Supplementary Appendix

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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)

(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)

(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)
- 114 "Randomized Controlled Trial (topic)"/ (170030)
- 115 Controlled Clinical Trial/ (558919)
- 116 exp Controlled Clinical Trials as Topic/ (311573)
- 117 "Controlled Clinical Trial (topic)"/ (10466)
- 118 Randomization/ (185218)
- 119 Random Allocation/ (181481)
- 120 Double-Blind Method/ (287236)
- 121 Double Blind Procedure/ (167007)
- 122 Double-Blind Studies/ (278151)
- 123 Single-Blind Method/ (62354)
- 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 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 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)
- (CPAP or nCPAP or APRV).mp. (26117) 218
- 219 airway pressure release ventilat*.mp. (778)
- 220 intermittent positive pressure.mp. (8199)
- 221 (IPPB or IPPV).mp. (2387)
- ((artificial* or controlled or mechanical*) adj3 (respirat* or ventilator? or ventilation or vent support)).mp. 222 (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
- MeSH descriptor: [Bifidobacterium] explode all trees 721 #2
- #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
- #6 MeSH descriptor: [Inulin] explode all trees 236
- #7 MeSH descriptor: [Leuconostocaceae] explode all trees
- #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 146
- #18 MeSH descriptor: [Synbiotics] explode all trees
- #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

0

2

#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 laezhribod 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

#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

 MeSH descriptor: [Nutritional Requirements] this term only 577 MeSH descriptor: [Nutritional Support] this term only 244 MeSH descriptor: [Parenteral Nutrition] explode all trees 1660 MeSH descriptor: [Enteral Nutrition] this term only 1844 (Nutrition* or feed* or enteral or parenteral or total): ti, ab 334435 #25 or #26 or #27 or #28 or #29 or #30 335004 (Microbiome* or microbiotica or microbial antagonism or bacterial interference): ti, ab 2165 MeSH descriptor: [Microbiota] explode all trees 710 MeSH descriptor: [Antibiosis] this term only 28 #32 or #33 or #342689 #36 (flora or microbiota or microflora): ti, ab 7823 MeSH descriptor: [Intestines] explode all trees 6343 MeSH descriptor: [Digestive System] explode all trees 16630 (gut or intestinal): ti, ab 19479 #41 #36 and #40 4550 #42 #35 or #41 6265 #43 #31 and #42 2154 #44 #24 and #43 1092 #45 MeSH descriptor: [Spiss] explode all trees 4557 MeSH descriptor: [Shock, Septic] explode all trees 973 MeSH descriptor: [Intensive Care Units] explode all trees 3621 MeSH descriptor: [Critical Care] explode all trees 2070 #49 MeSH descriptor: [Critical Illness] explode all trees 2289
 MeSH descriptor: [Parenteral Nutrition] explode all trees 1660 MeSH descriptor: [Enteral Nutrition] this term only 1844 (Nutrition* or feed* or enteral or parenteral or total):ti,ab 334435 #25 or #26 or #27 or #28 or #29 or #30 335004 (Microbiome* or microbiotica or microbial antagonism or bacterial interference):ti,ab 2165 MeSH descriptor: [Microbiota] explode all trees 710 MeSH descriptor: [Antibiosis] this term only 28 #32 or #33 or #342689 #36 (flora or microbiota or microflora):ti,ab 7823 MeSH descriptor: [Intestines] explode all trees 6343 MeSH descriptor: [Digestive System] explode all trees 16630 (gut or intestinal):ti,ab 19479 #40 #37 or #38 or #3933801 #41 #36 and #40 4550 #43 #31 and #42 2154 #44 #24 and #43 1092 #45 MeSH descriptor: [Spesis] explode all trees 4557 #46 MeSH descriptor: [Shock, Septic] explode all trees 973 #47 MeSH descriptor: [Intensive Care Units] explode all trees 3621
 MeSH descriptor: [Enteral Nutrition] this term only 1844 (Nutrition* or feed* or enteral or parenteral or total):ti, ab 334435 #25 or #26 or #27 or #28 or #29 or #30 335004 (Microbiome* or microbiotica or microbial antagonism or bacterial interference):ti, ab 2165 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 #43 #31 and #42 2154 #44 #24 and #43 1092 #45 MeSH descriptor: [Sock, Septic] explode all trees 973 #47 MeSH descriptor: [Intensive Care Units] explode all trees 3621 #48 MeSH descriptor: [Critical Care] explode all trees 2070
 #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
 #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: [Spesis] 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
 #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
 MeSH descriptor: [Microbiota] explode all trees 710 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
 #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
 #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
 #36 (flora or microbiotary 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 #33801 #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: [Critical Care] explode all trees 2070
 #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 2070
 #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
#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 McSH descriptor: [Sepsis] explode all trees 4557 #46 McSH descriptor: [Shock, Septic] explode all trees 973 #47 McSH descriptor: [Intensive Care Units] explode all trees 3621 #48 McSH descriptor: [Critical Care] explode all trees 2070
#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
#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
 #42 #35 or #41 6265 #43 #31 and #42 2154 #44 #24 and #43 1092 #45 MeSH descriptor: [Sepsis] explode all trees 457 #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
 #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
#44#24 and #431092#45MeSH descriptor: [Sepsis] explode all trees4557#46MeSH descriptor: [Shock, Septic] explode all trees973#47MeSH descriptor: [Intensive Care Units] explode all trees3621#48MeSH descriptor: [Critical Care] explode all trees2070
 #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
#46MeSH descriptor: [Shock, Septic] explode all trees973#47MeSH descriptor: [Intensive Care Units] explode all trees3621#48MeSH descriptor: [Critical Care] explode all trees2070
#47MeSH descriptor: [Intensive Care Units] explode all trees3621#48MeSH descriptor: [Critical Care] explode all trees2070
#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"

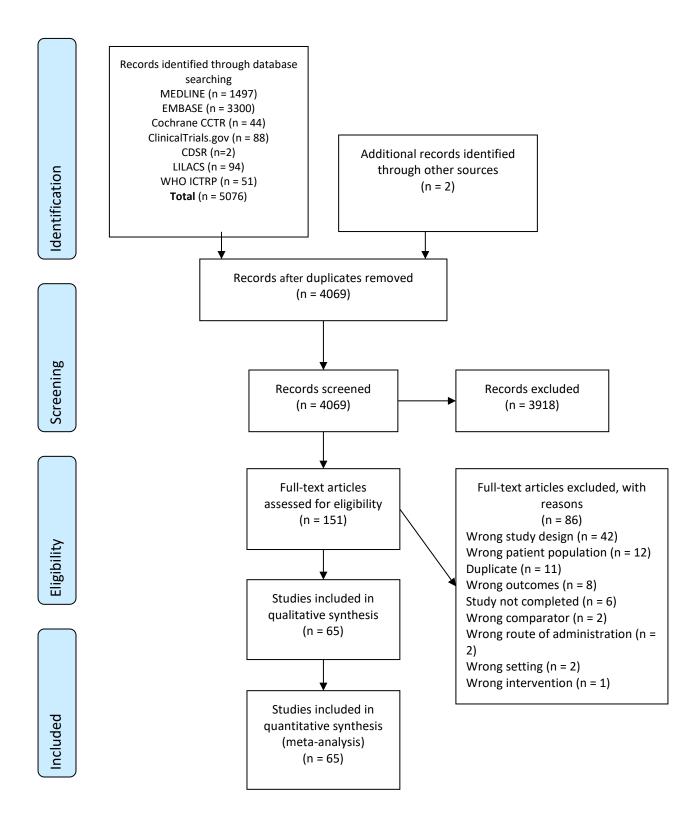
AND

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

<u>Supplement Figure 2. Forest plot. Healthcare Associated Pneumonia (HAP)</u>: 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)</u>

	Probiotics/Synbio	otics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Olah 2002	2	22	2	23	1.6%	1.05 [0.16, 6.79]	2002	
Rayes 2005	0	33	1	33	0.6%	0.33 [0.01, 7.90]	2005	
Honeycutt 2007	2	31	0	30	0.6%	4.64 [0.24, 96.69]	2007	
Olah 2007	2	33	4	29	2.1%	0.44 [0.09, 2.23]	2007	
Alenka 2007	4	26	34	87	6.4%	0.39 [0.15, 1.01]	2007	
Besselink 2008	24	152	16	144	16.2%	1.42 [0.79, 2.56]	2008	
Xie 2010	4	20	7	19	5.1%	0.54 [0.19, 1.56]	2010	
Tan 2013	2	26	1	26	1.0%	2.00 [0.19, 20.72]	2011	
Xiong 2013	7	17	14	21	13.6X	0.62 [0.32, 1.18]	2013	—•+
Rammohan 2015	2	39	3	36	1.9%	0.62 [0.11, 3.47]	2015	
Xie 2017	3	48	4	48	2.7%	0.75 [0.18, 3.17]	2017	
Wan 2019	17	38	28	38	35.1%	0.61 [0.41, 0.91]	2019	
Wang 2020	0	28	1	33	0.6%	0.39 [0.02, 9.23]	2020	
Kate 2020	9	39	15	37	11.6%	0.57 [0.28, 1.14]	2020	
Litton 2021	2	110	0	108	0.6%	4.91 [0.24, 101.10]	2021	
Total (95% CI)		662		712	100.0%	0.70 [0.55, 0.89]		•
Total events	60		130					-
Heterogeneity: Tau ² =	- 0.00; Chi ² = 13.00), df =	14 (P =	0.53); I	ř = 0%			0.01 0.1 1 10 100
Test for overall effect	: Z = 2.96 (P = 0.00	3)						Favours Probiotics Favours Placebo

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)

	Probiotics/Syn	biotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Klarin 2005	0	9	3	6	5.3%	0.13 [0.01, 2.16]	2005	
Alenka 2007	0	26	3	87	5.0%	0.47 [0.02, 8.73]	2007	
Klarin 2008	2	22	3	22	10.6%	0.67 [0.12, 3.61]	2008	
Qin 2008	5	36	13	38	17.5%	0.41 [0.16, 1.02]	2008	
Barraud 2010	3	87	11	80	14.3%	0.25 [0.07, 0.87]	2010	
Angurana 2018	2	50	5	50	11.3%	0.40 [0.08, 1.97]	2018	
Thoma 2019	6	28	12	30	18.4%	0.54 [0.23, 1.23]	2019	
Cook 2021	19	1318	6	1332	17.6%	3.20 [1.28, 7.99]	2021	_
Total (95% CI)		1576		1647	100.0%	0.57 [0.27, 1.19]		
Total events	37		56					-
Heterogeneity: Tau ² =	 0.58; Chl² = 16. 	81, df =	7(P = 0)	.02); f ²	- 58%			0.01 0.1 1 10 100
Test for overall effect								0.01 0.1 1 10 100 Favours Probiotics Favours Placebo

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)

	Probiotics/Synt	oiotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Olah 2002	1	22	7	23	0.6%	0.15 [0.02, 1.12]	2002	
jain 2004	33	45	26	45	6.6X	1.27 [0.93, 1.72]	2004	
Falcao De Arruda 2004	5	10	10	10	4.4%	0.52 [0.29, 0.96]	2004	
Rayes 2005	1	33	16	33	0.6%	0.06 [0.01, 0.44]	2005	
McNaught 2005	21	52	22	51	5.4%	0.94 [0.59, 1.48]	2005	
Klarin 2005	6	9	5	6	3.7%	1.07 [0.53, 2.17]	2005	
Olah 2007	9	33	15	29	4.0%	0.53 [0.27, 1.02]	2007	
Honeycutt 2007	6	31	3	30	1.7%	1.94 [0.53, 7.04]	2007	
Sramek 2007	9	15	4	10	3.0%	1.50 [0.63, 3.56]	2007	
Giamarellos-Bourboulis 2009	7	36	22	36	3.7%	0.32 [0.16, 0.65]	2009	
Barraud 2010	30	87	30	60	5.6%	0.92 [0.61, 1.38]	2010	
Xie 2010	7	20	10	19	3.6%	0.67 [0.32, 1.39]	2010	
Tan 2013	9	26	15	26	4.2%	0.60 [0.32, 1.12]	2011	
Xie 2013	7	21	12	26	3.6%	0.72 [0.35, 1.50]	2013	- _
Xiong 2013	6	17	17	21	4.6%	0.58 [0.34, 1.00]	2013	
Cul 2013	2	23	17	47	1.5%	0.24 [0.06, 0.95]	2013	
Wang 2013	6	62	37	121	3.6%	0.42 [0.21, 0.85]	2013	_ _
Lopez de Toro Martin-Consuegra 2014	14	46	19	43	4.7%	0.69 [0.40, 1.20]	2014	
Sanale 2014	2	20	5	20	1.3%	0.40 [0.09, 1.83]	2014	
Rammohan 2015	5	39	14	36	2.6%	0.33 [0.13, 0.82]	2015	
Wu 2017	4	56	12	48	2.2%	0.29 [0.10, 0.83]	2017	
Shimizu 2016	10	35	25	37	4.6%	0.42 [0.24, 0.75]	2018	_ -
Mallick 2018	10	40	19	40	4.2%	0.53 [0.28, 0.99]	2018	
Angurana 2018	7	50	10	50	2.9%	0.70 [0.29, 1.69]	2018	
Thoma 2019	3	28	8	30	1.6%	0.40 [0.12, 1.36]	2019	
Kate 2020	23	35	24	37	6.3%	1.01 [0.72, 1.42]	2020	+
Cook 2021	414	1318	418	1332	7.6%	1.00 [0.89, 1.12]	2021	+
Total (95% CI)		2209		2288	100.0%	0.66 [0.55, 0.80]		•
Total events	661		822					-
Heterogeneity: $Tau^2 = 0.11$; $Chl^2 = 70.8$ Test for overall effect: $Z = 4.28$ (P < 0.00		00001);	r ² = 63%	í				0.01 0.1 1 10 10 Favours Probiotics Favours Placebo

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)

	Probiotics/Synt	oiotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Klarin 2008	0	22	4	22	9.7%	0.11 [0.01, 1.95]	2008	
Morrow 2010	4	68	13	70	28.6%	0.32 [0.11, 0.92]	2010	_ _
Zarinfar 2016	1	30	6	30	15.4%	0.17 [0.02, 1.30]	2016	
Cook 2021	32	1318	28	1332	38.1%	1.15 [0.70, 1.91]	2021	_ _
Litton 2021	0	110	1	108	6.1%	0.33 [0.01, 7.95]	2021	
Total (95% CI)		1548		1562	100.0%	0.43 [0.15, 1.17]		-
Total events	37		52					
Heterogeneity: Tau ² =	• 0.64; Chl ² = 9.3(0, df = 4	P = 0.0)5); P =	57%			
Test for overall effect:	: Z = 1.65 (P = 0.)	10)						0.005 0.1 1 10 200 Favours Probiotics Favours Placebo

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)

	Probiotics/Synb	iotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Klarin 2005	2	9	1	6	0.7%	1.78 [0.20, 16.10]	2005	
Rayes 2005	1	33	12	33	0.6%	0.08 [0.01, 0.60]	2005	
Alenka 2007	0	26	1	67	0.3%	1.09 [0.05, 25.90]	2007	
Honeycutt 2007	2	31	0	30	0.4%	4.64 [0.24, 96.69]	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	60	1.6%	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	26	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	1316	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: $Tau^2 = 0.00$; Ch Test for overall effect: $Z = 0.71$.7 (P = ().73); l ² ·	- 0%				0.01 0.1 1 10 10 Favours Probiotics Favours Placebo

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)

	Probioti	cs/Synbi	otics	Р	lacebo			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
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	6.7%	-4.70 [-7.43, -1.97]	2008	
Forestler 2008	28.6	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	66	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	6	25	7.0%	-5.60 [-9.03, -2.17]	2016	
Zeng 2016	13.1	9.8	116	19.5	11.3	117	6.6%	-6.40 [-9.11, -3.69]	2016	
Angurana 2018	7	1.48	50	7	1.46	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; Chl² =	67.89, d	f = 10 (f	< 0.00	0001);	r ² = 85	×			-20 -10 0 10 20
Test for overall effect: Z	= 4.07 (P <	: 0.0001))							Favours Probiotics Favours Placebo

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)

	Probiot	ics/Synbi	otics	P	lacebo			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
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	<u> </u>
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	16.6	4.6	129	5.4%	1.70 [0.46, 2.94]	2009	-
Morrow 2010	21.4	14.9	66	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	60	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	36	5.0%	-2.01 [-3.82, -0.20]	2012	
Cul 2013	10.4	3.9	23	19.2	8.5	47	4.0%	-8.60 [-11.71, -5.69]	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	5.6%	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	<u> </u>
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	116	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	3.6%	-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	5.6%	-0.20 [-0.73, 0.33]	2018	4
Madmoodpoor 2019	14.2	8.6	46	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%	-7.60 [-13.75, -1.65]	2020	
Cook 2021	25.7	21.5	1316	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: Tau ² = 4.71; Ch ² = 224. Test for overall effect: $Z = 4.20$ (P < 0.0)		6 (P < 0.0)0001);	l ² = 667	6				-	-20 -10 0 10 20 Favours Probiotics Favours Placebo

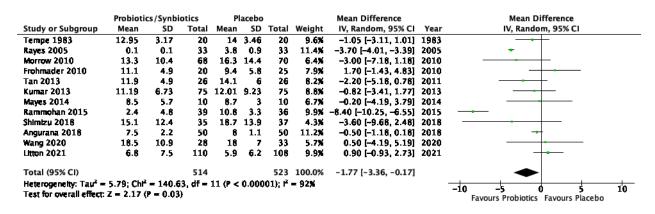
Supplement Figure 9. Forest plot. ICU Length of Stay:

