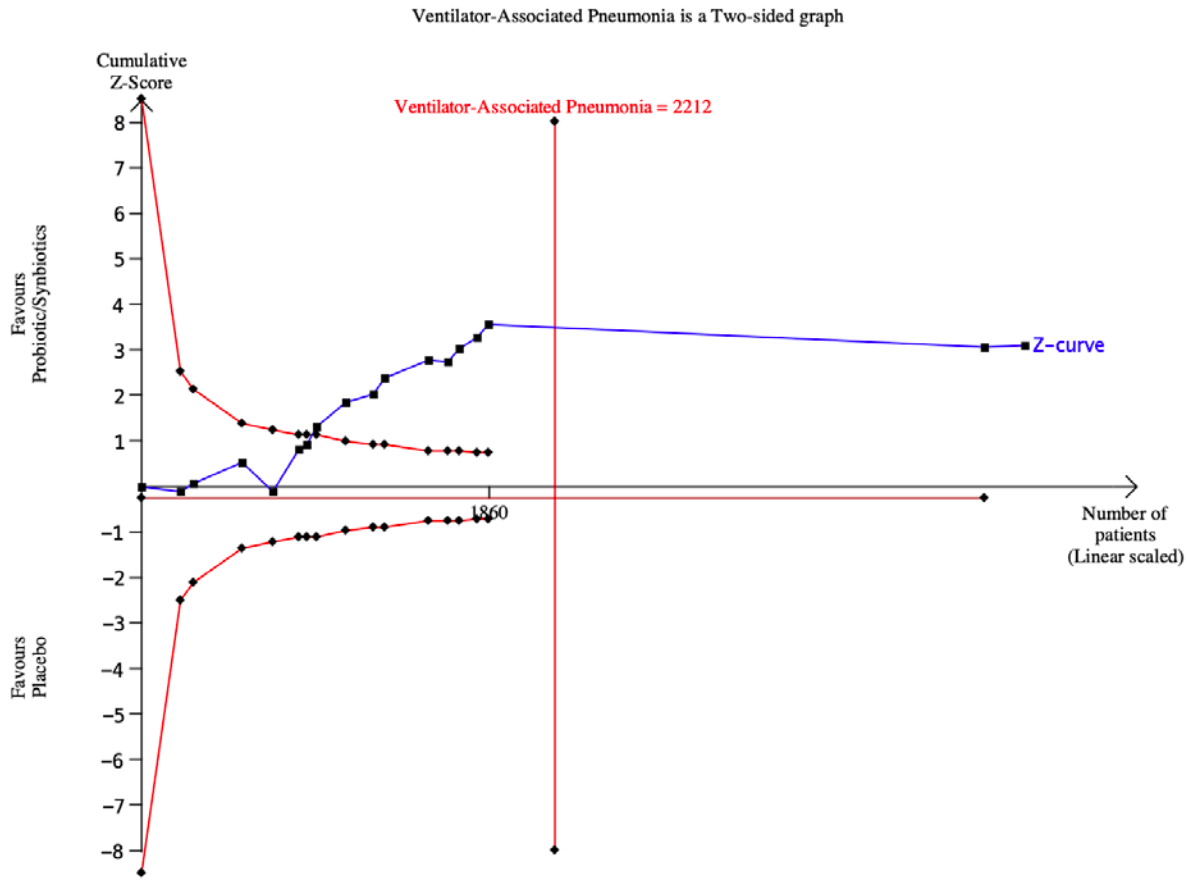
Supplement Figure 43. Forest plot. Hospital Length of Stay (LOS) in Low Risk of Bias Studies (Sensitivity Analysis):

Comparing probiotics/synbiotics and placebo for the outcome of Hospital Length of Stay in Low Risk of Bias studies; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)



Appendix 8. Supplement Figure 44. Trial Sequential Analysis (TSA) for Ventilator-Associated Pneumonia.

Trial sequential analysis (TSA) of 17 trials comparing probiotics/synbiotics with placebo for ventilator associated pneumonia in critically ill patients. The TSA was conducted with a control event proportion of 24.8% (588/2371) and the accrued number of patients of 4,738. The TSA shows that the optimal information size was reached. A required information size of 2,212 was calculated using $\alpha = 0.05$ (two sided) and ß = 0.20 (power 80%).


Ventilator-Associated Pneumonia is a Two-sided graph
Cumulative Z-Score
Ventilator-Associated Pneumonia = 2212
Favours Probiotic/Synbiotics
Favours Placebo
Z-curve
1860
Number of patients (Linear scaled)
8
7
6
5
4
3
2
1
−1
−2
−3
−4
−5
−6
−7
−8

Appendix 9. Tables:

Supplement Table 1. Baseline Characteristics of Included Studies

Population		Intervention				Outcomes
Study / Population	**Illness Severity**	**Intervention/dose/duration**	**Control**	**Enrollment Time**	**Follow Up**	**Primary Outcome(s)***
Alberda 2007 Adult ICU Patients n = 28	APACHE II *Mean (SD)* Placebo = 15.9 (4.2) Viable Probiotics = 19.1 (4.1) Probiotic sonicates = 14.3 (4.4)	EN (Jevity Plus) + VSL#3 Probiotics[1] 1 package BID for 7 days until ICU discharge or EN discontinuation	EN (Jevity Plus) + placebo	Within 48H of admission	7 days	Multiple Organ Dysfunction (MODS score)
Alenka 2007 Adult ICU Patients n = 113	APACHE II *Mean (SD)* All patients = 13 (7) Illness Severity Score *Mean (SD)* All patients = 41 (18.9)	Group D – EN (Nutricomp standard) + Synbiotic 2000[2] dissolved in 100mL of sterile water	Group C - Nutricomp peptide	Within 24 H of admission	7 days	Intestinal permeability
Angurana 2018 Pediatric ICU Patients (3m – 12y) with severe sepsis n = 100	PRISM III (Pediatric Risk of Mortality III Score) *Median (IQR)* Probiotic = 17 (13 - 21) Placebo = 15 (12 - 20)	VSL#3[3] one sachet BID for 7 days EN not reported	Placebo group – maltose and silicon dioxide one sachet BID for 7 days	< 72 hours post admission	7 days	Change in cytokine levels in probiotic and placebo groups from day 1 – 7
Banupriya 2015 Medical Pediatric PICU patients (< 12y) n = 150	PRISM III Score *Mean (SD)* Probiotic = 11.61 (5.63) Control = 11.25 (6.58)	One probiotic capsule[4] BID with milk or 5mL of 5% dextrose for 7 days or until ICU discharge EN not reported	Standard care, no placebo	On ICU Admission	Until discharge from hospital	VAP
Barraud 2010 Intubated adult ICU patients (severe sepsis vs. non severe sepsis) n = 167	Simplified Acute Physiology (SAPSII) Score *Mean (SD)* All = 59.8 (18.5) Probiotics = 58.6 (17.3) Placebo = 60.5 (19.6)	EN (Fresubin)+ 5 Ergyphilus[5] daily for duration of mechanical ventilation (not exceeding 28 days) + 2 additional days post-weaning in case of successful extubation, or continued in case of extubation failure	EN (Fresubin) + placebo capsules (excipient).	Days, *Mean (SD)* 2.4 (1.8)	ICU length of stay and up to 90 days	28-day mortality
Besselink 2008 Adult patients with predicted severe acute pancreatitis n = 296	APACHE II *Mean (SD)* Probiotics = 8.6 (4.4) Placebo = 8.4 (4.5)	EN (Nutrison Multi Fibre) + Ecologic 641[6] BID for maximum of 28 days – stopped if diagnosed with infected pancreatic necrosis	Cornstarch and maltodextrons + EN (Nutrison Multi Fibre).	≤72 hours after symptom onset of pancreatitis	90 days	Infectious complications – infected pancreatic necrosis, bacteraemia, pneumonia, urosepsis, or infected ascites – during admission and 90-day follow up
Bleichner 1997	N/A	EN + *S. boulardii* 500 mg QID for 21 days or withdrawal of EN	EN + placebo powder.	*Median (range)*	21 days	Diarrhea

Adult medical and surgical ICU patients requiring EN n = 128				Placebo = 4.5 (4.9) Probiotics = 4.8 (5.0)		
Chung 2011 Pediatric PICU patients < 17y n = 15	N/A	*Lactobacillus GG* (30 x 10^9 CFU) BID for duration of antibiotic therapy EN not reported	Matching placebo capsule BID for duration of antibiotic therapy.	N/A	N/A	Antibiotic associated diarrhea
Cui 2013 Adult patients with severe acute pancreatitis n = 48	APACHE II 8	EN + *Bifidobacterium*, 4 capsules every 12 hours, given through nasal gastric tube, each capsule weighing 210 mg	EN	0	N/A	Biochemical analysis (IL-8, TNF-alfa, CRP, LDH, WBC, amylase, lipase), GI dysfunction, upper GI bleeding, infection and abscess, hospital days, mortality rate.
Falcao De Arruda 2004 ICU patients with brain injury n = 20	Therapeutic Intervention Scoring System (TISS) *Mean (SD)* Study = 34 (8) Control = 32 (5) Glasgow score *Median (range)* Study = 7 (6 – 10) Control = 7 (5 – 9)	EN + 240mL of fermented milk with *Lactobacillus johnsonii* (La 1) (LC1®; Nestle´, Sa˜o Paulo, Brazil) for 6 days or at most for 14 days, beginning no later than 48 h after admission and continuing for a minimum of 5 days	EN	≤48h from admission	Duration of ICU stay	Incidence of infection, duration of ICU stay, and duration of mechanical ventilation
Ferrie 2011 Mixed adult ICU patients with reported diarrhea n = 36	APACHE II *Mean (SD)* Probiotic = 27.7 (6.3) Placebo = 29.6 (6.1)	EN (standard) + 10^{10} CFU *Lactobacillus rhamnosus* GG (Culturelle) + 280mg inulin powder - 1 capsule every 12 hours for 7 days	EN + placebo capsule containing 280 mg inulin powder	N/A	14 days and up to 6 months follow up	Duration of diarrhea
Foresterier 2008 Adult mixed ICU patients n = 208	Simplified Acute Physiology Score (SAPS II) *Mean (SD)* Probiotic = 44.6 (16.0) Placebo = 44.2 (15.3)	*L. casei rhamnosus* 10^9 CFU (pharmaceutical form no E01-A02- S06) BID from third day of ICU admission until discharge or death EN not reported	Placebo (growth medium without bacteria)	N/A	Duration of hospitalization	Time to *P. aeruginosa* colonization in the gastric and respiratory tract
Frohmader 2010 Mixed adult ICU patients requiring EN n = 45	APACHE II *Mean (SD)* Probiotic = 22.2 (8.9) Placebo = 23.8 (10.2) SAPS II *Mean (SD)* Probiotic = 43.9 (15.0) Placebo = 46.1 (19.4)	EN - Isosource / Renal / Diabetic Resource (Novartis) + nutritional supplement (Sustagen) + VSL#3[7] one sachet BID until hospital discharge	EN - Isosource / Renal / Diabetic Resource (Novartis)+ nutritional supplement (Sustagen) + placebo solution	≤24 hours of ICU admission	21 days post ICU transfer to general unit or until discharge from the hospital. Mean study duration = 11.9 days (SD 5.6).	Stool frequency
Giamarellos-Bourboulis 2009	APACHE II *Mean* Synbiotic = 19.36	Synbiotic 2000FORTE[2] in 12g sachets diluted in 100mL of tap water and	Placebo once daily for 15 days.	On ICU admission	Followed up for 28 days	Bloodstream infections, VAP, serum levels of CRP, and endotoxins (LPS)

Adult mixed multiple organ trauma patients in surgical ICUs n = 72	Placebo = 19.36	administered by a NG or gastrostomy tube once daily for 15 days EN not reported				
Hayakawa 2012 Adult patients receiving mechanical ventilation and enteral tube feeding for ≥1 month n = 47	N/A	EN (Medief) + Yakult[8] 1 g and Oligomate S-HP (Yakult) 5 g TID during 8 week study period	EN (Medief)	N/A	8 week study period	Colonization of *P. aeruginosa* in the lower respiratory tract
Honeycutt 2007 Medical-surgical pediatric ICU patients n = 61	N/A	One capsule *Lactobacillus rhamnosus* GG 10 x 10^9 cells/capsule (Culturelle) once daily in 5mL of 5% dextrose until discharge from hospital, parental request to withdraw from the study, or until death EN not reported	One capsule of insulin once a day in 5mL of 5% dextrose.	≤72 hours after PICU admission	Until hospital discharge or death and for 48 hours after discharge/transfer from the hospital.	Nosocomial infection, bloodstream infection, pneumonia, tracheobronchitis, and UTI
Jain 2004 Adult ICU patients n = 90	APACHE II *Median (IQR)* Synbiotics = 11 (9-14) Control = 11 (10-15) POSSUM *Median (IQR)* Synbiotics = 36(32-40) Control = 37(33-40)	EN or PN + synbiotic (Trevis™) one capsule TID + 7.5 g Raftilose™ prebiotic (oligofructose) BID. Administered until hospital discharge	EN or PN + placebo – powdered sucrose and placebo-capsules (Chr Hansen Biosystem)	≤24 hours from admission	Until discharge from hospital – mean duration of study medication was 10 days in both groups.	Gastric colonisation
Kate 2020 Adult patients treated for moderately severe and severe acute pancreatitis as per the Atlanta 2012 criteria n = 86	N/A	1 gram of synbiotic containing both pre and probiotics given in 100 ml of saline BID x 14 days EN not reported	A similar-looking placebo	N/A	90 days	Septic complications during hospital stay or within 90 days follow up and inflammatory marker levels – IL-8, IL-10, LDH, and TNF-α
Klarin 2005 Adult mixed critically ill patients on broad spectrum antibiotics n = 17	APACHE II *Median (IQR)* Probiotics = 17 (13 - 29) Control = 19 (14 - 36)	EN (Nutrodrip) + 10^9 CFU/mL Lp (*Lactobacillus plantarum*) 299v (Probi AB). Administered 50mL q6 hours x 3 days then 25mL q6 hours for rest of ICU stay	EN (Nutrodrip)	≤12 hours from admission	Duration of ICU stay and 6-month mortality	Survival and adherence of Lp 299v to the mucosa in the lower GI tract
Klarin 2008	APACHE II *Median (Range)*	EN + 8x 10^8 (CFU)/ml of *Lactobacillus plantarum* 299v (Probi AB). Administered	EN + fermented oatmeal gruel without	≤24 hours from ICU admission	Duration of ICU stay and up to 6	*C. difficile* infection

Adult mixed ICU patients treated with antibiotics n = 44	Probiotics = 17 (7 - 29) Control = 20 (11 - 38)	6 x 100mL doses q12H followed by 50mL BID for duration of ICU stay	Lp299v bacteria, but with lactic acid		months post inclusion in study	
Knight 2009 Adult mixed medical and surgical ICU patients requiring mechanical ventilation n = 259	APACHE II Median (IQR) Synbiotics = 17 (12 - 23) Placebo = 17 (12 - 22)	EN (Nutrison Energy) + Synbiotic 2000FORTE (Medipharm)[2] BID until day 28, death, or discharge	EN (Nutrison Energy) + crystalline cellulose-based placebo	On admission to ICU	Earliest of the following time points: day 28 after admission, death or discharge from a critical care area.	VAP
Kumar 2013 Pediatric (3m – 12y) PICU patients on broad spectrum antibiotics n = 150	PRISM III *Median (10th - 90th percentile)* Probiotic = 9 (2 - 16) Placebo = 9 (1.2 - 1.8)	Probiotics EUGI (Wallace pharma)[11] one sachet BID for 7 days EN not reported	Lactose placebo one sachet	N/A	Duration of study period – 14 days, or death	Prevalence of rectal colonization with *Candida* on day 14 post enrollment
Kwon 2015 Adult medical or coronary ICU patients n = 103	Probiotics APACHE II 1 - 17 = 12/30 (40%) 18 - 24 = 12/30 (40%) > 25 = 6/30 (20%) Standard of Care APACHE II 1 - 17 = 17/40 (43%) 18 - 24 = 15/40 (38%) > 25 = 8/40 (20%)	1 capsule containing 1×10^{10} cells of *Lactobacillus rhamnosus* GG (Culturelle) BID for 14 days or until study exit (death or hospital discharge) EN not reported	Standard of care	Pre-enrollment ICU length of stay *Median (range)* Probiotic = 4.5 (1-16) Standard of care = 3.5 (1-22)	14 days or death or hospital discharge	Gastrointestinal colonization with multidrug-resistant organism
Li 2007 Adult patients with severe acute pancreatitis n = 25	APACHE II score 8-20	Live Combined Bifidobacterium and Lactobacillus Tablets, 2.0 g/time, TID for 7 days EN not reported	N/A	0 days from admission	N/A	N/A
Litton 2021 Adult patients requiring > 48H admission n = 221	APACHE II Mean (SD) Placebo = 14.6 (6.9) Probiotic = 14.5 (6)	2×10^{10} CFU/L *Lactobacillus plantarum* 299v per capsule – one capsule daily for 60 days EN not reported	One capsule microcrystalline cellulose	Within 48H of ICU admission	60 days	Days alive and out of hospital to Day 60
Lopez de Toro Martin Consuegra 2014 ICU patients with multi-organ failure n = 89	APACHE II *Median (IQR)* Symbiotic = 20 (15 – 26) Control = 22 (18 – 26.5)	EN or PN + Simbiotic Drink®at a dose of 200 ml / 12 h x 7 days	EN or PN	N/A	Duration of ICU stay	Evolution of multiorgan dysfunction