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)

		cs/Synbi			lacebo			Mean Difference		Mean Difference
tudy or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
ain 2004	8.2	3	45	6.6	2.5	45	5.2%	1.40 [0.26, 2.54]	2004	+
alcao De Arruda 2004	11.25	4.8	10	27	16.2	10	0.5%	-15.75 [-26.22, -5.28]	2004	
IcNaught 2005	5.3	5.3	52	4.3	5	51	4.3%	1.00 [-0.99, 2.99]	2005	+
ayes 2005	6.6	0.9	33	10.2	1.8	33	5.6%	-1.40 [-2.09, -0.71]	2005	+
larin 2005	16.2	11	9	16.6	15.7	6	0.4%	-2.60 [-15.64, 10.44]	2005	
amek 2007	16.2	16	15	10.7	15.5	10	0.4%	5.50 [-7.74, 18.74]	2007	
lenka 2007	13.4	3.7	26	14.8	4.2	26	4.1%	-1.40 [-3.55, 0.75]	2007	
larin 2006	8.9	5.1	22	21.4	17.2	22	1.0%	-12.50 [-20.00, -5.00]	2008	
esselink 2008	6.6	17.1	152	3	9.3	144	3.1%	3.60 [0.49, 6.71]	2008	
night 2009	6.5	1.5	130	7.8	2.1	129	5.7%	-1.30 [-1.74, -0.86]	2009	•
orrow 2010	14.8	11.8	68	14.6	11.6	70	2.5%	0.20 [-3.71, 4.11]	2010	
ohmader 2010	7.3	5.7	20	6.1	4	25	3.3%	-0.80 [-3.75, 2.15]	2010	
arraud 2010	18.7	12.4	87	20.2	20.8	60	1.7%	-1.50 [-6.75, 3.75]	2010	
errie 2011	32.04	24.46	13	29.75	18.81	14	0.2%	2.29 [-14.26, 18.84]	2011	
an 2013	6.6	3.8	26	10.7	7.3	26	3.1%	-3.90 [-7.06, -0.74]	2011	
ong 2013	6.36	5.68	17	12.2	6.43	21	2.5%	-5.82 [-9.67, -1.97]	2013	
pez de Toro Martin-Consuegra 2014	10	3.6	46	6.6	3.2	43	4.9%	1.20 [-0.21, 2.61]	2014	+
ongrungruang 2015	33.3	19.6	75	18.6	5.2	75	2.0%	14.50 [9.91, 19.09]	2015	
inupriya 2015	7.7	4.6	75	12.54	9.91	75	3.6%	-4.64 [-7.31, -2.37]	2015	
ammohan 2015	4.3	3.1	39	4.2	2.2	36	5.1%	0.10 [-1.11, 1.31]	2015	+
arinfar 2016	14.2	4.7	30	17.6	6.5	30	3.4%	-3.40 [-6.27, -0.53]	2016	
alik 2016	10.9	3.9	24	15.8	7.8	25	2.6%	-4.90 [-8.33, -1.47]	2016	
ang 2016	21.5	13.5	118	30.1	33.8	117	1.2%	-8.60 [-15.19, -2.01]		
ngurana 2016	7	2	50	6.6	1.4	50	5.6%	-1.60 [-2.46, -1.12]	2018	+
nimizu 2016	26.6	23.2	35	30.1	21.6	37	0.6%	-3.50 [-13.87, 6.87]	2018	
allick 2018	8.1	5.9	40	9.2	5.9	40	3.6%	-1.10 [-3.69, 1.49]	2018	-+-
admoodpoor 2019	11.6	6	48	18.6	6.3	54	3.4%	-7.00 [-9.82, -4.18]	2019	<u> </u>
an 2019	10.32	5.31	38	14.24	6.79	36	3.5%	-3.92 [-6.66, -1.18]		
ate 2020	5.58	1.73	35	8.8	1.5	37	5.5%	-3.22 [-3.97, -2.47]		+
tton 2021	2.25	3.3	110	2.25	3.3	108	5.4%	0.00 [-0.88, 0.88]		+
ook 2021	12.7	8.9	1318	12.7	7.4	1332	5.6X	0.00 [-0.62, 0.62]		+
otal (95% CI)			2806			2811	100.0%	-1.38 [-2.19, -0.57]		•
eterogeneity: Tau ² = 2.93; Chl ² = 213.	07, df = 34	0 (P < 0.0	0001):	r ² = 86%	"				-	do do do do do
st for overall effect: Z = 3.34 (P = 0.0)										-20 -10 0 10 20 Favours Probiotics Favours Placebo

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)



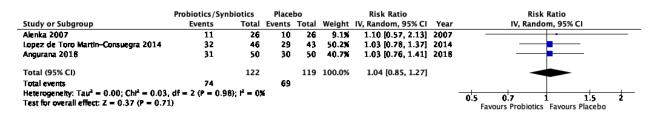
Supplement Figure 11. Forest plot. Organ Dysfunction:

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)

	Probioti	cs/Synbi	otics	Р	lacebo			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Alenka 2007	3.6	0.43	26	2.65	0.5	26	10.5%	2.01 [1.33, 2.68]	2007	
Alberda 2007	4	1.9	19	4.2	1.6	9	9.9%	-0.11 [-0.90, 0.69]	2007	
Sesselink 2008	1.6	1.6	152	1.5	1.5	144	12.1%	0.06 [-0.16, 0.29]	2008	
Qin 2008	4	6.2	38	7	6.2	36	11.4%	-0.48 [-0.94, -0.02]	2008	
Tan 2013	3.5	4.2	26	4.4	4.7	26	11.1%	-0.20 [-0.74, 0.35]	2011	
Sanale 2014	7.5	2.01	20	11.3	3.78	20	10.5%	-1.23 [-1.91, -0.55]	2014	
Lopez de Toro Martin-Consuegra 2014	6	3.1	46	7.2	4.2	43	11.6%	-0.32 [-0.74, 0.09]	2014	
Angurana 2018	1	0.37	50	3	1.46	50	11.4%	-1.84 [-2.31, -1.37]	2018	(
Wan 2019	2.39	1.52	38	2.02	1.69	36	11.5%	0.23 [-0.22, 0.68]	2019	- +-
Total (95% CI)			415			392	100.0%	-0.22 [-0.78, 0.35]		
Heterogeneity: $Tau^2 = 0.67$; $Chl^2 = 106.1$	80, df = 8	(P < 0.00))001); P	- 93%						<u> </u>
Test for overall effect: Z = 0.76 (P = 0.4)										-2 -1 0 1 2 Favours Probiotics Favours Placebo

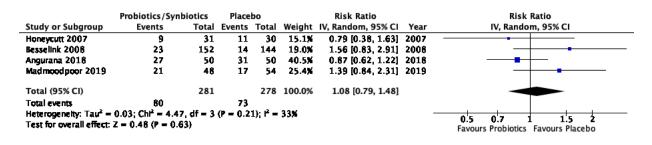
Supplement Figure 12. Forest plot. Incidence of Invasive Mechanical Ventilation:

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)



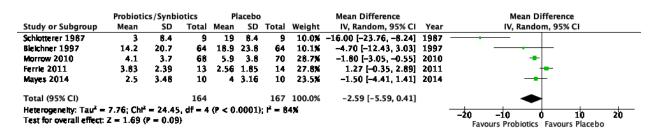
Supplement Figure 14. Forest plot. Incidence of diarrhea:

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)

	Probiotics/Syn	biotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Bleichner 1997	18	64	24	64	6.2%	0.75 [0.45, 1.24]	1997	-+-
Alberda 2007	0	19	0	9		Not estimable	2007	
Yu 2007	0	100	11	100	0.2%	0.04 [0.00, 0.73]	2007	
Besselink 2008	25	152	28	144	6.5%	0.85 [0.52, 1.38]	2008	
Knight 2009	7	130	9	129	1.9%	0.77 [0.30, 2.01]	2009	
Morrow 2010	42	68	44	70	16.7%	0.98 [0.76, 1.27]	2010	+
Barraud 2010	48	87	42	60	15.1%	1.05 [0.79, 1.39]	2010	+
Chung 2011	4	6	3	7	1.5%	1.17 [0.39, 3.51]	2011	
Shimizu 2011	3	46	17	121	1.3%	0.46 [0.14, 1.51]	2011	
Rongrungruang 2015	19	75	14	75	4.4%	1.36 [0.74, 2.50]	2015	_
Madmoodpoor 2019	7	46	15	54	2.6%	0.53 [0.23, 1.18]	2019	
Wang 2020	12	28	6	33	3.1%	1.77 [0.84, 3.70]	2020	
Cook 2021	861	1316	855	1332	40.4%	1.02 [0.96, 1.08]	2021	•
Total (95% CI)		2143		2218	100.0%	0.98 [0.85, 1.12]		•
Total events	1046		1070					
Heterogeneity: Tau ² = Test for overall effect: 1			1 (P = 0	.21); ľ	= 24%			0.005 0.1 1 10 200 Favours Probiotics Favours Placebo

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)

	Probiotics/Synl	biotics	Place	bo		Risk Ratio		Ris	k Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Rand	lom, 95% Cl
Shinotsuka 2008	0	23	0	16		Not estimable	2008		
Morrow 2010	0	68	0	70		Not estimable	2010		
Tan 2013	0	26	0	26		Not estimable	2011		
Simakachorn 2011	0	41	0	39		Not estimable	2011		
Kumar 2013	0	75	0	75		Not estimable	2013		
Sanale 2014	0	20	0	20		Not estimable	2014		
Rongrungruang 2015	0	75	0	75		Not estimable	2015		
Wang 2018	0	45	0	45		Not estimable	2018		
Cook 2021	15	1316	1	1332	100.0%	15.16 [2.01, 114.60]	2021		
Total (95% CI)		1691		1698	100.0%	15.16 [2.01, 114.60]			
Total events	15		1						
Heterogeneity: Not appl	icable								مله مله ل
Test for overall effect: Z		08)						0.01 0.1 Favours Probiotic	1 10 100 s Favours Placebo

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)

	Probiot	ics/Synbi	otics		lacebo			Mean Difference		Mean Difference
itudy or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
.27.1 Hospital LOS – Adults										
ain 2004	16.2	3.9	45	16.5	4.5	45	5.0%	-0.30 [-2.04, 1.44]	2004	+
AcNaught 2005	5.35	5.34	52	4.35	3.81	51	5.0%	1.00 [-0.79, 2.79]	2005	
ayes 2005	27.8	2.4	33	27.9	2.1	33	5.5%	-0.10 [-1.19, 0.99]	2005	+
2007	42	5	14	49	6.8	11	2.6%	-7.00 [-11.80, -2.20]	2007	
esselink 2008	28.9	41.5	152	23.5	25.9	144	1.3×	5.40 [-2.44, 13.24]	2008	
prestler 2006	29.5	16.9	102	30.5	17.6	106	2.7%	-1.00 [-5.69, 3.69]	2008	
night 2009	20.5	5.4	130	16.6	4.8	129	5.4%	1.70 [0.46, 2.94]	2009	-
arraud 2010	26.6	22.3	87	28.9	26.4	60	1.4%	-2.30 [-9.74, 5.14]	2010	
lorrow 2010	21.4	14.9	66	21.7	17.4	70	2.3%	-0.30 [-5.70, 5.10]	2010	
errie 2011	54.5	31.26	13	59.04	33.92	14	0.2%	-4.54 [-29.13, 20.05]	2011	
hang 2012	42	5	33	45	6.1	33	4.2%	-3.00 [-5.69, -0.31]	2012	
huang 2012	13.17	3.79	42	15.18	4.39	36	5.0%	-2.01 [-3.82, -0.20]		
ul 2013	10.4	3.9	23	19.2	8.5	47	4.0%	-8.60 [-11.71, -5.69]		
opez de Toro Martin-Consuegra 2014	20.8	5.9	46	24.2	6.4	43	4.3%	-3.40 [-5.96, -0.84]	2014	
layes 2014	1.04	0.03	10	1.02	0.64	10	5.6%	0.02 [-0.38, 0.42]		
ongrungruang 2015	24.6	21.7	75	28.2	35.1	75	1.0%	-3.60 [-12.94, 5.74]		
ammohan 2015	8.4	2.9	39	17.9	5.2	36	4.9%	-9.50 [-11.43, -7.57]	2015	
eng 2016	13.5	12.4	116	10.6	10.2	117	4.0%	2.90 [-0.00, 5.80]	2016	
arinfar 2016	24.1	5.6	30	27.4	6.6	30	3.6%	-3.30 [-6.40, -0.20]	2016	
íu 2017	29.7	12.3	58	40.5	15.7	51	2.3%	-10.80 [-16.15, -5.45]	2017	
tallick 2016	18.7	1.2	40	18.9	1.2	40	5.6%	-0.20 [-0.73, 0.33]	2018	4
ladmoodpoor 2019	14.2	8.6	48	21.1	5.7	54	4.0%	-6.90 [-9.77, -4.03]	2019	
/ang 2020	16.7	4.7	28	19.7	9.3	33	3.4%	-3.00 [-6.62, 0.62]	2020	
ate 2020	11.7	9.3	35	19.5	15.8	37	2.0%	-7.80 [-13.75, -1.85]	2020	
itton 2021	10	5.26	110	9	5.26	108	5.3%	1.00 [-0.40, 2.40]	2021	+
ook 2021	25.7	21.5	1316	25	20	1332	5.2%	0.70 [-0.88, 2.28]	2021	+-
ubtotal (95% CI)			2749			2767	96.5%	-2.06 [-3.10, -1.03]		◆
leterogeneity: $Tau^2 = 4.54$; $Chl^2 = 214$. lest for overall effect: $Z = 3.90$ (P < 0.00		5 (P < 0.0)0001);	I ² = 867	"					
.27.2 Hospital LOS - Pediatrics										
lanupriya 2015 Subtotal (95% CI)	13.13	7.71	75 75	19.17	13.51	75 75	3.5X 3.5%	-6.04 [-9.56, -2.52] -6.04 [-9.56, -2.52]	2015	→
ieterogeneity: Not applicable 'est for overall effect: Z = 3.36 (P = 0.00	06)									
otal (95% CI)			2824			2842	100.0%	-2.21 [-3.24, -1.18]		•
leterogeneity: Tau ² = 4.71; Chl ² = 224.4	42. df = 2	6 (P < 0.0	00001):	l ² = 889	"				-	
est for overall effect: Z = 4.20 (P < 0.00					-					-20 -10 0 10 20
est for subgroup differences: $Ch^2 = 4.5$										Favours Probiotics Favours Placebo

<u>Supplement Figure 18. Forest plot. Hospital Length of Stay (LOS) by Quality of Study</u>: 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)</u>

		ics/Synbi			lacebo			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.32.1 Hospital LOS – High ROB										
McNaught 2005	5.35	5.34	52	4.35	3.81	51	5.0%	1.00 [-0.79, 2.79]		+
LI 2007	42	5	14	49	6.8	11	2.6%	-7.00 [-11.80, -2.20]		
Zhuang 2012	13.17	3.79		15.18	4.39	36	5.0%	-2.01 [-3.82, -0.20]		
Zhang 2012	42	5	33	45	6.1	33	4.2%	-3.00 [-5.69, -0.31]		
Cul 2013	10.4	3.9	23	19.2	8.5	47	4.0%	-8.60 [-11.71, -5.69]		
Mayes 2014	1.04	0.03	10	1.02	0.64	10	5.6%	0.02 [-0.38, 0.42]		1
Banupriya 2015	13.13	7.71		19.17		75	3.5%	-6.04 [-9.56, -2.52]		
Rongrungruang 2015	24.6	21.7	75	28.2	35.1	75	1.0%	-3.60 [-12.94, 5.74]		
Rammohan 2015	8.4	2.9	39	17.9	5.2	36	4.9%	-9.50 [-11.43, -7.57]		
Zarinfar 2016	24.1	5.6	30	27.4	6.6	30	3.6%	-3.30 [-6.40, -0.20]		
Zeng 2016	13.5	12.4	118	10.6	10.2	117	4.0%	2.90 [-0.00, 5.80]		
Wu 2017	29.7	12.3	58	40.5	15.7	51		-10.80 [-16.15, -5.45]		
Mallick 2018	18.7	1.2	40	18.9	1.2	40	5.6%	-0.20 [-0.73, 0.33]		4
Wang 2020	16.7	4.7	28	19.7	9.3	33	3.4%	-3.00 [-6.62, 0.62]		
Kate 2020	11.7	9.3	35	19.5	15.8	37	2.0%	-7.80 [-13.75, -1.85]	2020	
Subtotal (95% CI) Heterogeneity: Tau ² = 6.15; Chi ² = 176			672			684	57.3%	-3.50 [-5.00, -1.99]		•
1.32.2 Hospital LOS – Low ROB 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]		+
Forestler 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	16.6	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	60	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	
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	
Madmoodpoor 2019	14.2	8.6	48	21.1	5.7	54	4.0%	-6.90 [-9.77, -4.03]	2019	
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	_
Subtotal (95% CI)			2152			2158	42.7%	-0.57 [-1.92, 0.78]		4
Heterogeneity: $Tau^2 = 3.07$; $Chl^2 = 41.4$		(P < 0.00)01); f ² •	- 73%						
Test for overall effect: $Z = 0.83$ (P = 0.4						2842	100.0%	-2.21 [-3.24, -1.18]		▲
Test for overall effect: Z = 0.83 (P = 0.4 Total (95% CI)			2824							•
·····	.42, df = 2	6 (P < 0.0		r² = 667	6				-	-20 -10 0 10 20
Total (95% CI)		i6 (P < 0.0		l² = 687	4				-	-20 -10 0 10 Favours Probiotics Favours Placeb