Madmoodpoor 2019 Adult surgical ICU patients undergoing mechanical ventilation n = 100	APACHE II Mean (SD) Probiotics = 24.1 (6.2) Control = 22.8 (4.7)	EN (Ensure) + 1 capsule of probiotic (Lactocare)[12] q12 hours daily for 14 days or until death	EN (Ensure) + placebo– sterile maize starch powder	N/A	Duration of ICU stay	VAP
Malian 2012 Surgical ICU patients with diarrhea or *C. difficile* positive culture n = 69	APACHE II Mean score = 16.7	Enterally or orally administered *Lactobacillus GG* EN not reported	Placebo	N/A	Hospital discharge	Incidence of diarrhea and infection in the ICU
Malik 2016 Adult critically ill patients admitted to the ICU requiring enteral feeding n = 49	APACHE II Mean (SD) Probiotic = 22.12 (6.0) Placebo = 23.00 (8.9)	EN + 30 billion CFU of *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus lactis, Bifidobacterium bifidum, Bifidobacterium longum,* and *Bifidobacterium infantis* diluted in 5mL water BID for 7 days once started enteral feeding	EN + placebo mixture	≤24 – 48 hours after admission	Duration of ICU stay	Duration to return to normal gut function defined as time in hours taken to achieve a minimum of 80% of calculated caloric requirement for a consecutive 48-hour period
Mallick 2018 Elective patients undergoing living donor liver transplantation n = 80	N/A	Prowel®[Lactobacillus Acidophilus-Bifidobacterium (Probiotic) and Fructooligosacccharide (Prebiotic)] starting 2 days prior to surgery until day 14 post-transplant EN not reported	Placebo – empty capsules	N/A	14th post-transplant day	Postoperative infectious complications up to 14 days
Masjedi 2017 Adult trauma ICU patients n = 139	N/A	Routine oral care procedures + Lactocare[12] (Zist Takhmir) suspended in 20cc of distilled water, sterile gauze was soaked in the suspension and was rubbed in the oropharyngeal cavity q12 hours for duration of study period EN not reported	Routine oral care procedures + placebo capsules made from dried milk powder (Zist Takhmir)	≤24 hours from ICU admission	N/A	VAP
Mayes 2014 Acutely burned pediatric patients (<22y) admitted to the burn centre n = 20	N/A	EN + 15 billion CFU per unit dose *Lactobacillus rhamnosus* GG(Culturelle®) BID within 10 days of burn and until 95% wound closure was achieved	EN + placebo (Amerifit) of identical appearance, with the same inactive ingredient base	Within 10 days of burn injury	Until discharge from hospital	Safety of probiotic administration
McNaught 2005 Mixed medical and surgical adult ICU patients n = 103	APACHE II *Median (IQR)* Probiotics = 12 (9 - 16) Control = 12 (8 - 17)	EN or PN + ProViva[13] oatmeal and fruit drink with $5x10^7$ CFU/ml of *L. plantarum299v* - 500mL per day until discharge from hospital or discontinuation of study	EN or PN	≤24 hours from admission	Until death or discharge from the hospital	Gut barrier function and systemic inflammatory response with CRP and IL-6 levels.

Morrow 2010 Adult mixed ICU patients requiring mechanical ventilation n = 138	APACHE II *Mean (SD)* Probiotics = 22.7 (7.5) Placebo = 23.7 (8.0)	2x10^9 CFU *Lactobacillus rhamnosus* GG BID administered as lubricant and through NG until extubation, tracheostomy placement, or death	Placebo containing inert plant starch inulin	≤24 hours from intubation	Duration of hospitalization	VAP
Olah 2002 Patients with acute pancreatitis including those with severe acute pancreatitis n = 45	Glasgow Score *Mean (SD)* Probiotics = 2.5 (1.3) Control = 2.8 (1.5)	EN (Nutrison Fibre®) + 10g oat fibre + 10^9 organisms of live *Lactobacillus plantarum* 299 BID during first 7 days	EN (Nutrison Fibre®) + 10g oat fibre + 10^9 organisms of heat killed *Lactobacillus plantarum* 299	N/A	7 days	Organ failure, septic complications requiring a surgical procedure, duration of hospital stay, and death
Olah 2007 Patients with severe acute pancreatitis n = 62	Imrie Score *Mean (SD)* Synbiotics = 2.9 (1.2) Control = 3.1 (1.5) APACHE II *Mean (SD)* Synbiotics = 11.7 (1.9) Control = 10.4 (1.5)	EN (Nutricia) + Synbiotic 2000^{TM2} daily for 7 days minimum	EN (Nutricia) + 2.5g betaglucan, 2.5g inulin, 2.5g pectin and 2.5g resistant starch, totally 10g plant fibers	On admission	Hospital stay or death	Multiorgan failure, septic complications, and mortality
PROSPECT 2021 Adult patients (≥ 18y) expected to be mechanically ventilated for ≥ 72 hours n = 2,650	APACHE II *Mean (SD)* Probiotics = 22.3 (7.8) Placebo = 21.7 (7.9)	Patients received 1x10^{10} colony forming units of *L. rhamnosus GG* (i-Health, Inc.) through feeding tubes twice daily. Administered for up to 60 days or until discharge from ICU, or if *Lactobacillus spp.* was isolated from a sterile site or cultured as the sole or predominant organism from a non-sterile site EN not reported	Placebo in 1 capsule suspended in water through feeding tubes twice daily	Within 24 hours of ICU admission.	Duration of ICU and/or hospital stay	VAP
Qin 2008 Adult acute pancreatitis (mild, moderate, and severe) patients n = 76	APACHE II *Mean (SD)* Probiotics = 8.8 (0.5) Control = 8.9 (0.7)	PN + EN (Nutrison) + A 100 ml *Lactobacillus plantarum* (activity 1 × 10^8 CFU/ml) (Shanghai Jiaotong University Only Inc) daily x 7 days	PN + 100mL of 0.9% normal saline	N/A	28 days follow up	Infectious complications
Rammohan 2015 Postoperative adult patients with chronic pancreatitis undergoing Frey procedure n = 75	ASA I Synbiotics = 15/39 Control = 14/36 II Synbiotics = 21/39 Control = 20/36 III Synbiotics = 3/39 Control = 2/36	Synbiotics - *Streptococcus faecalis* T-110-60 million, *Clostridium butyricum* TO- A-4 million, *Bacillus mesentericus* TO-A-2 million, *Lactobacillus sporogenes*-100 million, Fructooligosaccharides (Bifiliac HP) TID from 5 days preoperatively until 10 days postoperatively EN not reported	Placebo TID	N/A	First 30 days post-op, hospital duration, death	Incidence of postoperative infection up to day 30

Rayes 2005 Adult liver transplantation patients n = 66	ASA I Synbiotics = 0/33 Placebo = 0/33 ASA II Synbiotics = 8/33 Placebo = 11/33 ASA III Synbiotics = 22/33 Placebo = 22/33 ASA IV Synbiotics = 3/33 Placebo = 0/33	EN (Stresson) + 2000® (Medipharm)[2] BID from day of operation to first 14 days post-operatively	EN (Stresson) + four bioactive fibers	N/A	30 days post-operatively	Incidence of postoperative bacterial infection up to day 30
Rongrungruang 2015 Adult hospitalized medical patients expected to receive mechanical ventilation for ≥ 72 hours n = 150	APACHE II *Mean (SD)* Probiotics = 19.41 (7.04 Control = 19.88 (6.89)	80 ml of $8x10^9$ CFU *Lactobacillus casei* (Shirota strain) (Yakult®) for oral care after the standard oral care once daily. An additional 80 ml of the product was given via enteral feeding once daily for 28 days or when their endotracheal tubes were removed EN not reported	Oral care with 2% chlorhexidine solution QID as standard care	N/A	90 days	VAP and incidence rate of VAP episodes per 1,000 ventilator days
Sanaie 2014 Adult critically ill SIRS patients receiving EN with expected ICU length of stay ≥ 7 days n = 40	APACHE II *Mean (SD)* Probiotic = 22.80 (4.73) Placebo = 22.45 (4.57)	EN (Fresubin original fibre) + VSL#3[14], 2 sachets BID for 7 days	EN (Fresubin original fibre) + placebo	≤24 hours from admission	7 days	APACHE II and SOFA scores, biochemical analysis – IL-6, PCT, and Protein C levels
Schlotterer 1987 Adult patients with burns n = 18	N/A	EN with Polydiet® or Nutrigil® + 500 mg *Saccharomyces boulardii* QID for 8 – 28 days	EN with Polydiet® or Nutrigil® + placebo	N/A	Mean (SD) Probiotics = 22.7 (2.2) Placebo = 23.1 (2.5) 8 – 28 days	The number of diarrhea days and caloric level reached during continuous enteral nutrition
Shimizu 2011 Mechanically ventilated SIRS patients in the ICU n = 167	N/A	*Bifidobacterium breve, Lactobacillus casei*, and galactooligosaccharides within 3 days of admission EN not reported	No synbiotics group	≤3 days from admission	N/A	Diarrhea
Shimizu 2018 Adult ICU patients with sepsis who were mechanically ventilated within 3	APACHE II *Median (IQR)* Synbiotics = 19 (14 - 24) Control= 20 (14 - 26)	EN (Glucerna®-Ex) + Yakult BL Seichoyaku 3g/day (Yakult Honsha)[8] - 10^8 *B. breve* strain Yakult/g and 1×10^8 *L. casei* strain Shirota/g + galactooligosaccharides (Oligomate S-HP) 10g/day within 3 days	EN (Glucerna®-Ex) + no synbiotics	≤3 days from ICU admission	4 weeks from admission	Infectious complications including enteritis, VAP, and bacteremia up to 4 weeks