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)

		ics/Synbi			lacebo			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.61.1 Hospital LOS – L rhamnosus										
Forestier 2008	29.5	16.9	102	30.5	17.6	106	2.7%	-1.00 [-5.69, 3.69]		
Morrow 2010	21.4	14.9	68	21.7	17.4	70	2.3%	-0.30 [-5.70, 5.10]		
Ferrie 2011	54.5	31.26		59.04		14	0.2%	-4.54 [-29.13, 20.05]		
Mayes 2014	1.04	0.03	10	1.02	0.64	10	5.6%	0.02 [-0.38, 0.42]		1
Zarinfar 2016	24.1	5.6	30	27.4	6.6	30	3.6%	-3.30 [-6.40, -0.20]		
Cook 2021 Subtotal (95% CI)	25.7	21.5	1318 1541	25	20	1332 1562	19.9%	0.70 [-0.88, 2.28] -0.05 [-0.71, 0.61]	2021	+
Heterogeneity: $Tau^2 = 0.10$; $Chl^2 = 5.44$ Fest for overall effect: $Z = 0.15$ (P = 0.81		= 0.36);	l ² = 6%							
1.61.2 Hospital LOS – Others										
ain 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	+-
1 2007	42	5	14	49	6.8	11	2.6%	-7.00 [-11.80, -2.20]	2007	
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	16.6	4.8	129	5.4%	1.70 [0.46, 2.94]	2009	+
Barraud 2010	26.6	22.3	87	28.9	26.4	60	1.4%	-2.30 [-9.74, 5.14]	2010	
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	36	5.0%	-2.01 [-3.82, -0.20]	2012	
Cul 2013	10.4	3.9	23	19.2	6.5	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	
Sanupriya 2015	13.13	7.71	75	19.17		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]		
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]		
Nu 2017	29.7	12.3	58	40.5	15.7	51		-10.80 [-16.15, -5.45]		
Mallick 2018	18.7	1.2	40	18.9	1.2	40	5.8%	-0.20 [-0.73, 0.33]		4
Madmoodpoor 2019	14.2	8.6	48	21.1	5.7	54	4.0%	-6.90 [-9.77, -4.03]		
Kate 2020	11.7	9.3	35	19.5	15.8	37	2.0%	-7.80 [-13.75, -1.85]		
Wang 2020	16.7	4.7	28	19.7	9.3	33	3.4%	-3.00 [-6.62, 0.62]		
Litton 2021 Subtotal (95% CI)	10	5.26	110 1283	9	5.26	108 1280	80.1%	1.00 [-0.40, 2.40] -2.76 [-4.21, -1.32]	2021	
Heterogeneity: Tau ² = 6.41; Chi ² = 209.: Fest for overall effect: Z = 3.75 (P = 0.00		0 (P < 0.0)0001);	l² = 907	6					
Total (95% CI)			2824			2842	100.0%	-2.21 [-3.24, -1.18]		•
Heterogeneity: Tau ² = 4.71; Chl ² = 224.		6 (P < 0.0)0001);	r ² = 667	4				-	-20 -10 0 10 20
Test for overall effect: Z = 4.20 (P < 0.0)	0011									-20 -10 0 10 20

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)

	Probiotics/Syn	biotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.57.1 VAP – L. rhamnosus								
Forestier 2008	24	102	24	106	7.7%	1.04 [0.63, 1.71]	2008	
Morrow 2010	17	66	33	70	7.9%	0.53 [0.33, 0.86]	2010	_
Zarinfar 2016	7	30	15	30	5.0%	0.47 [0.22, 0.98]	2016	
Cook 2021	269	1316	284	1332	12.7%		2021	+
Subtotal (95% CI)		1518		1538	33.3%	0.77 [0.52, 1.15]		
Fotal events	337		356					
Heterogeneity: Tau ² = 0.11; Cl	nt² = 10.46, df =	3 (P = 0.	02); l ² =	71%				
Test for overall effect: $Z = 1.26$	S(P = 0.20)							
1.57.2 VAP - Others								
Knight 2009	12	130	17	129	5.4%	0.70 [0.35, 1.41]	2009	
Giamarellos-Bourboulis 2009	15	36	16	36	7.2%	0.94 [0.55, 1.60]	2009	
Barraud 2010	23	87	15	60	6.7%	1.41 [0.79, 2.51]	2010	
Tan 2013	7	26	13	26	5.0%	0.54 [0.26, 1.13]	2011	_
Hayakawa 2012	5	31	3	16	2.2%	0.86 [0.23, 3.15]	2012	
Banupriya 2015	12	75	35	75	6.7%	0.34 [0.19, 0.61]	2015	
Rongrungruang 2015	18	75	22	75	7.2%	0.82 [0.48, 1.40]	2015	
Zeng 2016	48	116	62	117	10.9%	0.77 [0.58, 1.01]	2016	
Angurana 2018	3	50	2	50	1.3%	1.50 [0.26, 8.60]	2018	
Shimizu 2016	5	35	16	37	4.0%	0.29 [0.12, 0.71]	2018	
Madmoodpoor 2019	7	48	13	54	4.3%	0.61 [0.26, 1.39]	2019	
Thoma 2019	9	28	16	30	6.0%	0.60 [0.32, 1.14]	2019	
Litton 2021	0	110	0	108		Not estimable	2021	
Subtotal (95% CI)		849		833	66.7%	0.69 [0.54, 0.89]		◆
Total events	164		232					
Heterogeneity: Tau ² = 0.07; Cl		11 (P = 0)).06); P	- 42%				
Test for overall effect: Z = 2.94	P = 0.003							
Total (95% CI)		2367		2371	100.0%	0.72 [0.59, 0.89]		•
Total events	501		566					
Heterogeneity: Tau ² = 0.08; Cl	ht ² = 36.36, df =	15 (P = ().002); ŕ	' = 59X	i		7	1 0 2 0 5 1 2 5
Test for overall effect: Z = 3.08	S(P = 0.002)						, i	Favours Probiotics Favours Placebo
est for subgroup differences:	$Cht^2 = 0.20. df =$	1 (P = 0)	.65). ř -	0%				ravours riobiolics ravours riacebo

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)

	Probiotics/Syr		Place			Risk Ratio		Risk Ratio
tudy or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
.58.1 Mortality - L. rhamnosus	•					A 40 M 40 A 451		
Ioneycutt 2007	2	31	4	30	0.3%	0.48 [0.10, 2.45]		
forrow 2010	12	68	15	70	1.6%	0.82 [0.42, 1.63]		
errie 2011	7	13	5	14	1.0%	1.51 [0.64, 3.58]		
layes 2014	1	10	0	10	0.1%	3.00 [0.14, 65.90]		
won 2015	11	50	11	53	1.4%	1.06 [0.51, 2.22]		
cook 2021	363	1318	361	1332	51.1%	0.96 [0.85, 1.09]	2021	
ubtotal (95% CI)		1490		1509	55.6%	0.97 [0.86, 1.09]		•
otal events	396		416					
leterogeneity: Tau ² = 0.00; Chl ² = 2.5 est for overall effect: Z = 0.57 (P = 0.		6); r = 0%	i					
.58.2 Mortality - Others								
empe 1983	3	20	3	30	0.3%	1.50 [0.34, 6.70]	1983	
llah 2002	1	22	2	23	0.1%	0.52 [0.05, 5.36]		
ain 2004	22	45	20	45	3.9%	1.10 [0.71, 1.71]	2004	
alcao De Arruda 2004	0	10	0	10		Not estimable		
IcNaught 2005	18	52	16	51	2.7%	0.98 [0.58, 1.66]	2005	
ayes 2005	0	33	0	33		Not estimable		
larin 2005	2	9	2	6	0.3%	0.89 [0.16, 4.93]	2005	
lberda 2007	2	19	1	9	0.1%	0.95 [0.10, 9.13]		
u 2007	6	100	23	100	1.3%	0.35 [0.16, 0.74]	2007	
Jenka 2007	2	26	5	87	0.3%	1.34 [0.28, 6.50]	2007	
lah 2007	2	33	6	29	0.3%	0.29 [0.06, 1.34]	2007	
esselink 2008	24	152	9	144	1.4%	2.53 [1.22, 5.25]	2008	
Un 2008	0	36	0	36		Not estimable		
larin 2008	3	22	6	22	0.5%	0.50 [0.14, 1.75]	2008	
night 2009	35	130	42	129	5.4%	0.83 [0.57, 1.21]	2009	
iamarellos-Bourboulis 2009	5	36	10	36	0.8%	0.50 [0.19, 1.32]	2009	
arraud 2010	27	87	24	60	3.6%	1.03 [0.65, 1.64]		
rohmader 2010	5	20	3	25	0.4%	2.08 [0.56, 7.68]		
himizu 2011	9	46	25	121	1.6%		2011	
an 2013	3	26	5	26	0.4%	0.60 [0.16, 2.26]		
Imakachorn 2011	4	41	2	39	0.3%	1.90 [0.37, 9.81]		
umar 2013	8	75	7	75	0.8%	1.14 [0.44, 2.99]		
ul 2013	í	23	4	47	0.2%	0.51 [0.06, 4.32]	2013	
long 2013	6	17	3	21	0.5%		2013	
ang 2013	5	62	13	121	0.8%	0.75 [0.28, 2.01]		
opez de Toro Martin-Consuegra 2014		46	16	43	3.1%	0.99 [0.60, 1.61]		
anupriya 2015	17	75	23	75	2.6%	0.74 [0.43, 1.27]		
ongrungruang 2015	25	75	26	75	3.8%	0.96 [0.62, 1.50]		
eng 2016	26	118	25	117	3.2%	1.03 [0.63, 1.68]		
le 2017	ō	48	0	48	5.20	Not estimable		
/u 2017	2	58	ě	51	0.3%	0.29 [0.06, 1.39]		
fang 2016	2	45	ŏ	45	0.1%		2018	
himizu 2016	3	35	Ă,	37	0.4%	0.79 [0.19, 3.29]		
ngurana 2016	6	50	5	50	0.6%	1.20 [0.39, 3.68]		
tallick 2016	4	40	6	40	0.5%	0.67 [0.20, 2.18]		
ladmoodpoor 2019	5	46	6	54	0.6%	0.94 [0.31, 2.88]		
homa 2019	3	28	2	30	0.3%			
An 2019	5	26	7	38	0.3%	1.61 [0.29, 8.92]		
	6	28	;	33	0.8%	0.71 [0.25, 2.05]		-
/ang 2020 ate 2020	5	39	5	33	0.6%	1.01 [0.38, 2.66]		
ate 2020 Itton 2021	6	39 110	-	108		0.95 [0.30, 3.01]	2020	
ubtotal (95% CI)	Q	2023	5	2230	0.6% 44.4%	1.18 [0.37, 3.75] 0.94 [0.82, 1.07]	2021	
	220	2023	2.70	2230	44.4%	0.34 [0.62, 1.07]		٦
iotal events leterogeneity: Tau ² = 0.00; Chi ² = 31.).67); I ² =	376 0%					
est for overall effect: Z = 0.96 (P = 0.								
est for overall effect: Z = 0.96 (P = 0. otal (95% Cl)		3513		3739	100.0%	0.95 [0.87, 1.04]		4
-	725	3513	794	3739	100.0%	0.95 [0.87, 1.04]		•

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)

	Probiotics/Syn		Place			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.59.1 HAP – L. rhan	nosus							
Honeycutt 2007 Subtotal (95% CI)	2	31 31	0	30 30	0.6% 0.6%	4.84 [0.24, 96.89] 4.84 [0.24, 96.89]	2007	
Fotal events	2		0					
Heterogeneity: Not ap	plicable							
Fest for overall effect:	Z = 1.03 (P = 0.)	30)						
1.59.2 HAP – Others								
Olah 2002	2	22	2	23	1.6%	1.05 [0.16, 6.79]	2002	
tayes 2005	0	33	1	33	0.6%	0.33 [0.01, 7.90]	2005	
Alenka 2007	4	26	34	87	6.4%	0.39 [0.15, 1.01]	2007	
Olah 2007	2	33	4	29	2.1%	0.44 [0.09, 2.23]	2007	
Sesselink 2008	24	152	16	144	16.2%	1.42 [0.79, 2.56]	2008	
(le 2010	4	20	7	19	5.1%	0.54 [0.19, 1.56]	2010	
Fan 2013	2	26	1	26	1.0%	2.00 [0.19, 20.72]	2011	
Clong 2013	7	17	14	21	13.6%	0.62 [0.32, 1.18]	2013	
Rammohan 2015	2	39	3	36	1.9%	0.62 [0.11, 3.47]	2015	
Cie 2017	3	46	4	48	2.7%	0.75 [0.18, 3.17]	2017	
Wan 2019	17	36	28	36	35.1%	0.61 [0.41, 0.91]	2019	
Wang 2020	0	28	1	33	0.6%	0.39 [0.02, 9.23]	2020	
Cate 2020	9	39	15	37	11.6%	0.57 [0.28, 1.14]	2020	
Litton 2021	2	110	0	108		4.91 [0.24, 101.10]	2021	
Subtotal (95% CI)		631		682	99.4%	0.69 [0.54, 0.88]		◆
Fotal events	76		130					
Heterogeneity: Tau ² =			13 (P =	0.58); I	² = 0%			
Fest for overall effects	z = 3.05 (P = 0.)	002)						
Fotal (95% CI)		662		712	100.0%	0.70 [0.55, 0.89]		•
Fotal events	80		130					
Heterogeneity: Tau ² =	 0.00; Chl² = 13. 	00, df =	14 (P =	0.53); I	² = 0%			0.01 0.1 1 10 1
Fest for overall effect:	Z = 2.96 (P = 0.	003)						Favours Probiotics Favours Placebo

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)

		ics/Synbi			lacebo			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.60.1 ICU LOS – L. rhamnosus										
Morrow 2010	14.6	11.8	68	14.6	11.6	70	2.5%	0.20 [-3.71, 4.11]	2010	_
Ferrie 2011	32.04	24.46	13	29.75	18.81	14	0.2%	2.29 [-14.26, 18.84]	2011	
Zarinfar 2016	14.2	4.7	30	17.6	6.5	30	3.4%	-3.40 [-6.27, -0.53]	2016	
Cook 2021	12.7	8.9	1318	12.7	7.4	1332	5.6X	0.00 [-0.62, 0.62]	2021	+
Subtotal (95% CI)			1429			1446	11.7%	-0.81 [-2.73, 1.12]		
Heterogeneity: Tau ² = 1.63; Chl ² = 5.26 Test for overall effect: Z = 0.82 (P = 0.4		= 0.15);	r² = 43%	í						
1.60.2 ICU LOS - Others										
Falcao De Arruda 2004	11.25	4.8	10	27	16.2	10	0.5%	-15.75 [-26.22, -5.28]	2004	
Jain 2004	8.2	3	45	6.8	2.5	45	5.2%	1.40 [0.26, 2.54]		-
Klarin 2005	16.2	11	9	18.8	15.7	6	0.4%	-2.60 [-15.64, 10.44]		
Raves 2005	8.6	0.9	33	10.2	1.8	33	5.6%	-1.40 [-2.09, -0.71]		+
McNaught 2005	5.3	5.3	52	4.3	5	51	4.3%	1.00 [-0.99, 2.99]		+-
Alenka 2007	13.4	3.7	26	14.8	4.2	26	4.1%	-1.40 [-3.55, 0.75]		-+
Sramek 2007	16.2	16	15	10.7	15.5	10	0.4%	5.50 [-7.74, 18.74]		
Klarin 2008	6.9	5.1	22	21.4	17.2	22		-12.50 [-20.00, -5.00]		
Besselink 2008	6.6	17.1	152	3	9.3	144	3.1%	3.60 [0.49, 6.71]		
Knight 2009	6.5	1.5	130	7.8	2.1	129	5.7%	-1.30 [-1.74, -0.86]		•
Barraud 2010	18.7	12.4	87	20.2	20.8	80	1.7%	-1.50 [-6.75, 3.75]		
Frohmader 2010	7.3	5.7	20	8.1	4	25	3.3×	-0.80 [-3.75, 2.15]		
Tan 2013	6.8	3.8	26	10.7	7.3	26	3.1%	-3.90 [-7.06, -0.74]		
Xiong 2013	6.38	5.68	17	12.2	6.43	21	2.5%	-5.82 [-9.67, -1.97]		
Lopez de Toro Martin-Consuegra 2014	10	3.6	46	6.6	3.2	43	4.9%	1.20 [-0.21, 2.61]		
Rammohan 2015	4.3	3.1	39	4.2	2.2	36	5.1%	0.10 [-1.11, 1.31]		+
Rongrungruang 2015	33.3	19.6	75	18.8	5.2	75	2.0%	14.50 [9.91, 19.09]		
Banupriya 2015	7.7	4.6	_	12.54	9.91	75	3.6%	-4.84 [-7.31, -2.37]		
Zeng 2016	21.5	13.5	118	30.1	33.8	117	1.2%	-8.60 [-15.19, -2.01]		
Malik 2016	10.9	3.9	24	15.8	7.8	25	2.6%	-4.90 [-8.33, -1.47]		
Mallick 2016	8.1	5.9	40	9.2	5.9	40	3.6%	-1.10 [-3.69, 1.49]		
Shimizu 2018	26.6	23.2	35	30.1	21.6	37	0.6%	-3.50 [-13.87, 6.87]		
Angurana 2018	20.0	23.2	50	6.6	1.4	50	5.6%	-1.60 [-2.46, -1.12]		+
Wan 2019	10.32	5.31		14.24	6.79	38	3.5%	-3.92 [-6.66, -1.18]		
Madmoodpoor 2019	11.6	5.51	48	18.6	6.3	54	3.4%	-7.00 [-9.82, -4.18]		
Kate 2020	5.58	1.73	35	8.6	1.5	37	5.5%	-3.22 [-3.97, -2.47]		+
Litton 2021	2.25	3.3	110	2.25	3.3	108	5.4%	0.00 [-0.88, 0.88]		1
Subtotal (95% CI)	2.25	3.5	1377	2.23	3.5	1365	88.3%	-1.46 [-2.36, -0.57]	2021	•
Heterogeneity: $Tau^2 = 3.28$; $Chl^2 = 195$. Test for overall effect: $Z = 3.20$ (P = 0.0)		6 (P < 0.1		l ² = 679	6	1303	00.070	1.10 [2.50, -0.57]		•
Total (95% CI)			2806			2811	100.0%	-1.38 [-2.19, -0.57]		•
Heterogeneity: Tau ² = 2.93; Chi ² = 213. Test for overall effect: $Z = 3.34$ (P = 0.00 Test for subcroup difference: Chi ² = 0.2	008)		00001);		6				-	-20 -10 0 10 20 Favours Probiotics Favours Placebo