days of ICU admission n = 72		post admission until PO intake was initiated				
Shinotsuka 2008 Adult ICU patients receiving mechanical ventilation and EN n = 49	APACHE II *Median (IQR)* Control = 20 (12 - 25) Probiotic = 17 (10 - 26) Synbiotic = 18 (15 - 22) SAPSII *Median (IQR)* Control = 34 (28 - 56) Probiotic = 32 (26 - 46) Synbiotic = 43 (24 - 49)	**Probiotic** – EN + *lactobacillus johnsonii* La1 in a 10^9 UFC dose, BID for 14 days **Synbiotic** – EN + *lactobacillus johnsonii* La1 in a 10^9 UFC dose BID + soybean polysaccharide for 14 days	EN	N/A	Discharge from ICU and hospital	Colonization of the gastrointestinal tract and trachea by aerobic pathogenic bacteria on admission, day 7, and day 14
Sramek 2007 Adult ICU patients n = 26	APACHE II *Median (IQR)* 24 (21 - 27)	Post-pyloric Synbiotic Forte (Medipharm)[2] EN not reported	Tea	N/A	N/A	ICU mortality, duration of ICU stay, nosocomial infections, occurrence of sepsis, antibiotic usage, and multiple organ dysfunction
Simakachorn 2011 Pediatric critically ill patients (1 – 3y) under mechanical ventilation and requiring enteral feeding n = 94	PRISM *Mean (SD)* 0.0 (2.4)	EN + 5 x 10^6 CFU/g *Lactobacillus paracasei* NCC 2461 and 2 x 10^6 CFU/g *Bifidobacterium longum* NCC 3001 + prebiotics (oligofructose/inulin [2.6 g/L], Acacia gum [2.8 g/L]), and DHA [43 mg/L]; Daily intake of probiotics and prebiotics estimated to be 10^9 CFU and 3.8 g, respectively. Administered for 1st 7 days through NG or orally, and subsequently orally up to 14 days	EN without probiotics or prebiotics or DHA	N/A	14 days	Percentage of caloric intake during the duration of PICU stay
Tan 2013 Severe craniocerebral trauma patients (GCS 5-8) admitted to the ICU n = 52	GCS before intervention *Mean (SD)* Probiotics = 6.3 (1.0) Control = 6.4 (1.0) APACHE II *Mean (SD)* Probiotic = 14.8 (3.6) Control = 14.3 (3.6)	EN + 1 x 10^9 probiotics (Golden Bifid, 3.5 g) TID for 21 days	EN	≤48 hours from admission	28 days	Fasting blood glucose levels, insulin use during hospitalization, GCS scores, and duration of ICU stay, and 28-day mortality
Tempe 1983 Adult ICU patients on continuous enteral feeding n = 40	N/A	EN + 2 capsules of probiotic (d'Ultra-Levure) *Saccharomyces boulardii* (one capsule containining 5 billion live lyophilized cells of *S. boulardi*i.) for 11 – 21 days	EN + placebo	N/A	Study duration *Mean (SD)* Probiotic = 19.45 (1.44) Placebo = 16.53 (1.39) "	Incidence of diarrhea
Thoma 2019 Multiple trauma ICU patients that	N/A	Commercially available, 4 probiotic combination – two capsules daily through days 1 – 15 of ICU stay	2 capsules of placebo	N/A	Length of ICU stay and 30 day mortality	Incidence of surgical site infections, duration of ICU stay, and 30 day mortality

required surgical intervention with or without mechanical ventilation > 10 days n = 58		EN not reported				
Wang 2013 Adult severe acute pancreatitis patients admitted to the ICU n = 183	APACHE II *Mean (SD)* EN = 13.27 (2.86) EN + probiotics = 42.6 (13.8)	EN (PEPTISORB) + 0.5 g combined *Bacillus subtilis* and *Enterococcus faecium* enteric-coated capsules (Beijing Han Mei Pharmaceutical Company Limited) TID	EN (PEPTISORB) or PN	N/A	14 days	Bacterial translocation and cytokine production – TNF-α, IL-6, and IL-10 levels
Wang 2018 Children (≤14 years) admitted to the PICU with acute lung injury n = 80	Lung Injury Score *Mean (SD)* Probiotics = 2.04 (0.64) Control = 1.96 (0.66)	EN or PN + 3 mL of 5% glucose liquid + one probiotic tablet *Eosinophil Lactobacillus* (Tonghua, China), containing 5×10^6 CFU *Lactobacillus acidophilus* of Chinese and Japanese strains TID for 10 days	EN or PN + 3 mL of 5% glucose liquid without *L. acidophilus*.	≤24 hours after diagnosis	N/A	Serum ghrelin levels and pulmonary function
Wan 2019 Adult patients with severe traumatic brain injury n = 76	APACHE II *Mean (SD)* Probiotic + EN = 13.26 (2.31) EN = 12.84 (2.37) SOFA *Mean (SD)* Probiotic + EN = 5.29 (1.35) EN = 5.02 (1.28)	EN (NengQuanLi) + probiotic tablet (210 mg/per tablet) with *Bifidobacterium longum,* *Lactobacillus bulgaricus*, and *Enterococcus faecalis* ≥1.0x 10^7 CFU (Xinyi Pharmaceutical Factory Co., Ltd.) – 6 tablets BID for 15 days	EN (NengQuanLi)	Within 48 hours of admission	30 days	Levels of inflammatory factors including Endothelin-1 (ET-1), CRP, TNF-α, IL-6, and IL-10
Wang 2020 Adult patients admitted to a Respiratory Intensive Care Unit n = 61	APACHE II *Median (IQR)* Control = 12 (11 - 15) Probiotic = 13 (11 - 15)	10^6 CFU *Clostridium butyricum* - MIYA-BM® one tablet TID EN not reported	Placebo	N/A	N/A	Duration of hospital stay, mortality, rate of hospital-acquired infection, cost of hospital stay, cost for antibiotics, and time of antibiotics treatment
Wu 2017 Adult patients with severe acute pancreatitis n = 127	APACHE II *Mean (SD)* Probiotic = 10.8 (2.9) Control = 11.3 (3.1)	EN + *Bifidobacterium* quadruple living bacterium 420 mg TID until abdominal symptoms disappeared, amylase returned to normal, and inflammatory necrosis was partly absorbed	EN	48 – 72 hours after onset of acute pancreatitis	N/A	APACHE II scores and multiple organ dysfunction
Xie 2010 Adult patients with severe head injury n = 39	GCS 6 - 8	Live Combined Bifidobacterium and Lactobacillus Tablets, 2g/time, TID EN not reported	N/A	N/A	16 days	N/A
Xie 2013 Patients with hypertensive	N/A	Early EN (RujSu) + synbiotics (Golden Bifid)[15] in the first 14 days of enteral nutritional support	Early EN (RujSu) within 24-48 hours after injury.	N/A	N/A	Normal intestinal flora, fecal SIgA, and infectious complications