Test for subgroup differences: $Chl^2 = 0.37$, df = 1 (P = 0.54), $l^2 = 0%$

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)

	Probiotics/Syn	biotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.72.1 VAP – L. plantarum								
Litton 2021 Subtotal (95% CI)	0	110 110	0	106 108		Not estimable Not estimable	2021	
Total events	0		0					
Heterogeneity: Not applicable Test for overall effect: Not appl	licable							
1.72.2 VAP – Others								
Forestier 2008	24	102	24	106	7.7%	1.04 [0.63, 1.71]		
Knight 2009	12	130	17	129	5.4%	0.70 [0.35, 1.41]		
Glamarellos-Bourboulis 2009	15	36	16	36	7.2%	0.94 [0.55, 1.60]		
Morrow 2010	17	66	33	70	7.9%	0.53 [0.33, 0.86]		
Barraud 2010	23	87	15	60	6.7%	1.41 [0.79, 2.51]		
Tan 2013	7	26	13	26	5.0%	0.54 [0.26, 1.13]		
Hayakawa 2012	5	31	3	16	2.2%	0.86 [0.23, 3.15]	2012	
Banupriya 2015	12	75	35	75	6.7%	0.34 [0.19, 0.61]		
Rongrungruang 2015	16	75	22	75	7.2%	0.82 [0.48, 1.40]	2015	
Zeng 2016	46	118	62	117	10.9%	0.77 [0.58, 1.01]	2016	
Zarinfar 2016	7	30	15	30	5.0X	0.47 [0.22, 0.98]	2016	-
Angurana 2018	3	50	2	50	1.3×	1.50 [0.26, 8.60]	2018	
Shimizu 2018	5	35	16	37	4.0%	0.29 [0.12, 0.71]	2018	
Thoma 2019	9	26	16	30	6.0%	0.60 [0.32, 1.14]	2019	
Madmoodpoor 2019	7	48	13	54	4.3%	0.61 [0.26, 1.39]	2019	
Cook 2021	269	1318	264	1332	12.7%	1.03 [0.89, 1.19]	2021	+
Subtotal (95% CI)		2257		2263	100.0%	0.72 [0.59, 0.89]		•
Total events	501		588					
Heterogeneity: Tau ² = 0.08; Cl Test for overall effect: Z = 3.06		15 (P = ().002); P	- 59X	i			
Total (95% CI)		2367		2371	100.0%	0.72 [0.59, 0.89]		•
Total events	501		588					•
Heterogeneity: Tau ² = 0.08; Cl		15 (P = (- 59%	i		-	
Test for overall effect: $Z = 3.06$				200	•			0.1 0.2 0.5 1 2 5
Test for subgroup differences:								Favours Probiotics Favours Placebo

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)

	Probiotics/Syn		Place			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.73.1 Mortality – L. plantarum								
Diah 2002	1	22	2	23	0.1%	0.52 [0.05, 5.36]		
Klarin 2005	2	9	2	6	0.3%	0.89 [0.16, 4.93]		
AcNaught 2005	16	52	16	51	2.7%	0.98 [0.58, 1.66]		
Qin 2006	0	36	0	36		Not estimable	2008	
Clarin 2008	3	22	6	22	0.5%	0.50 [0.14, 1.75]	2008	
httpn 2021	6	110	5	108	0.6%	1.18 [0.37, 3.75]	2021	
Subtotal (95% CI)		251		250	4.2%	0.91 [0.59, 1.39]		•
lotal events	30		33					
teterogeneity: $Tau^2 = 0.00$; $Chl^2 = 1.36$; fest for overall effect: Z = 0.46 (P = 0.6)		5);						
1.73.2 Mortality - Others								
empe 1963	3	20	3	30	0.3%	1.50 [0.34, 6.70]	1983	
aln 2004	22	45	20	45	3.9%	1.10 [0.71, 1.71]	2004	_
alcao De Arruda 2004	0	10	0	10		Not estimable	2004	
taves 2005	Ó	33	Ó	33		Not estimable		
Ioneycutt 2007	2	31	4	30	0.3%	0.48 [0.10, 2.45]	2007	
Alberda 2007	2	19	1	9	0.1%	0.95 [0.10, 9.13]	2007	
u 2007	8	100	23	100	1.3%		2007	<u> </u>
Jenka 2007	ž	26	-5	87	0.3%	1.34 [0.28, 6.50]		
Jah 2007	2	33	6	29	0.3%	0.29 [0.06, 1.34]		
iesselink 2008	24	152	9	144	1.4%	2.53 [1.22, 5.25]	2008	
(night 2009	35	130	42	129	5.4%	0.83 [0.57, 1.21]		
Giamarellos-Bourboulis 2009	5	36	10	36	0.8%	0.50 [0.19, 1.32]		
rohmader 2010	5	20	3	25	0.4%			
Aorrow 2010	12	66	15	70	1.6%	2.08 [0.56, 7.68]		
						0.82 [0.42, 1.63]	2010	
arraud 2010	27	87	24	60	3.6%	1.03 [0.65, 1.64]	2010	
ihimizu 2011	9	46	25	121	1.6%	0.95 [0.48, 1.87]		
an 2013	3	26	5	26	0.4%	0.60 [0.16, 2.26]		
errie 2011	7	13	5	14	1.0%	1.51 [0.64, 3.58]	2011	
Simakachorn 2011	4	41	2	39	0.3%	1.90 [0.37, 9.81]		
Cumar 2013	6	75	7	75	0.6%	1.14 [0.44, 2.99]	2013	
Cul 2013	1	23	4	47	0.2%	0.51 [0.06, 4.32]		
Klong 2013	6	17	3	21	0.5%	2.47 [0.72, 8.45]	2013	
Wang 2013	5	62	13	121	0.8%	0.75 [0.28, 2.01]	2013	
Mayes 2014	1	10	0	10	0.1%	3.00 [0.14, 65.90]	2014	
Lopez de Toro Martin-Consuegra 2014	19	46	16	43	3.1%	0.99 [0.60, 1.61]	2014	
Kwon 2015	11	50	11	53	1.4%	1.06 [0.51, 2.22]		
Banupriya 2015	17	75	23	75	2.6%	0.74 [0.43, 1.27]		
tongrungruang 2015	25	75	26	75	3.6%	0.96 [0.62, 1.50]		
Zeng 2016	26	118	25	117	3.2%	1.03 [0.63, 1.68]		
(le 2017	ō	48	õ	48		Not estimable		
Nu 2017	ž	58	ě	51	0.3%	0.29 [0.06, 1.39]		
Wang 2018	2	45	ŏ	45	0.1%		2018	
Shimizu 2018	3	35	4	37	0.4%			
	-			-		0.79 [0.19, 3.29]		
Angurana 2018	6	50	5	50	0.6%	1.20 [0.39, 3.68]		
Mallick 2018	4	40	6	40	0.5%	0.67 [0.20, 2.18]	2018	
Madmoodpoor 2019	5	48	6	54	0.6%		2019	
fhoma 2019	3	28	2	30	0.3%	1.61 [0.29, 8.92]		<u> </u>
Wan 2019	5	36	7	36	0.7%	0.71 [0.25, 2.05]		
Wang 2020	6	28	7	33	0.8%	1.01 [0.38, 2.66]		
(ate 2020	5	39	5	37	0.6%	0.95 [0.30, 3.01]	2020	
Cook 2021	363	1318	361	1332	51.1%	0.96 [0.85, 1.09]	2021	•
Subtotal (95% CI)		3262		3489	95.8%	0.96 [0.87, 1.05]		•
fotal events leterogeneity: Tau² = 0.00; Chi² = 32.9 lest for overall effect: Z = 0.99 (P = 0.32).66); I ² =	761 0%					
Total (95% CI)		3513		3739	100.0%	0.95 [0.87, 1.04]		
	725	3313	794	3733	100.0%	0.55 [0.67, 1.04]		٦
Fotal events								
Heterogeneity: $Tau^2 = 0.00$; $Chl^2 = 34.3$ Fest for overall effect: $Z = 1.06$ (P = 0.2) Fest for subgroup differences: $Chl^2 = 0.0$	9)							0.02 0.1 1 10 Favours Probiotics Favours Placebo

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)

	Probiotics/Syn	biotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.74.1 HAP – L. plan	tarum							
Olah 2002	2	22	2	23	1.6%	1.05 [0.16, 6.79]	2002	
Litton 2021	2	110	0	108		4.91 [0.24, 101.10]	2021	
Subtotal (95% CI)		132		131	2.2%	1.60 [0.33, 7.87]		
Total events	4		2					
Heterogeneity: Tau ² =	= 0.00; Cht ² = 0.7	'3, df = 1	(P = 0.3)	39); ۴ =	0%			
Test for overall effect	: Z = 0.58 (P = 0.	.56)						
1.74.2 HAP - Others	1							
Rayes 2005	0	33	1	33	0.6%	0.33 [0.01, 7.90]	2005	
Honeycutt 2007	2	31	0	30	0.6%	4.84 [0.24, 96.89]	2007	
Alenka 2007	4	26	34	87	6.4%	0.39 [0.15, 1.01]	2007	
Olah 2007	2	33	4	29	2.1%	0.44 [0.09, 2.23]	2007	
Besselink 2008	24	152	16	144	16.2%	1.42 [0.79, 2.56]	2008	+ •
Xie 2010	4	20	7	19	5.1%	0.54 [0.19, 1.56]	2010	
Tan 2013	2	26	1	26	1.0%	2.00 [0.19, 20.72]	2011	
Xiong 2013	7	17	14	21	13.6X	0.62 [0.32, 1.18]	2013	
Rammohan 2015	2	39	3	36	1.9%	0.62 [0.11, 3.47]		
Xie 2017	3	46	4	46	2.7%	0.75 [0.18, 3.17]	-	
Wan 2019	17	36	28	36	35.1%	0.61 [0.41, 0.91]		
Wang 2020	0	28	1	33	0.6%	0.39 [0.02, 9.23]		
Kate 2020	9	39	15	37	11.6%	0.57 [0.28, 1.14]	2020	
Subtotal (95% CI)		530		581	97.8%	0.68 [0.54, 0.87]		•
Total events	76		126		_			
Heterogeneity: Tau ² =			12 (P =	0.51);	f = 0%			
Test for overall effect	: Z = 3.08 (P = 0.	.002)						
Total (95% CI)		662		712	100.0%	0.70 [0.55, 0.89]		◆
Total events	60		130					
Heterogeneity: Tau ² -			14 (P =	0.53);	² = 0%			0.01 0.1 1 10 1
Test for overall effect								Favours Probiotics Favours Placebo
Test for subgroup diff	ferences: Cht ² = 1	.07, df =	1 (P = ().30), P	= 6.9%			

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)

	Probiot	ics/Synbi			lacebo			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.75.1 ICU LOS – L. plantarum										
Klarin 2005	16.2	11	9	16.6	15.7	6	0.4%	-2.60 [-15.64, 10.44]	2005	
McNaught 2005	5.3	5.3	52	4.3	5	51	4.3%	1.00 [-0.99, 2.99]		+
Klarin 2008	8.9	5.1	22	21.4	17.2	22	1.0%	-12.50 [-20.00, -5.00]		
Litton 2021	2.25	3.3	110	2.25	3.3	108	5.4%	0.00 [-0.88, 0.88]		+
Subtotal (95% CI)			193			189	11.1%	-1.21 [-4.19, 1.77]		
Heterogeneity: Tau ² = 4.94 ; Ch ² = 11.6 Test for overall effect: Z = 0.60 (P = 0.4)		P = 0.001	3); I ² = 7	5%						
1.75.2 ICU LOS – Others										
Falcao De Arruda 2004	11.25	4.8	10	27	16.2	10	0.5%	-15.75 [-26.22, -5.28]	2004	
Jain 2004	8.2	3	45	6.8	2.5	45	5.2%	1.40 [0.26, 2.54]	2004	-
Raves 2005	8.6	0.9	33	10.2	1.8	33	5.6X	-1.40 [-2.09, -0.71]		+
Alenka 2007	13.4	3.7	26	14.8	4.2	26	4.1%	-1.40 [-3.55, 0.75]		-+
Sramek 2007	16.2	16	15	10.7	15.5	10	0.4%	5.50 [-7.74, 18.74]		
Besselink 2008	6.6	17.1	152	3	9.3	144	3.1×	3.60 [0.49, 6.71]		
Knight 2009	6.5	1.5	130	7.8	2.1	129	5.7%	-1.30 [-1.74, -0.86]		-
Morrow 2010	14.8	11.6	66	14.6	11.6	70	2.5%	0.20 [-3.71, 4.11]		
Barraud 2010	14.0	12.4	87	20.2		80	1.7%	-1.50 [-6.75, 3.75]		
Frohmader 2010	7.3	5.7	20	8.1	20.0	25	3.3×			
Tan 2013	6.8	3.8	26	10.7	7.3	26	3.1%	-0.80 [-3.75, 2.15]		
								-3.90 [-7.06, -0.74]		
Ferrie 2011	32.04	24.46	13			14	0.2%	2.29 [-14.26, 18.84]		
Xiong 2013	6.38	5.68	17	12.2		21	2.5%	-5.82 [-9.67, -1.97]		
Lopez de Toro Martin-Consuegra 2014	10	3.6	46	6.6	3.2	43	4.9%	1.20 [-0.21, 2.61]		
Rammohan 2015	4.3	3.1	39	4.2	2.2	36	5.1%	0.10 [-1.11, 1.31]		Ť
Rongrungruang 2015	33.3	19.6	75	18.8	5.2	75	2.0%	14.50 [9.91, 19.09]		
Banupriya 2015	7.7	4.6		12.54	9.91	75	3.6%	-4.84 [-7.31, -2.37]		
Zeng 2016	21.5	13.5	116	30.1	33.8	117	1.2%	-8.60 [-15.19, -2.01]		
Malik 2016	10.9	3.9	24	15.8	7.8	25	2.6%	-4.90 [-8.33, -1.47]		
Zarinfar 2016	14.2	4.7	30	17.6	6.5	30	3.4%	-3.40 [-6.27, -0.53]	2016	
Mallick 2018	8.1	5.9	40	9.2	5.9	40	3.6X	-1.10 [-3.69, 1.49]	2018	-+-
Shimizu 2016	26.6	23.2	35	30.1	21.6	37	0.6%	-3.50 [-13.87, 6.87]	2018	
Angurana 2018	7	2	50	6.6	1.4	50	5.6%	-1.60 [-2.48, -1.12]	2018	+
Wan 2019	10.32	5.31	38	14.24	6.79	36	3.5%	-3.92 [-6.66, -1.18]	2019	
Madmoodpoor 2019	11.6	6	48	18.6	6.3	54	3.4%	-7.00 [-9.82, -4.18]		
Kate 2020	5.58	1.73	35	6.6	1.5	37	5.5%	-3.22 [-3.97, -2.47]		+
Cook 2021	12.7	8.9	1318	12.7		1332	5.6X	0.00 [-0.62, 0.62]		+
Subtotal (95% CI)			2613			2622	88.9%	-1.45 [-2.32, -0.59]		•
Heterogeneity: Tau ² = 2.96; Chl ² = 192. Test for overall effect: Z = 3.30 (P = 0.04		6 (P < 0.0)0001);	r ² = 873	6					
Total (95% CI)			2806			2811	100.0%	-1.38 [-2.19, -0.57]		◆
Heterogeneity: Tau ² = 2.93; Chl ² = 213.1 Test for overall effect: Z = 3.34 (P = 0.00 Test for subgroup differences: Chl ² = 0.0	008)	•			4				-	-20 -10 0 10 20 Favours Probiotics Favours Placebo