intracerebral hemorrhage n = 53						
Xie 2017 Adult patients with severe acute pancreatitis n = 96	APACHE II ≥8	Triple alive bacteria preparation (Shanghai Xinyi Pharmaceutical Factory) 6 g/d (TID) EN not reported	N/A	N/A	14 days	N/A
Xiong 2013 Adult patients with severe head injury n = 41	GCS 5 - 8	Live Combined *Bifidobacterium* and *Lactobacillus* Tablets, 3.5g/time, TID, total probiotics ≥ $1x10^8$ CFU/day EN not reported	N/A	1 – 3 days	15 days	N/A
Yu 2007 Patients with severe head injury n = 200	GCS 4 - 8	EN with homogenate diet and yogurt - *Lactobacillus* in yogurt: $4x10^{11}$/100g; intervention group: 150-300g yogurt/time,BID	EN with homogenate diet	2 days	N/A	Nutritional status, gastrointestinal complications, recovery of consciousness, and prognosis
Zarinfar 2016 ICU patients undergoing mechanical ventilation n = 60	N/A	*Lactobacillus rhamnosus* Gagavage TID in addition to a routine care EN not reported	Placebo in addition to routine care TID	N/A	N/A	VAP
Zeng 2016 Adult mixed critically ill patients expected to receive mechanical ventilation for ≥ 48 hours n = 235	APACHE II *Mean (SD)* Probiotics = 14.7 (3.9) Control = 16.6 (4.3)	Probiotics capsules (Medilac-S)[17] 0.5 g active *Bacillus subtilis* and *Enterococcus faecalis* at a concentration of 4.5 × 10^9/0.25 g and 0.5 × 10^9/0.25 g, respectively diluted in 50-80mL sterile water TID for maximum study duration of 14 days EN not reported	Standard preventative strategies of VAP	≤24 hours of admission to ICU or within 24 hours of tracheal intubation if occurred in ICU	Until tracheal extubation, discharge from the hospital or death – maximum study duration of 14 days.	VAP
Zhang 2012 Patients with severe acute pancreatitis n = 99	N/A	Live Combined *Bifidobacterium* and *Lactobacillus* Tablets, 2.0 g/time, TID EN not reported	N/A	2 – 3 days	7 – 10 days after the onset of severe acute pancreatitis	N/A
Zhuang 2012 Patients receiving enteral nutrition in the Respiratory Intensive Care Unit n = 80	N/A	Probiotic yogurt feeding EN not reported	Routine feeding	N/A	Duration of hospital stay	Incidence of diarrhea

**- duration of follow up for primary outcome where reported is indicated.*

CFU – colony forming units, *EN* - enteral nutrition, *PN* – parenteral nutrition, *VAP* – Ventilator associated pneumonia, HAP – Hospital acquired pneumonia, *POSSUM* – Physiological and Operative Severity Score for enumeration of Morbidity

1. VSL#3 Probiotics (900 billion viable lyophilized bacteria - *L. casei, L. plantarum, L. acidophilus,* and *L. delbrueckii* subsp. *Bulgaricus*), 3 strains of *Bifidobacterium* (*B. longum, B. breve,* and *B. infantis*) and *Streptococcus salivarius* subsp. *Thermophilus*

2. Synbiotic 2000[2] (Medipharm, Sweden and Des Moines, IA) - 10^{10} *Pediococcus pentosaceus* 5–33:3, 10^{10} *Lactococcus raffinolactis* 32–77:1, 10^{10} *Lactobacillus paracasei* subsp *paracasei* 19, 10^{10} *Lactobacillus plantarum 2362* and 2.5 g of each of the following 4 fibers: β-glucan, inulin, pectin, and resistant starch per sachet
3. VSL#3[3] (Danisco-Dupont), which contained 450 billion viable lyophilized bacteria per sachet consisting of a blend of 8 bacterial strains, namely, *Lactobacillus paracasei* DSM 24734, *L. plantarum* DSM 24730, *L. acidophilus* DSM 24735, *L. delbrueckii subsp. bulgaricus* DSM 24734, *Bifidobacterium longum* DSM 24736, *B. infantis* DSM 24737, *B. breve* DSM 24732, *Streptococcus thermophilus* DSM 24731; and maltose and silicon dioxide as excipients (currently sold under the brand Vivomixx [MENDES, S.A., Lugano, Switzerland] or Visbiome [ExeGi Pharmaceuticals, Rockville, MD]).
4. One probiotic capsule[4] contained a total of 3.3 billion CFU of probiotic organisms. Each capsule contained 700 million CFU of *Lactobacillus acidophilus*, 400 million CFU of *Bifidobacterium longum*, 400 million CFU of *Lactobacillus rhamnosus*, 300 million CFU of *Lactobacillus plantaris*, 300 million CFU of *Lactobacillus case*i, 300 million CFU of *Lactobacillus bulgaricus*, 300 million CFU of *Bifidobacterium infantis*, 300 million CFU of *Bifidobacterium breve*, and 300 million CFU of *Streptococcus thermophilus*.
5. 5 Ergyphilus (Nutergia, Capdenac, France) capsules[5] containing 2 x 10^{10} of mainly *Lactobacillus rhamnosus* GG, but also *Lactobacillus casei*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidum*).
6. Study product (Ecologic 641, Winclove Bio Industries, Amsterdam, Netherlands)[6] consisted of six different strains of freeze-dried, viable bacteria: *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus salivarius, Lactococcus lactis, Bifidobacterium bifidum*, and *Bifidobacterium lactis* (previously classified as *Bifidobacterium infantis*), in a total daily dose of 10^{10} bacteria, plus corn-starch and maltodextrins.
7. VSL#3[7] (VSL Pharmaceuticals, Gaithersburg, Maryland) - 450 billion live lactic acid bacteria in defined ratios of lyophilized *Bifidobacterium breve, Bifidoba terium longum* (>10 x 10^9/g), *Bifidobacterium infantis* (>10 x 10^9/g), *L acidophilus, Lactobacillus plantarum, Lactobacillus casei, L bulgaricus, Streptococcus thermophilus* (>100 x 10^9/g). (The exact composition of the bacteria of the VSL#3 product is not specified by the distributor (Orphan Australia Pty Ltd, Dandenong, Victoria, Australia), and the bacterial count of the strains listed without numbers may vary between batches.)
8. One gram of Yakult BL Seicho¯yaku contains 1 x 10^8 living *Bifidobacterium breve* strain Yakult and 1x10^8 living *Lactobacillus casei* strain Shirota.
9. Lactinex granules[9] (a viable mixed culture of *Lactobacillus acidophilus* and *L. bulgaricus*) provided by Becton Dickinson.
10. Trevis™ capsules contain 4 x 10^9 CFU *of L. acidophilus* La5 (La5), *B. lactis* Bb-12 (Bb-12), *S. thermophilus* and *L. bulgaricus.*
11. EUGI (Wallace pharma, Goa, India) (*Lactobacillus acidophilus* [0.24 billion CFU], *Lactobacillus rhamnosum* [0.24 billion CFU], *Bifidobacterium longum* [0.24 billion CFU], *Bifidobacterium bifidum* [0.24 billion CFU], *Saccharomyces boulardii* [0.05 billion CFU], *Saccharomyces thermophilus* [0.24 billion CFU], fructo-oligosaccharides [300 mg], and lactose as base)
12. Lactocare; Zist-Takhmir, Tehran, Iran - each capsule contained 10^{10} bacteria consisting of *Lactobacillus* species (*casei*, *acidophilus*, *rham- nosus*, *bulgaricus*), *Bifidobacterium* species (*breve*, *longum*), and *Streptococcus thermophilus*.
13. Proviva is an oatmeal and fruit drink containing 5x10^7 colony forming units per ml of *Lactobacillus plantarum* 299v
14. VSL#3; (VSL Pharmaceuticals, Sigma-Tau Pharmaceuticals Inc. Ft Lauderdale, FL) contained 450 billion viable lyophilized bacteria consisting of 4 strains of *Lactobacillus* (*Lactobacillus casei, Lactobacillus plantarum, Lactobacillus acidophilus,* and *Lactobacillus delbrueckii* subsp. *Bulgaricus*), 3 strains of *Bifidobacterium* (*Bifidobacterium longum, Bifidobacterium breve,* and *Bifidobacterium infantis*) and *Streptococcus salivarius* subsp. *Thermophilus*.
15. (Golden Bifid, Shuangqi Pharmaceutical Co., Ltd, Inner Mongolia, China)[16] - 10^9 bacteria for 21 days. Probiotic contained 0.5 × 10^8 *Bifido- bacterium longum*, 0.5 × 10^7 *Lactobacillus bulgaricus,* and 0.5 × 10^7 *Streptococcus thermophilus*.