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)

		ics/Synbi			Placebo			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.76.1 Hospital LOS – L plantarum										
McNaught 2005	5.35	5.34	52	4.35	3.81	51	5.0%	1.00 [-0.79, 2.79]		+
Litton 2021	10	5.26	110	9	5.26	108	5.3%	1.00 [-0.40, 2.40]	2021	
Subtotal (95% CI)			162			159	10.3%	1.00 [-0.10, 2.10]		•
Heterogeneity: Tau ² = 0.00; Chl ² = 0.00; Test for overall effect: Z = 1.76 (P = 0.0)		= 1.00);	l ² = 0%							
1.76.2 Hospital LOS – Others										
ain 2004	16.2	3.9	45	16.5	4.5	45	5.0%	-0.30 [-2.04, 1.44]	2004	-
tayes 2005	27.8	2.4	33	27.9	2.1	33	5.5%	-0.10 [-1.19, 0.99]	2005	+
1 2007	42	5	14	49	6.8	11	2.6%	-7.00 [-11.80, -2.20]	2007	
orestler 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]		
Knight 2009	20.5	5.4	130	16.6	4.8	129	5.4%	1.70 [0.46, 2.94]		
Worrow 2010	21.4	14.9	68	21.7	17.4	70	2.3%	-0.30 [-5.70, 5.10]	2010	
Sarraud 2010	26.6	22.3	87	28.9	26.4	60	1.4%	-2.30 [-9.74, 5.14]	2010	
errie 2011	54.5	31.26	13	59.04	33.92	14	0.2%	-4.54 [-29.13, 20.05]	2011	• • • • • • • • • • • • • • • • • • • •
(hang 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	
Cul 2013	10.4	3.9	23	19.2	8.5	47	4.0%	-8.60 [-11.71, -5.69]	2013	<u> </u>
Mayes 2014	1.04	0.03	10	1.02	0.64	10	5.6%	0.02 [-0.38, 0.42]	2014	+
opez de Toro Martin-Consuegra 2014	20.8	5.9	46	24.2	6.4	43	4.3%	-3.40 [-5.96, -0.84]	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	
tammohan 2015	8.4	2.9	39	17.9	5.2	36	4.9%	-9.50 [-11.43, -7.57]	2015	
Zarinfar 2016	24.1	5.6	30	27.4	6.6	30	3.6%	-3.30 [-6.40, -0.20]	2016	
Zeng 2016	13.5	12.4	116	10.6	10.2	117	4.0%	2.90 [-0.00, 5.80]		⊢
Nu 2017	29.7	12.3	58	40.5	15.7	51	2.3%	-10.80 [-16.15, -5.45]	2017	
Wallick 2018	18.7	1.2	40	18.9	1.2	40	5.6%	-0.20 [-0.73, 0.33]	2018	4
Aadmoodpoor 2019	14.2	8.6	48	21.1	5.7	54	4.0%	-6.90 [-9.77, -4.03]	2019	
(ate 2020	11.7	9.3	35	19.5	15.8	37	2.0%	-7.80 [-13.75, -1.85]	2020	
Wang 2020	16.7	4.7	28	19.7	9.3	33	3.4%	-3.00 [-6.62, 0.62]		
Cook 2021	25.7	21.5	1318	25	20	1332	5.2%	0.70 [-0.88, 2.28]	2021	. +-
Subtotal (95% CI)			2662			2683	89.7%	-2.60 [-3.72, -1.48]		◆
Heterogeneity: $Tau^2 = 5.07$; Chl ² = 217.1 Test for overall effect: Z = 4.56 (P < 0.04		4 (P < 0.()0001);	r ² = 69)	ĸ					
Fotal (95% CI)			2824			2842	100.0%	-2.21 [-3.24, -1.18]		•
Heterogeneity: Tau ² = 4.71; Chl ² = 224.	42. df = 2	6 (P < 0.0	00001);	l ² = 667	Ni l					
lest for overall effect: Z = 4.20 (P < 0.0)					-					-20 -10 0 10 2
Test for subgroup differences: $Chi^2 = 20$.		(P < 0.0	00013-1	² = 95 1	154					Favours Probiotics Favours Placebo

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)

	Probiotics/Syn	biotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.52.1 VAP – Probiotics								
Forestier 2008	24	102	24	106	7.7%	1.04 [0.63, 1.71]	2008	_
Barraud 2010	23	87	15	60	6.7%	1.41 [0.79, 2.51]	2010	_
Morrow 2010	17	68	33	70	7.9%	0.53 [0.33, 0.86]	2010	.
Tan 2013	7	26	13	26	5.0%	0.54 [0.26, 1.13]	2011	
Hayakawa 2012	5	31	3	16	2.2%	0.86 [0.23, 3.15]	2012	
Rongrungruang 2015	16	75	22	75	7.2%	0.82 [0.48, 1.40]	2015	
Banupriya 2015	12	75	35	75	6.7%	0.34 [0.19, 0.61]	2015	
Zarinfar 2016	7	30	15	30	5.0%	0.47 [0.22, 0.98]	2016	
Zeng 2016	48	118	62	117	10.9%	0.77 [0.58, 1.01]	2016	
Shimizu 2016	5	35	16	37	4.0%	0.29 [0.12, 0.71]	2018	
Angurana 2018	3	50	2	50	1.3%	1.50 [0.26, 8.60]	2018	
Madmoodpoor 2019	7	48	13	54	4.3×	0.61 [0.26, 1.39]	2019	
Thoma 2019	9	28	16	30	6.0%	0.60 [0.32, 1.14]	2019	
Cook 2021	269	1318	264	1332	12.7%	1.03 [0.89, 1.19]	2021	+
Litton 2021	0	110	0	108		Not estimable	2021	
Subtotal (95% CI)		2201		2206	87.4%	0.70 [0.56, 0.89]		◆
Total events	474		555					
Heterogeneity: $Tau^2 = 0.10$; C Test for overall effect: Z = 2.9		13 (P = ().0006);	r ² = 64	*			
1.52.2 VAP – Synbiotics								
Giamarellos-Bourboulis 2009	15	36	16	36	7.2%	0.94 [0.55, 1.60]	2009	
Knight 2009	12	130	17	129	5.4%	0.70 [0.35, 1.41]	2009	
Subtotal (95% CI)		166		165	12.6%	0.84 [0.55, 1.29]		
Total events	27		33					
Heterogeneity: $Tau^2 = 0.00$; C Test for overall effect: $Z = 0.8$		(P = 0.5	1);)%				
Total (95% CI)		2367		2371	100.0%	0.72 [0.59, 0.89]		◆
Total events	501		588					
Heterogeneity: Tau ² = 0.08; C	hl² = 36.36, df =	15 (P = 0)).002); P	ⁱ = 59%	i		-	0.2 0.5 1 2 5
Test for overall effect: Z = 3.0		-						Favours Probiotics Favours Placebo
Test for subgroup differences:	$Cht^2 = 0.54$ df =	1 (P = 0)	46) P -	08				ravours riobiolics ravours riacebo

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)

Study or Subaroup	Probiotics/Syn		Place		Wolaht	Risk Ratio	Vear	Risk Ratio
tudy or Subgroup	Events	iotal	events	rotal	weight	IV, Random, 95% CI	rear	IV, Random, 95% CI
.53.1 Mortality – Probiotics		20	~		A	1 50 10 2 . 0	1000	
empe 1983	3		3	30	0.4%	1.50 [0.34, 6.70]		
Diah 2002	1	22		23	0.1%	0.52 [0.05, 5.36]		
alcao De Arruda 2004	0	10	0	10	~ ~~	Not estimable		
AcNaught 2005	16	52	16	51	2.6%	0.98 [0.58, 1.66]	2005	
(larin 2005	2	9	2	6	0.3%	0.69 [0.16, 4.93]		
Uberda 2007	2	19	1	9	0.2%	0.95 [0.10, 9.13]		
ioneycutt 2007	2	31	4	30	0.3%	0.48 [0.10, 2.45]		
ru 2007	8	100	23	100	1.4%	0.35 [0.16, 0.74]		
Jin 2006	0	36	0	36		Not estimable		
Clarin 2008	3	22	6	22	0.5%	0.50 [0.14, 1.75]		
iesselink 2008	24	152	9	144	1.5%	2.53 [1.22, 5.25]		
Aorrow 2010	12	68	15	70	1.7%	0.82 [0.42, 1.63]		
larraud 2010	27	87	24	60	3.6%	1.03 [0.65, 1.64]		
rohmader 2010	5	20	3	25	0.5%	2.08 [0.56, 7.68]	2010	
errie 2011	7	13	5	14	1.1%	1.51 [0.64, 3.58]		
ilmakachorn 2011	4	41	2	39	0.3%	1.90 [0.37, 9.81]	2011	
an 2013	3	26	5	26	0.5%	0.60 [0.16, 2.26]		
Cul 2013	1	23	4	47	0.2%	0.51 [0.06, 4.32]	2013	
Vang 2013	5	62	13	121	0.8%	0.75 [0.28, 2.01]	2013	
lumar 2013	6	75	7	75	0.9%	1.14 [0.44, 2.99]	2013	
(long 2013	6	17	3	21	0.5%	2.47 [0.72, 8.45]	2013	
Mayes 2014	1	10	0	10	0.1%	3.00 [0.14, 65.90]	2014	
opez de Toro Martin-Consuegra 2014	19	46	16	43	3.3%	0.99 [0.60, 1.61]	2014	
lanupriya 2015	17	75	23	75	2.7%	0.74 [0.43, 1.27]	2015	
(won 2015	11	50	11	53	1.4%	1.06 [0.51, 2.22]	2015	
tongrungruang 2015	25	75	26	75	4.0%	0.96 [0.62, 1.50]	2015	
teng 2016	26	118	25	117	3.4%	1.03 [0.63, 1.68]	2016	
Ge 2017	Ó	48	Ö	46		Not estimable		
Vu 2017	2	58	6	51	0.3%	0.29 [0.06, 1.39]	2017	
Angurana 2018	6	50	5	50	0.6%	1.20 [0.39, 3.68]	2018	
Vang 2018	2	45	ō	45	0.1%			
Wallick 2018	4	40	6	40	0.6%	0.67 [0.20, 2.18]		
Wan 2019	5	38	7	38	0.7%	0.71 [0.25, 2.05]	2019	
Wadmoodpoor 2019	5	48	6	54	0.6%	0.94 [0.31, 2.66]		
Thoma 2019	3	28	2	30	0.3%	1.61 [0.29, 8.92]		
Wang 2020	6	28	7	33	0.8%	1.01 [0.38, 2.66]		
Cook 2021	363	1318	381		53.2%	0.96 [0.85, 1.09]	2021	
litton 2021	6	110	5	108	0.6%	1.18 [0.37, 3.75]		
ubtotal (95% CI)	•	3090	-	3185	90.2%	0.97 [0.88, 1.06]		•
otal events	642		677					1
Heterogeneity: $Tau^2 = 0.00$; $Chl^2 = 29.0$? Fest for overall effect: $Z = 0.72$ (P = 0.42), df = 34 (P = 0	.71); ř =	-					
.53.2 Mortality - Synbiotics	•		~				2005	
tayes 2005	0	33	0	33	0.00	Not estimable		
denka 2007	2	26	5	67	0.3%	1.34 [0.28, 6.50]		
)lah 2007	2	33	6	29	0.3%	0.29 [0.06, 1.34]		
Giamarellos-Bourboulis 2009	5	36	10	36	0.8%	0.50 [0.19, 1.32]		
Inight 2009	35	130	42	129	5.6%	0.83 [0.57, 1.21]		
ihimizu 2011	9	46	25	121	1.7%	0.95 [0.48, 1.87]		
himizu 2016	3	35	4	37	0.4%	0.79 [0.19, 3.29]		
Late 2020	5	39	5	37	0.6%	0.95 [0.30, 3.01]	2020	
ubtotal (95% CI)		378	_	509	9.8%	0.80 [0.60, 1.06]		\bullet
fotal events	61		97					
Heterogeneity: $Tau^2 = 0.00$; $Chl^2 = 3.34$, Fest for overall effect: $Z = 1.54$ (P = 0.12		7);	6					
Total (95% CI)		3468		3694	100.0%	0.95 [0.87, 1.04]		•
otal events	703	_	774					
leterogeneity: $Tau^2 = 0.00$; $Ch^2 = 33.96$ lest for overall effect: $Z = 1.17$ (P = 0.24		.77); i² =	0%					0.05 0.2 1 5

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)

	Probiotics/Syn	biotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.54.1 HAP – Probio	tics							
Olah 2002	2	22	2	23	1.6%	1.05 [0.16, 6.79]	2002	
Besselink 2008	24	152	16	144	16.3%	1.42 [0.79, 2.56]	2008	- +
Xie 2010	4	20	7	19	5.1%	0.54 [0.19, 1.56]	2010	
Tan 2013	2	26	1	26	1.0%	2.00 [0.19, 20.72]	2011	
Xiong 2013	7	17	14	21	13.7%	0.62 [0.32, 1.18]	2013	
Xie 2017	3	48	4	48	2.7%	0.75 [0.18, 3.17]	2017	
Wan 2019	17	38	28	38	35.3%	0.61 [0.41, 0.91]	2019	
Wang 2020	0	26	1	33	0.6%	0.39 [0.02, 9.23]	2020	
Litton 2021	2	110	0	108		4.91 [0.24, 101.10]	2021	
Subtotal (95% CI)		461		460	77.1%	0.78 [0.57, 1.05]		◆
Total events	61		73					
Test for overall effect: 1.54.2 HAP – Synbio		10)						
Raves 2005	0	33	1	33	0.6%	0.33 [0.01, 7.90]	2005	
Olah 2007	2	33	4	29	2.2%			
Alenka 2007	4	26	34	87	6.5%	0.39 [0.15, 1.01]		
Rammohan 2015	2	39	3	36	1.9%			
Kate 2020 Subtotal (95% CI)	9	39 170	15	37 222	11.6× 22.9%	0.57 [0.28, 1.14]		•
Total events	17		57					-
Heterogeneity: Tau ² = Test for overall effect:			(P = 0.1	97); I ² =	- 0%			
Total (95% CI)		631		682	100.0%	0.69 [0.54, 0.88]		◆
Total events	78		130					
Heterogeneity: Tau ² =	• 0.00; Chl ² = 11.	39, df =	13 (P =	0.58);	² = 0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 3.05 (P = 0.	002)						Favours Probiotics Favours Placebo
Test for subgroup diff	ferences: $Chl^2 = 2$.21. df =	1/P = 0	14) 1	ⁱ = 54.8%	1		avours riobiolics ravours ridcebo

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

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)

	Probioti	cs/Synbi			lacebo			Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI	
1.55.1 ICU LOS – Probiotics											
Falcao De Arruda 2004	11.25	4.8	10	27	16.2	10	0.6%	-15.75 [-26.22, -5.28]	2004		
Klarin 2005	16.2	11	9	16.6	15.7	6	0.4%	-2.60 [-15.64, 10.44]	2005		
McNaught 2005	5.3	5.3	52	4.3	5	51	4.5%	1.00 [-0.99, 2.99]	2005		
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	3.3%	3.60 [0.49, 6.71]	2008		
Morrow 2010	14.6	11.6	68	14.6	11.6	70	2.6%	0.20 [-3.71, 4.11]	2010	<u> </u>	
Barraud 2010	16.7	12.4	87	20.2	20.8	60	1.6%	-1.50 [-6.75, 3.75]			
Frohmader 2010	7.3	5.7	20	6.1	4	25	3.5%	-0.80 [-3.75, 2.15]	2010	-+-	
Tan 2013	6.6	3.8	26	10.7	7.3	26	3.3%	-3.90 [-7.06, -0.74]			
Ferrie 2011	32.04	24.46	13	29.75	18.81	14	0.2%	2.29 [-14.26, 18.84]			_
Xiong 2013	6.38	5.68	17	12.2	6.43	21	2.7%	-5.82 [-9.67, -1.97]			
Lopez de Toro Martin-Consuegra 2014	10	3.6	46	8.8	3.2	43		1.20 [-0.21, 2.61]			
Banupriva 2015	7.7	4.6		12.54	9.91	75		-4.84 [-7.31, -2.37]			
Rongrungruang 2015	33.3	19.6	75	18.8	5.2	75		14.50 [9.91, 19.09]			
Zarinfar 2016	14.2	4.7	30	17.6	6.5	30		-3.40 [-6.27, -0.53]			
Malik 2016	10.9	3.9	24	15.8	7.8	25	3.0%	-4.90 [-8.33, -1.47]			
Zeng 2016	21.5	13.5	118	30.1	33.8	117	1.3×	-8.60 [-15.19, -2.01]			
Angurana 2018	7	2	50	8.8	1.4	50		-1.80 [-2.48, -1.12]		+	
Mallick 2018	8.1	5.9	40	9.2	5.9	40		-1.10 [-3.69, 1.49]			
Madmoodpoor 2019	11.6	6	48	18.6	6.3	54	3.6×	-7.00 [-9.82, -4.18]			
Wan 2019	10.32	5.3 1	38	14.24	6.79	38	3.7%	-3.92 [-6.66, -1.16]			
Cook 2021	12.7	6.9	1318	12.7		1332		0.00 [-0.62, 0.62]		Ţ	
Litton 2021	2.25	3.3	110	2.25	3.3	108	5.7%	0.00 [-0.88, 0.88]		1	
Subtotal (95% CI)	2.23	3.5	2448	2.23	3.3	2458		-1.71 [-2.91, -0.50]	2021	▲	
Heterogeneity: $Tau^2 = 5.30$; $Chl^2 = 154.3$	01 df = 21	2/2 - 01		r - 869	e e	2.00	. 10,0	101 [101, 000]		•	
Test for overall effect: $Z = 2.76$ (P = 0.00		- (1 - 0.1			•						
1.55.2 ICU LOS – Synbiotics											
ain 2004	6.2	3	45	6.8	2.5	45	5.5%	1.40 [0.26, 2.54]	2004	-	
Rayes 2005	8.6	0.9	33	10.2	1.6	33		-1.40 [-2.09, -0.71]		-	
Alenka 2007	13.4	3.7	26	14.8	4.2	26	4.3%	-1.40 [-3.55, 0.75]		-+	
Sramek 2007	16.2	18	15	10.7	15.5	10		5.50 [-7.74, 18.74]			_
Knight 2009	6.5	1.5	130	7.8	2.1	129	6.0%	-1.30 [-1.74, -0.86]		-	
Shimizu 2018	26.6	23.2	35	30.1	21.6	37		-3.50 [-13.87, 6.87]			
Kate 2020	5.58	1.73	35	8.8	1.5	37		-3.22 [-3.97, -2.47]		+	
Subtotal (95% CI)			319			317		-1.20 [-2.40, 0.01]		•	
Heterogeneity: $Tau^2 = 1.63$; $Chl^2 = 47.0$ Test for overall effect: $Z = 1.95$ (P = 0.0)		P < 0.001	001); ř	- 87%							
Total (95% CI)			2767			2775	100.0%	-1.46 [-2.30, -0.62]		•	
Heterogeneity: $Tau^2 = 3.02$; $Chl^2 = 209.1$	00 df = 21	9 (P < 1) I	000011-	P = 865	4				_	-20 -10 0 10	20