Supplement Table 2. Risk of Bias Assessment

Study	Bias arising from the randomization process	Bias due to Protocol Deviations	Bias due to missing outcome data	Bias in outcome measurement	Bias due to Selected Outcome Reporting	Overall ROB
Alberda 2007	Probably Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Probably Low ROB
Alenka 2007	Probably Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Probably Low ROB
Angurana 2018	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB
Banupriya 2015	Low ROB	High ROB	Low ROB	Probably Low ROB	Low ROB	Probably High ROB
Barraud 2010	Low ROB	Low ROB	Low ROB	Probably High ROB	Low ROB	Probably Low ROB
Besselink 2008	Probably Low ROB	Low ROB	Low ROB	Low ROB	Probably Low ROB	Probably Low ROB
Bleichner 1997	Probably Low ROB	Low ROB	Low ROB	Low ROB	Probably Low ROB	Probably Low ROB
Chung 2011	Probably Low ROB	Probably High ROB	Low ROB	Probably High ROB	Low ROB	Probably Low ROB
Cui 2013	Probably High ROB	Probably High ROB	Probably High ROB	Probably Low ROB	Probably High ROB	Probably High ROB
Falcao De Arruda 2004	Probably Low ROB	Probably Low ROB	Low ROB	Low ROB	Probably Low ROB	Probably Low ROB
Ferrie 2011	Low ROB	Low ROB	Low ROB	Probably Low ROB	Low ROB	Probably Low ROB
Forestier 2008	Low ROB	Low ROB	Low ROB	Low ROB	Probably Low ROB	Probably Low ROB
Frohmader 2010	Low ROB	Low ROB	Low ROB	Probably Low ROB	Low ROB	Probably Low ROB
Giamarellos-Bourboulis 2009	Probably Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Probably Low ROB
Hayakawa 2012	Probably Low ROB	Probably High ROB	Low ROB	Probably Low ROB	Low ROB	Probably High ROB
Honeycutt 2007	Low ROB	Low ROB	Low ROB	Probably High ROB	Low ROB	Probably Low ROB
Jain 2004	Low ROB	Low ROB	Probably Low ROB	Low ROB	Low ROB	Probably Low ROB
Kate 2020	Low ROB	Low ROB	Probably High ROB	Probably Low ROB	Probably High ROB	Probably High ROB

Klarin 2005	Low ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Low ROB	Probably Low ROB
Klarin 2008	Low ROB	Low ROB	Low ROB	Probably Low ROB	Low ROB	Probably Low ROB
Knight 2009	Low ROB	Low ROB	Probably Low ROB	Low ROB	Low ROB	Probably Low ROB
Kumar 2013	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB
Kwon 2015	Probably High ROB	Probably High ROB	Low ROB	Probably Low ROB	Low ROB	Probably High ROB
Li 2007	Probably High ROB	Probably High ROB	Probably Low ROB	Probably High ROB	Probably High ROB	Probably High ROB
Litton 2021	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB
Lopez de Toro Martin-Consuegra 2014	Low ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Low ROB	Probably Low ROB
Madmoodpoor 2019	Low ROB	Low ROB	Probably Low ROB	Low ROB	Low ROB	Probably Low ROB
Malian 2012	Probably Low ROB	Probably Low ROB	Probably High ROB	Probably Low ROB	Probably High ROB	Probably High ROB
Malik 2016	Low ROB	Low ROB	Probably Low ROB	Low ROB	Low ROB	Probably Low ROB
Mallick 2018	Probably High ROB	Low ROB	Probably High ROB	Probably Low ROB	Probably Low ROB	Probably High ROB
Masjedi 2017	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB
Mayes 2014	Probably High ROB	Probably High ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably High ROB
McNaught 2005	Probably High ROB	Probably High ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably High ROB
Morrow 2010	Probably Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Probably Low ROB
Olah 2002	Probably Low ROB	Low ROB	Low ROB	Probably Low ROB	Low ROB	Probably Low ROB
Olah 2007	Probably Low ROB	Low ROB	Probably Low ROB	Low ROB	Low ROB	Probably Low ROB
PROSPECT 2021	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB
Qin 2008	Low ROB	Probably High ROB	Probably Low ROB	Low ROB	Low ROB	Probably High ROB
Rammohan 2015	Low ROB	Probably High ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably High ROB
Rayes 2005	Low ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB

Rongrungruang 2015	Probably Low ROB	Probably High ROB	Low ROB	Probably Low ROB	Probably Low ROB	Probably High ROB
Sanaie 2014	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB
Schlotterer 1987	Probably Low ROB	Low ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB
Shimizu 2011	Probably High ROB	Probably High ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably High ROB
Shimizu 2018	Low ROB	Probably High ROB	Low ROB	Low ROB	Low ROB	Probably High ROB
Shinotsuka 2008	Probably Low ROB	Probably High ROB	Probably Low ROB	Probably Low ROB	High ROB	High ROB
Simakachorn 2011	Low ROB	Low ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB
Sramek 2007	Probably High ROB	Probably High ROB	Probably High ROB	Probably High ROB	Probably Low ROB	Probably High ROB
Tan 2013	Probably High ROB	Probably High ROB	Probably High ROB	Probably High ROB	Probably High ROB	Probably High ROB
Tempe 1983	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB
Thoma 2019	Probably High ROB	Probably High ROB	Probably High ROB	Probably High ROB	Probably Low ROB	Probably High ROB
Wan 2019	Probably High ROB	Probably High ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably High ROB
Wang 2013	Probably High ROB	Low ROB	Probably High ROB	Probably Low ROB	Low ROB	Probably High ROB
Wang 2018	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB
Wang 2020	Probably High ROB	Probably High ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably High ROB
Wu 2017	Probably Low ROB	Probably Low ROB	Probably High ROB	Probably Low ROB	Low ROB	Probably High ROB
Xie 2010	Probably High ROB	Probably High ROB	Probably Low ROB	Probably High ROB	Probably High ROB	Probably High ROB
Xie 2013	Probably High ROB	Probably High ROB	Probably High ROB	Probably High ROB	Probably High ROB	Probably High ROB
Xie 2017	Probably High ROB	Probably High ROB	Probably Low ROB	Probably High ROB	Probably High ROB	Probably High ROB
Xiong 2013	Probably High ROB	Probably High ROB	Probably Low ROB	Probably High ROB	Low ROB	Probably High ROB
Yu 2007	Probably High ROB	Probably High ROB	Probably Low ROB	Probably High ROB	Probably High ROB	Probably High ROB
Zarinfar 2016	Probably High ROB	Probably High ROB	Probably Low ROB	Probably Low ROB	Probably Low ROB	Probably High ROB
Zeng 2016	Probably	Probably	Low ROB	Probably	Low ROB	Probably

	Low ROB	High ROB		Low ROB		High ROB
Zhang 2012	Probably High ROB	Probably High ROB	Probably Low ROB	Probably High ROB	Probably High ROB	Probably High ROB
Zhuang 2012	High ROB	High ROB	Probably High ROB	Probably High ROB	Probably High ROB	High ROB

Supplement Table 3. Adverse Events

Study	Serious Adverse Events (as defined by the study)	Isolation of Invasive Probiotic Organism	Associated Mortality
Besselink 2008	Placebo = 0 Probiotics = 9 (all had mesenteric ischemia)	Placebo = 0 Probiotics = 0	Placebo = 0 Probiotics = 8
PROSPECT 2021	Placebo = 0 Probiotics = 2	Placebo = 1 Probiotics = 15	Placebo = 0 Probiotics = 9 (1 death attributed to invasive probiotic infection)