<u>Supplement Figure 33. Forest plot. Hospital Length of Stay (LOS) comparing Probiotics</u> 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)

		ics/Synbi			lacebo			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.56.1 Hospital LOS – Probiotics										
McNaught 2005	5.35	5.34	52	4.35	3.61	51	5.0%	1.00 [-0.79, 2.79]		+
LI 2007	42	5	14	49	6.8	11	2.6%	-7.00 [-11.80, -2.20]		
Forestier 2008	29.5	16.9	102	30.5	17.6	106	2.7%	-1.00 [-5.69, 3.69]		
Besselink 2008	28.9	41.5	152	23.5	25.9	144	1.3×	5.40 [-2.44, 13.24]		
Barraud 2010	26.6	22.3	87	28.9	26.4	60	1.4%	-2.30 [-9.74, 5.14]		
Morrow 2010	21.4	14.9	66	21.7	17.4	70	2.3%	-0.30 [-5.70, 5.10]		—
Ferrie 2011	54.5	31.26	13		33.92	14	0.2%	-4.54 [-29.13, 20.05]		
Zhuang 2012	13.17	3.79			4.39	38	5.0%	-2.01 [-3.82, -0.20]		
Zhang 2012	42	5	33	45	6.1	33	4.2%	-3.00 [-5.69, -0.31]	2012	
Cul 2013	10.4	3.9	23	19.2	8.5	47	4.0%	-8.80 [-11.71, -5.89]		<u> </u>
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]		t
Banupriya 2015	13.13	7.71		19.17		75	3.5%	-6.04 [-9.56, -2.52]		
Rongrungruang 2015	24.6	21.7	75	28.2	35.1	75	1.0%	-3.60 [-12.94, 5.74]	2015	
Zarinfar 2016	24.1	5.6	30	27.4	6.6	30	3.6%	-3.30 [-6.40, -0.20]	2016	
Zeng 2016	13.5	12.4	118	10.6	10.2	117	4.0%	2.90 [-0.00, 5.80]	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	16.9	1.2	40	5.6%	-0.20 [-0.73, 0.33]	2018	4
Madmoodpoor 2019	14.2	6.6	46	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	
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	+
Subtotal (95% CI)			2542			2562	77.2%	-2.03 [-3.05, -1.01]		•
Heterogeneity: $Tau^2 = 3.14$; $Chl^2 = 121$. Test for overall effect: Z = 3.90 (P < 0.0)		1 (P < 0.0)0001);	l ² = 837	6					
1.56.2 Hospital LOS – Synbiotics										
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	+
Knight 2009	20.5	5.4	130	16.6	4.8	129	5.4%	1.70 [0.46, 2.94]		-
Rammohan 2015	8.4	2.9	39	17.9	5.2	36	4.9%	-9.50 [-11.43, -7.57]		
Kate 2020	11.7	9.3	35	19.5	15.8	37	2.0%	-7.80 [-13.75, -1.85]		
Subtotal (95% CI)			282			280	22.8%	-2.83 [-6.62, 0.96]		•
Heterogeneity: $Tau^2 = 16.84$; $Chl^2 = 100$ Test for overall effect: $Z = 1.46$ (P = 0.1)		4 (P < 0.0)0001);	r ² = 967	6					
Total (95% CI)			2824			2842	100.0%	-2.21 [-3.24, -1.18]		•
Heterogeneity: Tau ² = 4.71; Chl ² = 224.	42. df = 2	6 (P < 0.0	00001):	r ² = 687	6				-	da da da da da da da
Test for overall effect: $Z = 4.20$ (P < 0.0)					-					-20 -10 0 10 20
Test for subgroup differences: $Chi^2 = 0.1$		/e _ 0 co	1 H - 01							Favours Probiotics Favours Placebo

<u>Supplement Figure 34. Forest plot. Ventilator-Associated Pneumonia in Adults Only</u> (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)

	Probiotics/Syn	biotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M–H, Random, 95% CI
Forestier 2008	24	102	24	106	8.3%	1.04 [0.63, 1.71]	2008	_ + _
Glamarellos-Bourboults 2009	15	36	16	36	7.6%	0.94 [0.55, 1.60]	2009	- _
Knight 2009	12	130	17	129	5.4%	0.70 [0.35, 1.41]	2009	
Barraud 2010	23	87	15	80	6.9%	1.41 [0.79, 2.51]	2010	+- -
Morrow 2010	17	68	33	70	8.5%	0.53 [0.33, 0.86]	2010	
Tan 2013	7	26	13	26	4.9%	0.54 [0.26, 1.13]	2011	
Hayakawa 2012	5	31	3	16	2.0%	0.86 [0.23, 3.15]	2012	
Rongrungruang 2015	16	75	22	75	7.6%	0.82 [0.48, 1.40]	2015	_
Zarinfar 2016	7	30	15	30	4.9%	0.47 [0.22, 0.98]	2016	
Zeng 2016	46	118	62	117	13.2%	0.77 [0.58, 1.01]	2016	
Shimizu 2018	5	35	18	37	3.6%	0.29 [0.12, 0.71]	2018	
Madmoodpoor 2019	7	48	13	54	4.1%	0.61 [0.26, 1.39]	2019	
Thoma 2019	9	28	16	30	6.1%	0.60 [0.32, 1.14]	2019	
Litton 2021	0	110	0	108		Not estimable	2021	
Cook 2021	289	1318	284	1332	16.5%	1.03 [0.89, 1.19]	2021	+
Total (95% CI)		2242		2246	100.0%	0.77 [0.63, 0.93]		◆
Total events	466		551					
Heterogeneity: Tau ² = 0.05; Cl	hl ² = 25.88, df =	13 (P = 0)).02); P	- 50%				
Test for overall effect: Z = 2.71		-						0.01 0.1 1 10 10 Favours Probiotics Favours Placebo

<u>Supplement Figure 35. Forest plot. Mortality in Adults Only (Sensitivity Analysis)</u>: 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)</u>

tudy or Subgroup	Probiotics/Syn Events	Total	Place		Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H. Random. 95% Cl
, , ,			Events 3					m-n, kandom, 95% Cl
empe 1963	3	20		30	0.4%	1.50 [0.34, 6.70]		
lah 2002	1	22	2	23	0.1%	0.52 [0.05, 5.36]		
ain 2004	22	45	20	45	4.1%	1.10 [0.71, 1.71]		
alcao De Arruda 2004	0	10	0	10		Not estimable		
larin 2005	2	9	2	6	0.3%	0.69 [0.16, 4.93]		
AcNaught 2005	18	52	16	51	2.9%	0.98 [0.58, 1.66]		
ayes 2005	0	33	0	33		Not estimable		
lah 2007	2	33	6	29	0.3%	0.29 [0.06, 1.34]	2007	
lberda 2007	2	19	1	9	0.2%	0.95 [0.10, 9.13]		
Ioneycutt 2007	2	31	4	30	0.3%	0.46 [0.10, 2.45]	2007	
lenka 2007	2	26	5	67	0.3%	1.34 [0.28, 6.50]		
'u 2007	6	100	23	100	1.4%	0.35 [0.16, 0.74]	2007	
esselink 2008	24	152	9	144	1.5%	2.53 [1.22, 5.25]	2008	
Un 2006	0	36	0	38		Not estimable	2008	
larin 2008	3	22	6	22	0.5%	0.50 [0.14, 1.75]		
inight 2009	35	130	42	129	5.6%	0.83 [0.57, 1.21]		
iamarellos-Bourboulis 2009	5	36	10	36	0.6%	0.50 [0.19, 1.32]		
arraud 2010	27	87	24	80	3.6%	1.03 [0.65, 1.64]		
forrow 2010	12	68	15	70	1.7%	0.82 [0.42, 1.63]		
rohmader 2010	5	20	3	25	0.5%	2.08 [0.56, 7.68]		
an 2013	3	26	5	26	0.5%	0.60 [0.16, 2.26]		
himizu 2011	9	46	25	121	1.7%	0.95 [0.48, 1.87]		
errie 2011	ž	13		14	1.1%	1.51 [0.64, 3.58]		
imakachorn 2011	4	41	2	39	0.3×	1.90 [0.37, 9.81]		
2013	i	23	4	47	0.2%	0.51 [0.06, 4.32]		
long 2013	é	17	3	21	0.5%	2.47 [0.72, 8.45]		
Vang 2013	5	62	13	121	0.6%	0.75 [0.28, 2.01]		
opez de Toro Martin-Consuegra 2014	19	46	18	43	3.3%	0.99 [0.60, 1.61]		
won 2015	11	50	11	53	1.4%	1.06 [0.51, 2.22]		
	25	75	26	75	4.0%			
Congrungruang 2015	26	-				0.96 [0.62, 1.50]		
eng 2016	20	118 58	25 6	117 51	3.4×	1.03 [0.63, 1.68]		
Yu 2017			-	-	0.3%	0.29 [0.06, 1.39]		
lie 2017	0	48	0	46	A	Not estimable		
himizu 2018	3	35	4	37	0.4%	0.79 [0.19, 3.29]		
Aallick 2018	4	40	6	40	0.6%	0.67 [0.20, 2.18]		
Madmoodpoor 2019	5	48	6	54	0.6%	0.94 [0.31, 2.88]		
Van 2019	5	38	7	36	0.7%	0.71 [0.25, 2.05]		
homa 2019	3	28	2	30	0.3%	1.61 [0.29, 8.92]		
Vang 2020	6	28	7	33	0.6%	1.01 [0.36, 2.66]		
ate 2020	5	39	5	37	0.6%	0.95 [0.30, 3.01]		<u> </u>
Cook 2021	363	1318		1332	53.4%	0.96 [0.85, 1.09]		•
httpn 2021	6	110	5	108	0.6%	1.18 [0.37, 3.75]	2021	
otal (95% CI)		3258		3484	100.0%	0.96 [0.87, 1.04]		•
otal events	691		759					
leterogeneity: $Tau^2 = 0.00$; $Chl^2 = 31.56$.72): I ² =						0.01 0.1 1 10

<u>Supplement Figure 36. Forest plot. Healthcare-Associated Pneumonia in Adults Only</u> (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)

	Probiotics/Syn	biotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Olah 2002	2	22	2	23	1.6%	1.05 [0.16, 6.79]	2002	
Rayes 2005	0	33	1	33	0.6%	0.33 [0.01, 7.90]	2005	
Olah 2007	2	33	4	29	2.1%	0.44 [0.09, 2.23]	2007	
Alenka 2007	4	26	34	87	6.4%	0.39 [0.15, 1.01]	2007	
Honeycutt 2007	2	31	0	30	0.6%	4.84 [0.24, 96.89]	2007	· · · · · · · · · · · · · · · · · · ·
Besselink 2008	24	152	16	144	16.2%	1.42 [0.79, 2.56]	2008	
Xie 2010	4	20	7	19	5.1%	0.54 [0.19, 1.56]	2010	
Tan 2013	2	26	1	26	1.0%	2.00 [0.19, 20.72]	2011	
Xiong 2013	7	17	14	21	13.6%	0.62 [0.32, 1.18]	2013	_
Rammohan 2015	2	39	3	36	1.9%	0.62 [0.11, 3.47]	2015	
Xie 2017	3	48	4	48	2.7%	0.75 [0.18, 3.17]	2017	
Wan 2019	17	38	28	38	35.1%	0.61 [0.41, 0.91]	2019	
Kate 2020	9	39	15	37	11.6%	0.57 [0.28, 1.14]	2020	_ _
Wang 2020	0	28	1	33	0.6%	0.39 [0.02, 9.23]	2020	
Litton 2021	2	110	0	108	0.6%	4.91 [0.24, 101.10]	2021	
Total (95% CI)		662		712	100.0%	0.70 [0.55, 0.89]		•
Total events	60		130					-
Heterogeneity: Tau2 -		.21. df =	14(P =	0.51):	² = 0%			hay aly day in
Test for overall effect			·	/1				0.01 0.1 1 10 10 Favours Probiotics Favours Placebo

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)

	Probioti	cs/Synbi	iotics Placebo Mean Difference			Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
ain 2004	8.2	3	45	6.8	2.5	45	5.9%	1.40 [0.26, 2.54]	2004	+
Falcao De Arruda 2004	11.25	4.8	10	27	16.2	10	0.7%	-15.75 [-26.22, -5.28]	2004	
McNaught 2005	5.3	5.3	52	4.3	5	51	4.9%	1.00 [-0.99, 2.99]	2005	+
tayes 2005	6.6	0.9	33	10.2	1.8	33	6.2%	-1.40 [-2.09, -0.71]	2005	+
Clarin 2005	16.2	11	9	16.6	15.7	6	0.4%	-2.60 [-15.64, 10.44]	2005	
iramek 2007	16.2	16	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	4.7%	-1.40 [-3.55, 0.75]	2007	
iesselink 2008	6.6	17.1	152	3	9.3	144	3.7%	3.60 [0.49, 6.71]	2008	_
Clarin 2008	6.9	5.1	22	21.4	17.2	22	1.2%	-12.50 [-20.00, -5.00]	2008	
Inight 2009	6.5	1.5	130	7.8	2.1	129	6.4%	-1.30 [-1.74, -0.86]	2009	•
arraud 2010	18.7	12.4	87	20.2	20.8	60	2.0%	-1.50 [-6.75, 3.75]	2010	
rohmader 2010	7.3	5.7	20	8.1	4	25	3.6%	-0.80 [-3.75, 2.15]	2010	
Aprrow 2010	14.8	11.8	66	14.6	11.6	70	2.9%	0.20 [-3.71, 4.11]	2010	
an 2013	6.6	3.6	26	10.7	7.3	26	3.6%	-3.90 [-7.06, -0.74]	2011	
errie 2011	32.04	24.46	13	29.75	16.61	14	0.3%	2.29 [-14.26, 18.84]	2011	
llong 2013	6.36	5.68	17	12.2	6.43	21	3.0%	-5.82 [-9.67, -1.97]	2013	
opez de Toro Martin-Consuegra 2014	10	3.6	46	6.6	3.2	43	5.6%	1.20 [-0.21, 2.61]	2014	<u> </u>
tongrungruang 2015	33.3	19.6	75	16.6	5.2	75	2.4%	14.50 [9.91, 19.09]	2015	
tammohan 2015	4.3	3.1	39	4.2	2.2	36	5.6%	0.10 [-1.11, 1.31]	2015	+
Aalik 2016	10.9	3.9	24	15.8	7.8	25	3.3%	-4.90 [-8.33, -1.47]	2016	
arinfar 2016	14.2	4.7	30	17.6	6.5	30	3.9%	-3.40 [-6.27, -0.53]	2016	
leng 2016	21.5	13.5	116	30.1	33.8	117	1.5%	-8.60 [-15.19, -2.01]	2016	
himizu 2016	26.6	23.2	35	30.1	21.6	37	0.7%	-3.50 [-13.87, 6.87]	2018	
Aadmoodpoor 2019	11.6	8	48	18.6	6.3	54	4.0%	-7.00 [-9.82, -4.18]	2019	
Van 2019	10.32	5.31	38	14.24	6.79	36	4.1%	-3.92 [-6.66, -1.18]	2019	
(ate 2020	5.58	1.73	35	6.6	1.5	37	6.2%	-3.22 [-3.97, -2.47]	2020	+
ltton 2021	2.25	3.3	110	2.25	3.3	108	6.1%	0.00 [-0.88, 0.88]	2021	+
Cook 2021	12.7	8.9	1316	12.7	7.4	1332	6.3%	0.00 [-0.62, 0.62]	2021	+
otal (95% CI)			2641			2646	100.0%	-1.24 [-2.14, -0.33]		•
eterogeneity: Tau ² = 3.26; Chl ² = 199.	51, df = 2	7 (P < 0.1)0001);	r ² = 867	"				-	-20 -10 0 10 20
Test for overall effect: $Z = 2.68$ (P = 0.007)									Favours Probiotics Favours Placebo	

<u>Supplement Figure 38. Forest plot. Hospital Length of Stay (LOS) in Adults Only</u> (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)

tudy or Subgroup In 2004 IcNaught 2005 ayes 2005	Mean 16.2 5.35	SD 3.9	Total	Mean	SD	Total	Waight			D/ Dandam OFN/ Cl
kNaught 2005		3.9	4.7				weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
	5.35		45	16.5	4.5	45	5.2%	-0.30 [-2.04, 1.44]	2004	
1107 2005		5.34	52	4.35	3.81	51	5.2%	1.00 [-0.79, 2.79]	2005	+
11C3 COOD	27.8	2.4	33	27.9	2.1	33	5.6%	-0.10 [-1.19, 0.99]	2005	+
2007	42	5	14	49	6.8	11	2.7%	-7.00 [-11.80, -2.20]	2007	
prestler 2006	29.5	16.9	102	30.5	17.6	106	2.7%	-1.00 [-5.69, 3.69]	2008	
esselink 2008	28.9	41.5	152	23.5	25.9	144	1.4%	5.40 [-2.44, 13.24]	2008	
night 2009	20.5	5.4	130	16.6	4.8	129	5.6%	1.70 [0.46, 2.94]	2009	-
lorrow 2010	21.4	14.9	66	21.7	17.4	70	2.3%	-0.30 [-5.70, 5.10]	2010	
arraud 2010	26.6	22.3	87	28.9	26.4	60	1.5%	-2.30 [-9.74, 5.14]	2010	
errie 2011	54.5	31.26	13		33.92	14	0.2%	-4.54 [-29.13, 20.05]	2011	
huang 2012	13.17	3.79	42	15.18	4.39	36	5.2%	-2.01 [-3.82, -0.20]		
hang 2012	42	5	33	45	6.1	33	4.3%	-3.00 [-5.69, -0.31]	2012	
ul 2013	10.4	3.9	23	19.2	6.5	47	4.1%	-8.80 [-11.71, -5.89]	2013	
layes 2014	1.04	0.03	10	1.02	0.64	10	6.1%	0.02 [-0.38, 0.42]	2014	+
opez de Toro Martin-Consuegra 2014	20.8	5.9	46	24.2	6.4	43	4.5%	-3.40 [-5.96, -0.84]	2014	
ongrungruang 2015	24.6	21.7	75	28.2	35.1	75	1.0%	-3.60 [-12.94, 5.74]	2015	
ammohan 2015	8.4	2.9	39	17.9	5.2	36	5.1%	-9.50 [-11.43, -7.57]	2015	
eng 2016	13.5	12.4	118	10.6	10.2	117	4.1%	2.90 [-0.00, 5.80]	2016	
arinfar 2016	24.1	5.6	30	27.4	6.6	30	4.0%	-3.30 [-6.40, -0.20]	2016	
lu 2017	29.7	12.3	58	40.5	15.7	51	2.3%	-10.80 [-16.15, -5.45]	2017	
lallick 2018	18.7	1.2	40	18.9	1.2	40	6.1%	-0.20 [-0.73, 0.33]	2018	4
ladmoodpoor 2019	14.2	8.6	48	21.1	5.7	54	4.2%	-6.90 [-9.77, -4.03]	2019	
ang 2020	16.7	4.7	28	19.7	9.3	33	3.5%	-3.00 [-6.62, 0.62]	2020	
ate 2020	11.7	9.3	35	19.5	15.8	37	2.0%	-7.60 [-13.75, -1.85]	2020	
tton 2021	10	5.26	110	9	5.26	108	5.5%	1.00 [-0.40, 2.40]	2021	-
ook 2021	25.7	21.5	1318	25	20	1332	5.4%	0.70 [-0.88, 2.28]	2021	+
otal (95% CI)			2749			2767	100.0%	-2.06 [-3.10, -1.03]		•
eterogeneity: Tau ² = 4.54; Chl ² = 214.	59, df = 2	5 (P < 0.0	00001);	r ² = 66%	4					
est for overall effect: Z = 3.90 (P < 0.00										-20 -10 0 10 20 Favours Probiotics Favours Placebo

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)

	Probiotics/Syr	biotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Forestier 2008	24	102	24	106	13.3%	1.04 [0.63, 1.71]	2008	
Glamarellos-Bourboults 2009	15	36	16	36	12.0%	0.94 [0.55, 1.60]	2009	
Knight 2009	12	130	17	129	8.0%	0.70 [0.35, 1.41]	2009	
Morrow 2010	17	68	33	70	13.6%	0.53 [0.33, 0.86]	2010	_
Barraud 2010	23	87	15	80	10.8%	1.41 [0.79, 2.51]	2010	- -
Angurana 2018	3	50	2	50	1.5%	1.50 [0.26, 8.60]	2018	
Madmoodpoor 2019	7	48	13	54	6.0%	0.61 [0.26, 1.39]	2019	
Litton 2021	0	110	0	108		Not estimable	2021	
Cook 2021	289	1318	284	1332	34.7%	1.03 [0.89, 1.19]	2021	+
Total (95% CI)		1949		1965	100.0%	0.91 [0.73, 1.13]		•
Total events	390		404					-
Heterogeneity: Tau ² = 0.03; Cl	hl² = 10.70, df =	7 (P = 0.	.15); P =	35%			-	
Test for overall effect: Z = 0.85	5 (P = 0.39)							0.2 0.5 1 2 5 Favours Probiotics Favours Placebo

<u>Supplement Figure 40. Forest plot. Mortality in Low Risk of Bias Studies (Sensitivity</u> 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)

	Probiotics/Synt	oiotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M–H, Random, 95% Cl
Tempe 1983	3	20	3	30	0.4%	1.50 [0.34, 6.70]	1983	
Olah 2002	1	22	2	23	0.2%	0.52 [0.05, 5.36]	2002	
ain 2004	22	45	20	45	5.0%	1.10 [0.71, 1.71]	2004	+
Falcao De Arruda 2004	0	10	0	10		Not estimable	2004	
Klarin 2005	2	9	2	8	0.3%	0.89 [0.16, 4.93]	2005	
Rayes 2005	0	33	0	33		Not estimable	2005	
Olah 2007	2	33	6	29	0.4%	0.29 [0.06, 1.34]	2007	
Alenka 2007	2	26	5	87	0.4%	1.34 [0.28, 6.50]	2007	
Alberda 2007	2	19	1	9	0.2%	0.95 [0.10, 9.13]	2007	
Honeycutt 2007	2	31	- 4	30	0.4%	0.48 [0.10, 2.45]	2007	
Besselink 2008	24	152	9	144	1.6%	2.53 [1.22, 5.25]	2008	
Klarin 2006	3	22	6	22	0.6%	0.50 [0.14, 1.75]	2008	
Glamarellos-Bourboults 2009	5	36	10	36	1.0%	0.50 [0.19, 1.32]	2009	
(night 2009	35	130	42	129	6.9X	0.83 [0.57, 1.21]	2009	-++
rohmader 2010	5	20	3	25	0.6%	2.08 [0.56, 7.68]	2010	
Sarraud 2010	27	67	24	60	4.7%	1.03 [0.65, 1.64]	2010	_ + _
Morrow 2010	12	68	15	70	2.1%	0.82 [0.42, 1.63]	2010	
Ferrie 2011	7	13	5	14	1.3×	1.51 [0.64, 3.58]	2011	_
Simakachorn 2011	4	41	2	39	0.4%	1.90 [0.37, 9.81]	2011	
Cumar 2013	6	75	7	75	1.1×	1.14 [0.44, 2.99]	2013	
opez de Toro Martin-Consuegra 2014	19	46	16	43	4.0%	0.99 [0.60, 1.61]	2014	-+-
Angurana 2016	6	50	5	50	0.6%	1.20 [0.39, 3.68]	2018	
Wang 2016	2	45	0	45	0.1%	5.00 [0.25, 101.31]	2018	
Madmoodpoor 2019	5	48	6	54	0.6%	0.94 [0.31, 2.88]	2019	
Cook 2021	363	1318	361		65.8%	0.96 [0.85, 1.09]	2021	•
Litten 2021	6	110	5	108	0.7%	1.18 [0.37, 3.75]	2021	
Fotal (95% CI)		2509		2570	100.0%	0.98 [0.89, 1.08]		•
Fotal events	567		581					
leterogeneity: $Tau^2 = 0.00$; $Chl^2 = 19.0$ est for overall effect: $Z = 0.40$ (P = 0.6)		70); l² =	0%				ē	0.01 0.1 1 10 10 Favours Probiotics Favours Placebo

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

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)

	Probiotics/Syn	biotics	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
Olah 2002	2	22	2	23	10.5%	1.05 [0.16, 6.79]	2002	
Rayes 2005	0	33	1	33	4.2%	0.33 [0.01, 7.90]	2005	
Olah 2007	2	33	4	29	13.1%	0.44 [0.09, 2.23]	2007	
Alenka 2007	4	26	34	87	25.9%	0.39 [0.15, 1.01]	2007	
Honeycutt 2007	2	31	0	30	4.7%	4.84 [0.24, 96.89]	2007	
Besselink 2008	24	152	16	144	37.0%	1.42 [0.79, 2.56]	2008	
Litton 2021	2	110	0	108	4.6%	4.91 [0.24, 101.10]	2021	
Total (95% CI)		407		454	100.0%	0.89 [0.45, 1.76]		•
Total events	36		57					
Heterogeneity: Tau2 =	= 0.23; Chl ² = 8.7	4, df = 6	i (P = 0.1	19); 📍 -	31%			
Test for overall effect	z = 0.33 (P = 0.3)	74)						0.01 0.1 1 10 100 Favours Probiotics Favours Placebo

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)

	Probiotics/Synbiotics				Placebo			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI	
Falcao De Arruda 2004	11.25	4.8	10	27	16.2	10	0.6%	-15.75 [-26.22, -5.28]	2004		
jain 2004	8.2	3	45	6.6	2.5	45	9.1%	1.40 [0.26, 2.54]	2004	+	
Klarin 2005	16.2	11	9	16.6	15.7	6	0.4%	-2.60 [-15.64, 10.44]	2005		
Rayes 2005	6.6	0.9	33	10.2	1.8	33	10.1%	-1.40 [-2.09, -0.71]	2005	-	
Alenka 2007	13.4	3.7	26	14.8	4.2		6.3%	-1.40 [-3.55, 0.75]	2007		
Klarin 2008	8.9	5.1	22	21.4	17.2	22	1.1%	-12.50 [-20.00, -5.00]	2008		
Besselink 2006	6.6	17.1	152	3	9.3	144	4.4%				
Knight 2009	6.5	1.5	130	7.8	2.1	129	10.6%	-1.30 [-1.74, -0.86]	2009	•	
Frohmader 2010	7.3	5.7	20	6.1	4	25	4.6%	-0.60 [-3.75, 2.15]			
Morrow 2010	14.6	11.6	66	14.6	11.6	70	3.2%	0.20 [-3.71, 4.11]	2010		
Sarraud 2010	18.7	12.4	87	20.2	20.8	80	2.1%	-1.50 [-6.75, 3.75]			
errie 2011	32.04	24.46	13	29.75	16.61	14	0.3%	2.29 [-14.26, 18.84]	2011		
opez de Toro Martin-Consuegra 2014	10	3.6	46	6.6	3.2	43	8.3×	1.20 [-0.21, 2.61]	2014		
Malik 2016	10.9	3.9	24	15.8	7.8	25	3.9%	-4.90 [-8.33, -1.47]	2016		
Angurana 2016	7	2	50	6.6	1.4	50	10.2%	-1.60 [-2.46, -1.12]		-	
Madmoodpoor 2019	11.6	6	46	16.6	6.3	54	4.9%	-7.00 [-9.82, -4.18]			
Cook 2021	12.7	6.9	1318	12.7	7.4	1332	10.3%	0.00 [-0.62, 0.62]		+	
Litton 2021	2.25	3.3	110	2.25	3.3	108	9.7%	0.00 [-0.88, 0.88]	2021	+	
Total (95% CI)			2211			2218	100.0%	-1.00 [-1.84, -0.16]		•	
leterogeneity: Tau ² = 1.68; Chl ² = 97.0	0, df = 17	(P < 0.00	0001); P	= 82%						to to the sh	
est for overall effect: Z = 2.34 (P = 0.0)										-20 -10 0 10 20 Favours Probiotics Favours Placebo	

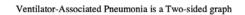
<u>Supplement Figure 43. Forest plot. Hospital Length of Stay (LOS) in Low Risk of Bias</u> Studies (Sensitivity Analysis):

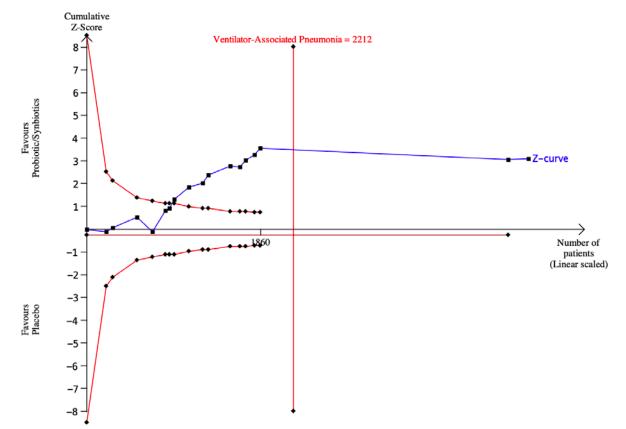
Comparing probiotics/synbiotics and placebo for the outcome of Hospital Length of Stay in Low Risk of Bias studies; results are shown by using the random-effects model with relative risk and 95% confidence intervals (CI)

	Probiot	ics/Synbi	iotics	P	lacebo		Mean Difference			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
jain 2004	16.2	3.9	45	16.5	4.5	45	12.3%	-0.30 [-2.04, 1.44]	2004	+
Rayes 2005	27.8	2.4	33	27.9	2.1	33	14.0%	-0.10 [-1.19, 0.99]	2005	*
Forestier 2008	29.5	16.9	102	30.5	17.6	106	5.4%	-1.00 [-5.69, 3.69]	2008	+
Besselink 2008	28.9	41.5	152	23.5	25.9	144	2.5%	5.40 [-2.44, 13.24]	2008	
Knight 2009	20.5	5.4	130	16.6	4.6	129	13.6%	1.70 [0.46, 2.94]	2009	-
Morrow 2010	21.4	14.9	66	21.7	17.4	70	4.4%	-0.30 [-5.70, 5.10]	2010	-+-
Barraud 2010	26.6	22.3	67	28.9	26.4	60	2.7%	-2.30 [-9.74, 5.14]	2010	
Ferrie 2011	54.5	31.26	13	59.04	33.92	14	0.3%	-4.54 [-29.13, 20.05]	2011	
Lopez de Toro Martin-Consuegra 2014	20.8	5.9	46	24.2	6.4	43	9.9%	-3.40 [-5.96, -0.84]	2014	
Madmoodpoor 2019	14.2	6.6	46	21.1	5.7	54	9.1%	-6.90 [-9.77, -4.03]	2019	
Cook 2021	25.7	21.5	1318	25	20	1332	12.7%	0.70 [-0.88, 2.28]	2021	+
Litton 2021	10	5.26	110	9	5.26	108	13.2%	1.00 [-0.40, 2.40]	2021	-
Total (95% CI)			2152			2158	100.0%	-0.57 [-1.92, 0.78]		•
Heterogeneity: $Tau^2 = 3.07$; $Chl^2 = 41.4$	0. df = 11	(P < 0.00	001); ř •	- 73%						- da da da da da
Test for overall effect: Z = 0.83 (P = 0.4)										-20 -10 0 10 20 Favours Probiotics Favours Placebo

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 α = 0.05 (two sided) and β = 0.20 (power 80%).





Appendix 9. Tables: Supplement Table 1. Baseline Characteristics of Included Studies

Ро	pulation		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	<u>PRISM III Score</u> 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 + <i>S. boulardii</i> 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 + <i>Bifidobacterium</i> , 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 InterventionScoring System (TISS)Mean (SD)Study = 34 (8)Control = 32 (5)Glasgow scoreMedian (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	<u>APACHE II</u> Mean (SD) Probiotic = 27.7 (6.3) Placebo = 29.6 (6.1)	EN (standard) + 10 ¹⁰ CFU <i>Lactobacillus</i> <i>rhamnosus</i> 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 <i>P. aeruginosa</i> 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	Placebo = 19.36	administered by a NG or gastrostomy				1
	Placebo = 19.36	tube once daily for 15 days				
multiple organ		tube office daily for 15 days				
trauma patients in		EN and an entrol				
surgical ICUs		EN not reported				
n = 72				N1/A	0	
Hayakawa 2012	N/A	EN (Medief) + Yakult ⁸ 1 g and Oligomate S-HP (Yakult) 5 g TID during 8 week study	EN (Medief)	N/A	8 week study	Colonization of <i>P</i> .
Adult patients		period			period	aeruginosa in the lower
receiving		period				respiratory tract
mechanical ventilation and						
enteral tube feeding						
for ≥1 month						
n = 47						
Honeycutt 2007	N/A	One capsule Lactobacillus rhamnosus GG	One capsule of insulin	≤72 hours after	Until hospital	Nosocomial infection,
Medical-surgical		10 x 10 ⁹ cells/capsule (Culturelle) once	once a day in 5mL of	PICU admission	discharge or	bloodstream infection,
pediatric ICU		daily in 5mL of 5% dextrose until	5% dextrose.		death and for 48	pneumonia,
patients		discharge from hospital, parental request			hours after	tracheobronchitis, and UTI
n = 61		to withdraw from the study, or until			discharge/transfer	
		death			from the hospital.	
		EN not reported				
Jain 2004	APACHE II	EN or PN + synbiotic (Trevis™) one	EN or PN + placebo –	≤24 hours from	Until discharge	Gastric colonisation
Adult ICU patients	Median (IQR)	capsule TID + 7.5 g Raftilose [™] prebiotic	powdered sucrose and	admission	from hospital –	
n = 90	Synbiotics = 11 (9-14)	(oligofructose) BID. Administered until	placebo-capsules (Chr		mean duration of	
	Control = 11 (10-15)	hospital discharge	Hansen Biosystem)		study medication	
					was 10 days in	
	POSSUM				both groups.	
	Median (IQR)					
	Synbiotics = 36(32-40)					
	Control = 37(33-40)					
Kate 2020	N/A	1 gram of synbiotic containing both pre	A similar-looking	N/A	90 days	Septic complications during
Adult patients		and probiotics given in 100 ml of saline	placebo			hospital stay or within 90
treated for		BID x 14 days				days follow up and
moderately severe						inflammatory marker levels
and severe acute		EN not reported				– IL-8, IL-10, LDH, and TNF- α
pancreatitis as per						
the Atlanta 2012						
criteria						
n = 86						
Klarin 2005	APACHE II	EN (Nutrodrip) + 10 ⁹ CFU/mL Lp	EN (Nutrodrip)	≤12 hours from	Duration of ICU	Survival and adherence of
Adult mixed	Median (IQR)	(Lactobacillus plantarum) 299v (Probi		admission	stay and 6-month	Lp 299v to the mucosa in
critically ill patients	Probiotics = 17 (13 - 29)	AB). Administered 50mL q6 hours x 3			mortality	the lower GI tract
on broad spectrum	Control = 19 (14 - 36)	days then 25mL q6 hours for rest of ICU				
antibiotics		stay				
n = 17			-			
Klarin 2008	APACHE II	EN + 8x 10 ⁸ (CFU)/ml of <i>Lactobacillus</i>	EN + fermented	≤24 hours from	Duration of ICU	C. difficile infection
	Median (Range)	plantarum 299v (Probi AB). Administered	oatmeal gruel without	ICU admission	stay and up to 6	