Supplement Table 4. GRADE Summary of Findings for all outcomes.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics/Synbiotics	Placebo	Relative (95% CI)	Absolute (95% CI)		
Ventilator Associated Pneumonia												
17	randomised trials	serious [a]	serious [b]	not serious	not serious	none	501/2367 (21.2%)	588/2371 (24.8%)	RR 0.72 (0.59 to 0.89)	69 fewer per 1,000 (from 102 fewer to 27 fewer)	⨁⨁◯◯ LOW [c]	CRITICAL
Healthcare-Associated Pneumonia												
15	randomised trials	serious [d]	not serious	not serious	serious [e]	none	80/662 (12.1%)	130/712 (18.3%)	RR 0.70 (0.55 to 0.89)	55 fewer per 1,000 (from 82 fewer to 20 fewer)	⨁⨁◯◯ LOW	CRITICAL
Mortality												
47	randomised trials	not serious	not serious	not serious	serious [e]	none	725/3513 (20.6%)	794/3739 (21.2%)	RR 0.95 (0.87 to 1.04)	11 fewer per 1,000 (from 28 fewer to 8 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious Adverse Events												
18	randomised trials	not serious	not serious	not serious	very serious [e]	none	11/2197 (0.5%)	0/2193 (0.0%)	RR 9.96 (1.25 to 79.09)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
Other Healthcare Infections												
27	randomised trials	serious [f]	serious [g]	not serious	not serious	none	661/2209 (29.9%)	822/2288 (35.9%)	RR 0.66 (0.55 to 0.80)	122 fewer per 1,000 (from 162 fewer to 72 fewer)	⨁⨁◯◯ LOW	IMPORTANT
ICU Length of Stay												
31	randomised trials	not serious [h]	serious [i]	not serious	serious [j]	none	2806	2811	-	MD 1.38 lower (2.19 lower to 0.57 lower)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics/Synbiotics	Placebo	Relative (95% CI)	Absolute (95% CI)		
Duration of Mechanical Ventilation												
12	randomised trials	serious [k]	serious	not serious	not serious	none	785	801	-	MD 2.53 **lower** (3.74 lower to 1.31 lower)	⨁⨁◯◯ LOW	IMPORTANT
Hospital Length of Stay												
27	randomised trials	serious [l]	serious [m]	not serious	not serious	none	2824	2842	-	MD 2.21 **lower** (3.24 lower to 1.18 lower)	⨁⨁◯◯ LOW [c]	IMPORTANT
Antibiotic Days												
12	randomised trials	serious [n]	serious [o]	not serious	serious [j]	none	514	523	-	MD 1.77 **lower** (3.36 lower to 0.17 lower)	⨁◯◯◯ VERY LOW	NOT IMPORTANT
Invasive Infection with Probiotic Organism												
9	randomised trials	not serious	not serious	not serious	very serious [p]	none	15/1691 (0.9%)	1/1698 (0.1%)	RR 15.16 (2.01 to 114.60)	8 more per 1,000 (from 1 more to 67 more)	⨁⨁◯◯ LOW	CRITICAL
Organ Dysfunction												
9	randomised trials	serious [q]	serious [r]	not serious	serious [s]	none	415	392	-	SMD 0.22 SD lower (0.78 lower to 0.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Diarrhea												
13	randomised trials	not serious	not serious	not serious	serious [s]	none	1046/2143 (48.8%)	1070/2218 (48.2%)	RR 0.98 (0.85 to 1.12)	10 fewer per 1,000 (from 72 fewer to 58 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Duration of Diarrhea												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics/Synbiotics	Placebo	Relative (95% CI)	Absolute (95% CI)		
5	randomised trials	serious [t]	serious [u]	not serious	serious [p]	none	164	167	-	MD 2.59 lower (5.59 lower to 0.41 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Inotropic/Vasopressor Therapy												
4	randomised trials	not serious	serious [v]	not serious	serious [p]	none	80/281 (28.5%)	73/278 (26.3%)	RR 1.08 (0.79 to 1.48)	21 more per 1,000 (from 55 fewer to 126 more)	⊕⊕◯◯ LOW	IMPORTANT
Invasive Mechanical Ventilation												
3	randomised trials	not serious	not serious	not serious	serious [p]	none	74/122 (60.7%)	69/119 (58.0%)	RR 1.04 (0.85 to 1.27)	23 more per 1,000 (from 87 fewer to 157 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Urinary Tract Infection												
18	randomised trials	not serious	not serious	not serious	serious [p]	none	204/2099 (9.7%)	227/2150 (10.6%)	RR 0.94 (0.78 to 1.12)	6 fewer per 1,000 (from 23 fewer to 13 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
C. Difficile Infection												
5	randomised trials	serious [w]	serious [x]	not serious	serious [p]	none	37/1548 (2.4%)	52/1562 (3.3%)	RR 0.43 (0.15 to 1.17)	19 fewer per 1,000 (from 28 fewer to 6 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Catheter Related Blood Stream Infections												
8	randomised trials	serious [y]	not serious	not serious	serious [p]	none	37/1576 (2.3%)	56/1647 (3.4%)	RR 0.57 (0.27 to 1.19)	15 fewer per 1,000 (from 25 fewer to 6 more)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference; SMD: Standardised mean difference

Explanations

a. 8 studies (Hayakawa 2012, Tan 2013, Rongruang 2015, Banupriya 2015, Zeng 2016, Zarinfar 2016, Shimizu 2018, and Thoma 2019) have high or probably high ROB and their contribution weight to this outcome is 46.9% overall, which lowers our certainty in effect. Furthermore, there was evidence of a subgroup effect when comparing high vs low ROB studies for the outcome of VAP.
b. High I squared (59%) suggests important inconsistency which lowers our certainty in effect.
c. Although statistical testing suggested small study effects (publication bias), we have already lowered certainty for risk of bias, and the funnel plot did not appear asymmetric based on visual inspection. The combination of borderline risk of bias, borderline inconsistency, and borderline publication bias did not add up to lowering by 3 levels but rather by 2.
d. 8 studies (Xie 2010, Tan 2013, Xiong 2013, Rammohan 2015, Xie 2017, Wan 2019, Kate 2020, Wang 2020) have probably high or high ROB and their contribution weight to this outcome is 72.2% overall, which lowers our certainty in effect.
e. Low number of events below optimal information size contributing to imprecision which lowers our certainty in effect.
f. 14 studies (McNaught 2005, Sramek 2007, Xie 2010, Tan 2013, Xiong 2013, Cui 2013, Wang 2013, Xie 2013, Rammohan 2015, Wu 2017, Shimizu 2018, Mallick 2018, Thoma 2019, Kate 2020) have probably high or high ROB and their contribution weight to this outcome is 51.8% overall, which lowers our certainty in effect.
g. High I squared (63%) and non-overlapping confidence intervals suggests important inconsistency which lowers our certainty in effect.
h. 13 studies (McNaught 2005, Sramek 2007, Tan 2013, Xiong 2013, Banupriya 2015, Rongrungruang 2015, Rammohan 2015, Zeng 2016, Zarinfar 2016, Shimizu 2018, Mallick 2018, Wan 2019, Kate 2020) have probably high or high ROB and their contribution weight to this outcome is 43.9% overall; however, upon subgroup analysis for RoB, there was no subgroup effect found. As such, we did not rate down for RoB.
i. High I squared (86%) and non-overlapping confidence intervals suggests important inconsistency which lowers our certainty in effect.
j. The lower end of the CI is less than 1 which lowers our certainty in effect for meaningful change of at least one day.
k. 2 studies (Banupriya 2015 and Zeng 2016) have probably high ROB and their contribution weight to this outcome is 19.4% overall, which lowers our certainty in effect.
l. 15 studies (McNaught 2005, Li 2007, Zhuang 2012, Zhang 2012, Cui 2013, Mayes 2014, Banupriya 2015, Rongrungruang 2015, Rammohan 2015, Zeng 2016, Zarinfar 2016, Wu 2017, Mallick 2018, Wang 2020, Kate 2020) have probably high or high ROB and their contribution weight to this outcome is 60.5% overall, which lowers our certainty in effect.
m. High I squared (89%) and non-overlapping confidence intervals suggests important inconsistency which lowers our certainty in effect.
n. 5 studies (Tan 2013, Mayes 2014, Rammohan 2015, Shimizu 2018, Wang 2020) have probably high or high ROB and their contribution weight to this outcome is 38.4% overall, which lowers our certainty in effect.
o. High I squared (92%) and non-overlapping confidence intervals suggests important inconsistency which lowers our certainty in effect.
p. Low number of events below optimal information size and wide confidence intervals that don't exclude harm or benefit contribute to imprecision which lowers our certainty in effect.
q. 3 studies (Qin 2008, Tan 2013 and Wan 2019) have probably high ROB and their contribution weight to this outcome is 27.4% overall, which lowers our certainty in effect.
r. High I squared (95%) and non-overlapping confidence intervals suggests important inconsistency which lowers our certainty in effect.
s. Wide confidence intervals that don't exclude harm or benefit contribute to imprecision which lowers our certainty in effect.
t. One study (Mayes 2014) has probably high ROB and their contribution weight to this outcome is 23.5% overall, which lowers our certainty in effect.
u. High I squared (84%) and non-overlapping confidence intervals suggests important inconsistency which lowers our certainty in effect.
v. Non-overlapping confidence intervals suggests important inconsistency which lowers our certainty in effect.
w. One study (Zarinfar 2016) has probably high ROB and their contribution weight to this outcome is 17.8% overall, which lowers our certainty in effect.
x. High I squared (67%) and non-overlapping confidence intervals suggests important inconsistency which lowers our certainty in effect.
y. 2 studies (Qin 2008 and Thoma 2019) have probably high ROB and their contribution weight to this outcome is 35.9% overall, which lowers our certainty in effect.

Supplement Table 5. Test of Funnel Plot Asymmetry

Outcome	Number of studies	Number of studies contributing to the meta-analysis*	p-value
Mortality	47	43	0.849
VAP	17	16	0.030
HAP	15	15	0.509
ICU LOS	31	31	0.615
Hospital LOS	27	27	0.014
SAE	18	1	-
Invasive infection with a probiotic organism	9	1	-

* For binary outcomes, the relative risk cannot be estimated for studies with 0 events in both arms. Therefore, such studies do not contribute to the meta-analysis.

For the test of funnel plot asymmetry, the null hypothesis is no asymmetry. Therefore, rejecting the null indicates that there is evidence of funnel plot asymmetry.

Appendix 10. Methods & Discussion:
Methods

Systematic Search

We did not apply language restrictions and included both full publications and abstracts. We developed the search strategy with the assistance of an expert medical librarian, including the following search terms: 'randomized,' 'clinical trial,' 'nutrition support,' 'enteral nutrition,' 'probiotics,' and 'synbiotics' (see supplementary appendix for search strategy, appendix 1-5). We used the Medical Subject Headings database for identification of synonyms. We examined the reference list of full-text articles for additional relevant studies. We also searched conference proceedings within the last 2 years for the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care and Emergency Medicine (ESICM).