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 <i>Candida</i> on day 14 post enrollment
Kwon 2015 Adult medical or coronary ICU patients n = 103	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	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 <i>Median (range)</i> 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	<u>APACHE II</u> Mean (SD) Placebo = 14.6 (6.9) Probiotic = 14.5 (6)	2×10 ¹⁰ CFU/L <i>Lactobacillus plantarum</i> 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	<u>APACHE II</u> <i>Median (IQR)</i> 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	<u>APACHE II</u> 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 <i>C.</i> <i>difficile</i> positive culture n = 69	<u>APACHE II</u> 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	<u>APACHE II</u> 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	14 th 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	<u>APACHE II</u> <i>Median (IQR)</i> Probiotics = 12 (9 - 16) Control = 12 (8 - 17)	EN or PN + ProViva ¹³ oatmeal and fruit drink with 5x10 ⁷ CFU/ml of <i>L.</i> <i>plantarum299v</i> - 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	APACHE II Mean (SD) Probiotics = 22.7 (7.5)	2x10 ⁹ CFU <i>Lactobacillus rhamnosus</i> GG BID administered as lubricant and through NG until extubation,	Placebo containing inert plant starch inulin	≤24 hours from intubation	Duration of hospitalization	VAP
mechanical ventilation n = 138	Placebo = 23.7 (8.0)	tracheostomy placement, or death				
Olah 2002 Patients with acute pancreatitis including those with severe acute pancreatitis n = 45	<u>Glasgow Score</u> Mean (SD) Probiotics = 2.5 (1.3) Control = 2.8 (1.5)	EN (Nutrison Fibre [®]) + 10g oat fibre + 10 ⁹ organisms of live <i>Lactobacillus plantarum</i> 299 BID during first 7 days	EN (Nutrison Fibre®) + 10g oat fibre + 10 ⁹ organisms of heat killed <i>Lactobacillus</i> <i>plantarum</i> 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 ^{™2} 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 <i>L. rhamnosus GG</i> (i-Health, Inc.) through feeding tubes twice daily. Administered for up to 60 days or until discharge from ICU, or if <i>Lactobacillus</i> <i>spp.</i> 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	<u>APACHE II</u> <i>Mean (SD)</i> 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 \geq 72 hours n = 150	APACHE II Mean (SD) Probiotics = 19.41 (7.04 Control = 19.88 (6.89)	80 ml of 8x10° CFU <i>Lactobacillus casei</i> (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 \geq 7 days n = 40	<u>APACHE II</u> <i>Mean (SD)</i> Probiotic = 22.80 (4.73) Placebo = 22.45 (4.57)	EN HOLTEDOITED 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 <i>Saccharomyces boulardii</i> 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	<u>APACHE II</u> <i>Median (IQR)</i> Synbiotics = 19 (14 - 24) Control= 20 (14 - 26)	EN (Glucerna®-Ex) + Yakult BL Seichoyaku 3g/day (Yakult Honsha) ⁸ - 10 ⁸ <i>B. breve</i> strain Yakult/g and 1 × 10 ⁸ <i>L. casei</i> 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	<u>APACHE II</u> <u>Median (IQR)</u> Control = 20 (12 - 25) Probiotic = 17 (10 - 26) Synbiotic = 18 (15 - 22) <u>SAPSII</u> <u>Median (IQR)</u> 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	<u>APACHE II</u> Median (IQR) 24 (21 - 27)	Post-pyloric Synbiotic Forte (Medipharm) ² EN not reported	Теа	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 <i>Lactobacillus</i> <i>paracasei</i> NCC 2461 and 2 x 10 ⁶ CFU/g <i>Bifidobacterium longum</i> 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 1 st 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) <i>Saccharomyces boulardii</i> (one capsule containining 5 billion live lyophilized cells of <i>S. boulardi</i> i.) for 11 – 21 days	EN + placebo	N/A	Study duration <i>Mean (SD)</i> 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

and the statement of the				1		1 1
required surgical intervention with or		EN not reported				
without mechanical						
ventilation > 10 days						
n = 58						
Wang 2013	APACHE II	EN (PEPTISORB) + 0.5 g combined	EN (PEPTISORB) or PN	N/A	14 days	Bacterial translocation and
Adult severe acute	Mean (SD)	Bacillus subtilis and Enterococcus				cytokine production – TNF-
pancreatitis patients admitted to the ICU	EN = 13.27 (2.86) EN + probiotics = 42.6	<i>faecium</i> enteric-coated capsules (Beijing Han Mei Pharmaceutical Company				α, IL-6, and IL-10 levels
n = 183	(13.8)	Limited) TID				
11 100	(10.0)					
Wang 2018	Lung Injury Score	EN or PN + 3 mL of 5% glucose liquid +	EN or PN + 3 mL of 5%	≤24 hours after	N/A	Serum ghrelin levels and
Children (≤14 years)	Mean (SD)	one probiotic tablet Eosinophil	glucose liquid without	diagnosis		pulmonary function
admitted to the	Probiotics = 2.04 (0.64)	Lactobacillus (Tonghua, China),	L. acidophilus.			
PICU with acute	Control = 1.96 (0.66)	containing 5×10^6 CFU Lactobacillus				
lung injury n = 80		acidophilus of Chinese and Japanese strains TID for 10 days				
Wan 2019	APACHE II	EN (NengQuanLi) + probiotic tablet (210	EN (NengQuanLi)	Within 48 hours	30 days	Levels of inflammatory
Adult patients with	Mean (SD)	mg/per tablet) with Bifidobacterium	(- 0 - (-)	of admission		factors including
severe traumatic	Probiotic + EN = 13.26	longum,				Endothelin-1 (ET-1), CRP,
brain injury	(2.31)	Lactobacillus bulgaricus, and				TNF-α, IL-6, and IL-10
n = 76	EN = 12.84 (2.37)	Enterococcus faecalis >1.0x 10 ⁷ CFU				
	CO.5.4	(Xinyi Pharmaceutical Factory Co., Ltd.) –				
	<u>SOFA</u> Mean (SD)	6 tablets BID for 15 days				
	Probiotic + EN = 5.29					
	(1.35)					
	EN = 5.02 (1.28)					
Wang 2020	APACHE II	10 ⁶ CFU Clostridium butyricum - MIYA-	Placebo	N/A	N/A	Duration of hospital stay,
Adult patients	Median (IQR)	BM [®] one tablet TID				mortality, rate of hospital-
admitted to a	Control = 12 (11 - 15)					acquired infection, cost of
Respiratory Intensive Care Unit	Probiotic = 13 (11 - 15)	EN not reported				hospital stay, cost for antibiotics, and time of
n = 61						antibiotics treatment
Wu 2017	APACHE II	EN + Bifidobacterium quadruple living	EN	48 – 72 hours	N/A	APACHE II scores and
Adult patients with	Mean (SD)	bacterium 420 mg TID until abdominal		after onset of	,	multiple organ dysfunction
severe acute	Probiotic = 10.8 (2.9)	symptoms disappeared, amylase		acute		
pancreatitis	Control = 11.3 (3.1)	returned to normal, and inflammatory		pancreatitis		
n = 127		necrosis was partly absorbed				
Xie 2010	GCS	Live Combined Bifidobacterium and	N/A	N/A	16 days	N/A
Adult patients with severe head injury	6 - 8	Lactobacillus Tablets, 2g/time, TID				
n = 39		EN not reported				
Xie 2013	N/A	Early EN (RujSu) + synbiotics (Golden	Early EN (RujSu) within	N/A	N/A	Normal intestinal flora, fecal
Patients with		Bifid) ¹⁵ in the first 14 days of enteral	24-48 hours after			SIgA, and infectious
hypertensive		nutritional support	injury.			complications

international						
intracerebral						
hemorrhage						
n = 53						
Xie 2017	APACHE II	Triple alive bacteria preparation	N/A	N/A	14 days	N/A
Adult patients with	≥8	(Shanghai Xinyi Pharmaceutical Factory)				
severe acute		6 g/d (TID)				
pancreatitis						
n = 96		EN not reported				
Xiong 2013	GCS	Live Combined Bifidobacterium and	N/A	1 – 3 days	15 days	N/A
Adult patients with	5 - 8	Lactobacillus Tablets, 3.5g/time, TID,				
severe head injury		total probiotics $\geq 1 \times 10^8$ CFU/day				
n = 41		EN not reported				
Yu 2007	GCS	EN with homogenate diet and yogurt -	EN with homogenate	2 days	N/A	Nutritional status,
Patients with severe	4 - 8	Lactobacillus in yogurt: 4x10 ¹¹ /100g;	diet			gastrointestinal
head injury		intervention group: 150-300g				complications, recovery of
n = 200		yogurt/time,BID				consciousness, and
						prognosis
Zarinfar 2016	N/A	Lactobacillus rhamnosus Gagavage TID in	Placebo in addition to	N/A	N/A	VAP
ICU patients		addition to a routine care	routine care TID			
undergoing						
mechanical		EN not reported				
ventilation						
n = 60						
Zeng 2016	APACHE II	Probiotics capsules (Medilac-S) ¹⁷ 0.5 g	Standard preventative	≤24 hours of	Until tracheal	VAP
Adult mixed	Mean (SD)	active Bacillus subtilis and Enterococcus	strategies of VAP	admission to	extubation,	
critically ill patients	Probiotics = 14.7 (3.9)	faecalis at a concentration of 4.5 ×	0	ICU or within 24	discharge from	
expected to receive	Control = 16.6 (4.3)	$10^9/0.25$ g and $0.5 \times 10^9/0.25$ g,		hours of	the hospital or	
mechanical		respectively diluted in 50-80mL sterile		tracheal	death – maximum	
ventilation for > 48		water TID for maximum study duration of		intubation if	study duration of	
hours		14 days		occurred in ICU	14 days.	
n = 235		EN not reported			,	
Zhang 2012	N/A	Live Combined Bifidobacterium and	N/A	2 – 3 days	7 – 10 days after	N/A
Patients with severe		Lactobacillus Tablets, 2.0 g/time, TID		2 0 0010	the onset of	
acute pancreatitis					severe acute	
n = 99		EN not reported			pancreatitis	
Zhuang 2012	N/A	Probiotic yogurt feeding	Routine feeding	N/A	Duration of	Incidence of diarrhea
Patients receiving					hospital stay	
enteral nutrition in		EN not reported			noopital stay	
the Respiratory						
Intensive Care Unit						
n = 80						
	n for primary outcome wher		1		I	1

*- 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 2000² (Medipharm, Sweden and Des Moines, IA) - 10¹⁰ Pediococcus pentosaceus 5–33:3, 10¹⁰ Lactococcus raffinolactis 32–77:1, 10¹⁰ Lactobacillus paracasei subsp paracasei 19, 10¹⁰ Lactobacillus plantarum 2362 and 2.5 g of each of the following 4 fibers: β-glucan, inulin, pectin, and resistant starch per sachet

VSL#3³ (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]).
 One probiotic capsule⁴ 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 casei*, 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) capsules⁵ containing 2 x 10¹⁰ 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 10¹⁰ bacteria, plus cornstarch and maltodextrins.

7. VSL#3⁷ (VSL Pharmaceuticals, Gaithersburg, Maryland) - 450 billion live lactic acid bacteria in defined ratios of lyophilized *Bifidobacterium breve, Bifidoba terium longum* (>10 x 10⁹/g), *Bifidobacterium infantis* (>10 x 10⁹/g), *L acidophilus, Lactobacillus plantarum, Lactobacillus casei, L bulgaricus, Streptococcus thermophilus* (>100 x 10⁹/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 10⁸ living *Bifidobacterium breve* strain Yakult and 1x10⁸ living *Lactobacillus casei* strain Shirota.

9. Lactinex granules⁹ (a viable mixed culture of Lactobacillus acidophilus and L. bulgaricus) provided by Becton Dickinson.

10. Trevis[™] capsules contain 4 x 10⁹ 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 10¹⁰ 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 5x10⁷ 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 - 10⁹ bacteria for 21 days. Probiotic contained 0.5 × 10⁸ Bifido- bacterium longum, 0.5 × 10⁷ Lactobacillus bulgaricus, and 0.5 × 10⁷ Streptococcus thermophilus.

Supplement Table 2. Risk of Bias Assessment

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

		Drehehly	Drahahlu	Drobobly		Drahahlu
Klarin 2005	Low ROB	Probably	Probably	Probably	Low ROB	Probably
<u> </u>		Low ROB	Low ROB	Low ROB		Low ROB
Klarin 2008	Low ROB	Low ROB	Low ROB	Probably	Low ROB	Probably
				Low ROB		Low ROB
Knight 2009	Low ROB	Low ROB	Probably	Low ROB	Low ROB	Probably
			Low ROB			Low ROB
Kumar 2013	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB
Kwon 2015	Probably	Probably	Low ROB	Probably	Low ROB	Probably
	High ROB	High ROB		Low ROB		High ROB
Li 2007	Probably	Probably	Probably	Probably	Probably	Probably
	High ROB	High ROB	Low ROB	High ROB	High ROB	High ROB
Litton 2021	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB
Lopez de	Low ROB	Probably	Probably	Probably	Low ROB	Probably
Toro Martin-		Low ROB	Low ROB	Low ROB		Low ROB
Consuegra						
2014						
Madmoodpo	Low ROB	Low ROB	Probably	Low ROB	Low ROB	Probably
or 2019			Low ROB			Low ROB
Malian 2012	Probably	Probably	Probably	Probably	Probably	Probably
	Low ROB	Low ROB	High ROB	Low ROB	High ROB	High ROB
Malik 2016	Low ROB	Low ROB	Probably	Low ROB	Low ROB	Probably
			Low ROB			Low ROB
Mallick 2018	Probably	Low ROB	Probably	Probably	Probably	Probably
	High ROB		High ROB	Low ROB	Low ROB	High ROB
Masjedi 2017	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB
Mayes 2014	Probably	Probably	Probably	Probably	Probably	Probably
-	High ROB	High ROB	Low ROB	Low ROB	Low ROB	High ROB
McNaught	Probably	Probably	Probably	Probably	Probably	Probably
2005	High ROB	High ROB	Low ROB	Low ROB	Low ROB	High ROB
Morrow	Probably	Low ROB	Low ROB	Low ROB	Low ROB	Probably
2010	Low ROB					Low ROB
Olah 2002	Probably	Low ROB	Low ROB	Probably	Low ROB	Probably
	Low ROB			Low ROB		Low ROB
Olah 2007	Probably	Low ROB	Probably	Low ROB	Low ROB	Probably
	Low ROB		Low ROB			Low ROB
PROSPECT	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB	Low ROB
2021						
Qin 2008	Low ROB	Probably	Probably	Low ROB	Low ROB	Probably
		, High ROB	Low ROB			, High ROB
Rammohan	Low ROB	Probably	Probably	Probably	Probably	Probably
2015		High ROB	Low ROB	Low ROB	Low ROB	High ROB
Rayes 2005	Low ROB	Probably	Probably	Probably	Probably	Probably
		Low ROB	Low ROB	Low ROB	Low ROB	Low ROB

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

	Low ROB	High ROB		Low ROB		High ROB
Zhang 2012	Probably	Probably	Probably	Probably	Probably	Probably
	High ROB	High ROB	Low ROB	High ROB	High ROB	High ROB
Zhuang 2012	High ROB	High ROB	Probably	Probably	Probably	High ROB
			High ROB	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	Placebo = 0	Placebo = 0
	Probiotics = 9 (all had	Probiotics = 0	Probiotics = 8
	mesenteric ischemia)		
PROSPECT 2021	Placebo = 0	Placebo = 1	Placebo = 0
	Probiotics = 2	Probiotics = 15	Probiotics = 9
			(1 death attributed to
			invasive probiotic
			infection)

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

			Certainty a	assessment			№ of pati	ients	Effec	t		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics/Synbiotics	Placebo	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Ventilator	Associated Pne	eumonia										
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)		CRITICAL
Healthcare	e-Associated Pr	neumonia										
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)		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)		CRITICAL
Serious A	dverse 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)		CRITICAL
Other Hea	Ithcare Infection	ns		1								
27	randomised trials	serious ^r	serious 9	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)		IMPORTANT
ICU Lengt	h 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)		IMPORTANT

			Certainty a	ssessment			№ of pati	ents	Effec	t		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics/Synbiotics	Placebo	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
Duration o	of Mechanical V	entilation										
12	randomised trials	serious ^k	serious	not serious	not serious	none	785	801	-	MD 2.53 lower (3.74 lower to 1.31 lower)		IMPORTANT
Hospital L	ength of Stay											
27	randomised trials	serious ^I	serious ^m	not serious	not serious	none	2824	2842	-	MD 2.21 lower (3.24 lower to 1.18 lower)		IMPORTANT
Antibiotic	Days											
12	randomised trials	serious "	serious °	not serious	serious ^j	none	514	523	-	MD 1.77 lower (3.36 lower to 0.17 lower)		NOT IMPORTANT
Invasive Ir	nfection with Pr	obiotic Organism							l			
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)		CRITICAL
Organ Dys	sfunction											
9	randomised trials	serious ª	serious ^r	not serious	serious ^s	none	415	392	-	SMD 0.22 SD lower (0.78 lower to 0.35 higher)		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)		IMPORTANT

Duration of Diarrhea

			Certainty a	ssessment			№ of pati	ents	Effec	t		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics/Synbiotics	Placebo	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
5	randomised trials	serious ¹	serious "	not serious	serious ^p	none	164	167	-	MD 2.59 lower (5.59 lower to 0.41 higher)		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)	IMPORTANT
										126 more)	

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)		IMPORTANT
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Urinary Tract Infection

(from 23 MODERATE fewer to 13 more)	18	randomised not ser trials	erious not se	t serious	not serious	serious ^p	none	204/2099 (9.7%)	227/2150 (10.6%)	RR 0.94 (0.78 to 1.12)			IMPORTANT
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C. Difficile Infection

more)		5	randomised trials	serious ^w	serious ×	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)		IMPORTANT
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Catheter Related Blood Stream Infections

more)	8	randomiseo 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)		IMPORTANT
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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.

I. 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.

g. 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.

Outcome	Number of studies	Number of studies contributing to the meta-analysis*	p-value
Mortality	47	43	0.849
VAP	17	16	0.030
НАР	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	-

Supplement Table 5. Test of Funnel Plot Asymmetry

* 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: <u>Methods</u>

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 dysfunctionrelated 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 fulltext 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

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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 l^2 statistic [3]. We constructed funnel plots and tested for asymmetry to assess for publication

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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, <u>www.ctu.dk/tsa</u>).

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 NFkB 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].

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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.

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