Study Selection

We included studies which reported on any of the following outcomes: infections including VAP, healthcare-associated pneumonia (HAP), catheter-related blood stream infections (CRBSI), *Clostridioides difficile* infections (CDI), urinary tract infections, and other healthcare-associated infections, mortality, ICU and hospital length of stay (LOS), duration of antibiotics, diarrhea (as per individual study definition), duration of diarrhea (days), organ dysfunction, isolation of an invasive probiotic organism from a sterile site or as the sole or predominant organism from a non-sterile site associated with persistent or significant disability or incapacity that is life-threatening or results in death, and serious adverse events (SAE; as per individual study

definition). We excluded trials that reported only nutritional, biochemical, metabolic, or immunologic outcomes.

In the protocol, we had planned to define diarrhea as greater than 3 liquid bowel movements per day; however, individual study details were insufficient to allow for this and instead we abstracted diarrhea based on the individual study definition. Organ dysfunction-related outcomes included the initiation of renal replacement therapy and invasive mechanical ventilation (IMV), and organ failure scales (assessed by any validated scoring system). We also collected data on the duration of IMV. We collected infectious outcomes based on individual study definitions, however, we defined CDI as positive toxin testing in the presence of clinical features (e.g. diarrhea, toxic megacolon) as per the Infectious Diseases Society of America definition [1]. If multiple endpoints were reported for any of the outcomes of interest, we used the longest duration of follow-up available for analysis.

Two reviewers independently screened, in duplicate, all potentially relevant citations generated by the search, blinded to each other's' assessments. Citations deemed potentially relevant by either screener were advanced to second stage full-text review. We subsequently reviewed full texts, again independently and in duplicate, with disagreements resolved by consensus and third-party adjudication, if required. We captured reasons for exclusion at the full-text screening stage.

Data Extraction and Quality Assessment:

We extracted the following information from included studies: study title, first author, demographic data, details of the intervention and control, outcomes, and risk of bias (RoB) for

each study. We examined the following RoB domains: sequence generation, allocation sequence concealment, blinding, selective outcome reporting, and other bias (such as stopping early and funding source). We contacted study authors for clarification when the population characteristics, method of follow-up, or outcome data were unclear or not reported. We resolved disagreements for data extraction, RoB, and GRADE assessment by discussion and consensus. We used the Guideline Development Tool (www.gradepro.org) to formulate the Summary of Findings table.

Statistical Analysis:

We performed 6 predefined subgroup analyses, comparing the effect of probiotics or synbiotics in: (1) adult versus pediatric ICU patients, (2) patients in shock versus those without shock, (3) patients with sepsis versus other critically ill patients, (4) surgical patients versus medical patients, (5) synbiotics versus probiotics alone, and (6) studies at high RoB compared to those at low RoB. We performed a post-hoc subgroup analysis comparing trials that assessed the probiotic *L. rhamnosus GG* to those that did not. We used the ICEMAN tool to judge subgroup credibility [2]. We also performed post-hoc sensitivity analyses without data from pediatric studies and without data from high ROB studies. Furthermore, at the request of reviewers, we performed additional post-hoc subgroup analyses comparing trials that assessed the probiotic *L. plantarum* to those that did not.

We assessed heterogeneity between trials using visual inspection of the forest plots, the chi-squared test for homogeneity (whereby $p < 0.1$ indicates important heterogeneity), and the I^2 statistic [3]. We constructed funnel plots and tested for asymmetry to assess for publication

bias [4]. We conducted trial sequential analysis (TSA) [5] using a random effects model for VAP. For the TSA, we used a statistical significance level of 5%, a power of 80%, and a relative risk reduction of 10%. We used a model variance-based heterogeneity correction and performed this analysis using Trial Sequential Analysis v.0.9.5.10 beta software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, www.ctu.dk/tsa).

Discussion

Probiotic prescriptions for hospitalized-patients have increased from 1.0% to 2.9% over a 6-year period due to their potentially promising health benefits [6]. Some commonly cited mechanisms include induction of host cell antimicrobial peptides, release of antimicrobial factors, suppression of immune cell proliferation, stimulation of IgA production, antioxidative activity, inhibition of epithelial NFκB activation, and other epithelial barrier protective effects maintaining microbiome biodiversity [7]. It is possible that a combination of these effects could contribute to improved health and the prevention of nosocomial infections. However, it is also possible that some of the proposed mechanisms of probiotics may be dependent upon the baseline comorbidities, pre-existing or perpetuating perturbations of the host microbiome, and as yet, unknown factors; as such, probiotics may be less effective in critically ill patients than other inpatient populations or community dwelling persons.

Recent evidence illustrates that probiotics also have the potential for harm by delaying or inhibiting re-establishment of the healthy microbiome following in critical illness [8]. This is especially important as the regulatory requirements for probiotics before marketing are vastly different than for drug trials [9], and their prescription in hospitals is growing [6].

There has been a considerable interest in the use of probiotics in critical illness as reflected in multiple systematic reviews published over the last decade [10-13]. The most recent Cochrane review of ICU patients who are mechanically ventilated indicated a reduction in VAP with the use of probiotics, albeit with low certainty evidence [13]. Clinical practice guidelines differ in their recommendations, with some suggesting probiotics for select medical and surgical patients for whom trials have documented safety and benefit such as patients post liver transplantation, pancreatectomy and trauma victims [14-16], whereas others make no recommendation due to insufficient or conflicting data [1, 17]. However, our prespecified subgroup analyses examining various specific populations do not support credible subgroup findings based on specific subsets of the critically ill population.

References

1. McDonald LC, Gerding DN, Johnson S *et al*: **Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)**. *Clinical Infectious Diseases* 2018, **66**(7):e1-e48.
2. Schandelmaier S, Briel M, Varadhan R *et al*: **Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses**. *Canadian Medical Association Journal* 2020, **192**(32):E901.
3. Higgins JP, Thompson SG, Deeks JJ *et al*: **Measuring inconsistency in meta-analyses**. *BMJ* 2003, **327**(7414):557-560.
4. Egger M, Davey Smith G, Schneider M *et al*: **Bias in meta-analysis detected by a simple, graphical test**. *BMJ* 1997, **315**(7109):629-634.
5. Wetterslev J, Jakobsen JC, Gluud C: **Trial Sequential Analysis in systematic reviews with meta-analysis**. *BMC Med Res Methodol* 2017, **17**(1):39.
6. Yi SH, Jernigan JA, McDonald LC: **Prevalence of probiotic use among inpatients: A descriptive study of 145 U.S. hospitals**. *Am J Infect Control* 2016, **44**(5):548-553.
7. Klingensmith NJ, Coopersmith CM: **The Gut as the Motor of Multiple Organ Dysfunction in Critical Illness**. *Crit Care Clin* 2016, **32**(2):203-212.
8. Suez J, Zmora N, Zilberman-Schapira G *et al*: **Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT**. *Cell* 2018, **174**(6):1406-1423.e1416.

9. Venugopalan V, Shriner KA, Wong-Beringer A: **Regulatory oversight and safety of probiotic use**. *Emerg Infect Dis* 2010, **16**(11):1661-1665.
10. Manzanares W, Lemieux M, Langlois PL *et al*: **Probiotic and synbiotic therapy in critical illness: a systematic review and meta-analysis**. *Crit Care* 2016, **19**:262.
11. Gou S, Yang Z, Liu T *et al*: **Use of probiotics in the treatment of severe acute pancreatitis: a systematic review and meta-analysis of randomized controlled trials**. *Critical Care* 2014, **18**(2):R57.
12. Petrof EO, Dhaliwal R, Manzanares W *et al*: **Probiotics in the critically ill: A systematic review of the randomized trial evidence**. *Critical Care Medicine* 2012, **40**(12):3290-3302.
13. Bo L, Li J, Tao T *et al*: **Probiotics for preventing ventilator-associated pneumonia**. *Cochrane Database Syst Rev* 2014, **10**(10):Cd009066.
14. Rayes N, Seehofer D, Müller AR *et al*: **[Influence of probiotics and fibre on the incidence of bacterial infections following major abdominal surgery - results of a prospective trial]**. *Z Gastroenterol* 2002, **40**(10):869-876.
15. Zhang Y, Chen J, Wu J *et al*: **Probiotic use in preventing postoperative infection in liver transplant patients**. *Hepatobiliary Surg Nutr* 2013, **2**(3):142-147.
16. Gu WJ, Deng T, Gong YZ *et al*: **The effects of probiotics in early enteral nutrition on the outcomes of trauma: a meta-analysis of randomized controlled trials**. *JPEN J Parenter Enteral Nutr* 2013, **37**(3):310-317.
17. McClave SA, Taylor BE, Martindale RG *et al*: **Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)**. *JPEN J Parenter Enteral Nutr* 2016, **40**(2):159-211.