Appendix 1 (as supplied by the authors): Supplementary material

Supplementary Table 1: Results of sensitivity analyses

Analysis	Pooled risk ratio Median (95% credible interval)	95% Prediction interval	Between-study standard deviation in log risk ratio Median (95% credible interval)
Results reported in the main text*	0.25 (0.08, 0.47)	(0.03, 1.38)	0.64 (0.06, 1.75)
Alternative prior over variance I (Standard Deviation** ~ Uniform (0,3))	0.24 (0.07, 0.47)	(0.02, 1.51)	0.65 (0.03, 2.15)
Alternative prior over variance II (Standard Deviation** ~ Cauchy (scale=25))	0.24 (0.07, 0.48)	(0.02, 1.77)	0.66 (0.06, 2.53)
Including studies that did not report results of testing	0.28 (0.11, 0.52)	(0.04, 1.36)	0.65 (0.07, 1.63)
Excluding study by Gao et al.[1]	0.25 (0.06, 0.55)	(0.02, 1.77)	0.79 (0.07, 1.88)
Including only studies with a strict definition of diarrhea (≥3 liquid stools in 24 hours)	0.25 (0.05, 0.77)	(0.01, 3.09)	1.01 (0.09, 1.93)

* Between-study standard deviation in log risk ratio ~ U(0,2); ** Between study standard-deviation in log risk ratio

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Search strategy for PubMed database:

Articles for this report were identified using the following search strategy on Dec 2015:

(((Probiotic*[Title/Abstract] AND Lactobacill*[Title/Abstract])) AND (Clostridium[Title/Abstract] OR difficile[Title/Abstract] OR antibiotic associated diarrhea[Title/Abstract])) AND Patients[Title/Abstract]

This search strategy returned 86 records on Dec 20, 2015. We applied different filters resulting in the following exclusions:

Non-English records: 8,

Animal studies: 2,

Pediatrics: 11,

Review: 21

Systematic reviews: 7,

Observational studies: 8,

Cost analysis: 2,

In vitro studies: 5,

Comment: 1,

HTA report: 1.

The total number of potentially relevant records (randomized controlled trials) remaining was 20 articles.

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WinBUGS program for Bayesian meta-analysis

```
model {

        for (i in 1:k) {

                TC1[i] ~ dbin(pc[i] ,N1c[i] ) # pc=probability of AAD in control group
                TT1[i] ~ dbin(pt[i] , N1t[i] ) # pt=probability of AAD in treatment group
                TC2[i] ~ dbin(qc[i] ,N2c[i] ) # qc=probability of CDAD+ among N2 AAD patients tested in control group
                TT2[i] ~ dbin(qt[i] ,N2t[i] ) # qt=probability of CDAD+ among N2 AAD patients tested in treatment group

                qc[i] <-min(risk0[i] /pc[i], 1) # risk0 = adjusted risk of CDAD in control group
                qt[i] <- min(risk1[i] /pt[i], 1) #  risk1 = adjusted risk of CDAD in treatment group

                log(risk1[i]) <- log(risk0[i]) + min(delta[i],-log(risk0[i]))
                delta[i] ~ dnorm(delt,precision.tau)

                rr.ind[i]<-exp(delta[i])
                pc[i] ~ dunif(0,1)
                pt[i] ~ dunif(0,1)
                risk0[i] ~ dbeta(0.5,0.5)

        }

mu.new~dnorm(delt,precision.tau)
rr.new<-exp(mu.new)          # predicted risk ratio in a future study

delt ~ dnorm(0, 0.0001)        # prior on log(pooled risk ratio)
rr<-exp(delt)          # pooled risk ratio

precision.tau <- 1/tau.squared
tau.squared <- tau*tau
tau ~ dunif(0, 2)     # prior on between-study standard deviation

# probability predicted risk ratio is less than 1
prob<-step(1-rr.new)

}

list(k=10,
N1t=c(1493, 336, 117, 171, 216, 23, 44, 69, 69, 16),
N1c=c(1488, 167, 112, 84,  221, 17, 45, 66, 69, 18),
TT1=c(159,  54,  5,   37,  47,  4,  7,  7,  15,  5),
TC1=c(153,  41,  10,  37,  65,  6,  16, 19, 15,  2),
N2t=c(93,   54,  5,   37,  16,  3,  2,  7,  15,  5),
N2c=c(88,   41,  4,   37,  30,  4,  13, 19, 15,  2),
TT2=c(12,   6,   0,   9,   1,   0,  1,  0,  2,   0),
TC2=c(17,   8,   0,   20,  4,   1,  7,  9,  5,   0) )
```


R program for frequentist meta-analysis models

```
# Loading metafor library
library(metafor)

# Reading data
dat=list(k=10, nt=c(1493, 336, 117,171, 216, 23, 44, 69, 69, 16), nc=c(1488, 167, 112,84, 221, 17, 45, 53, 69, 18),rt=c(20.5, 6, 0, 9, 2.9, 0, 3.5, 0, 2, 0),rc=c(29.6,8, 0,20, 8.7, 1.5, 8.6, 9, 5, 0))

a<-escalc(ai=dat$rt,bi=dat$nt-dat$rt,ci=dat$rc,di=dat$nc-dat$rc,measure="RR")

# Dersimonian-Laird method
res.DL<-rma(yi,vi,dat=a,method="DL")

# Sidik-Jonkman method
res.SJ<-rma(yi,vi,dat=a,method="SJ")
```

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Author	Randomization Technique	Allocation Concealment	Double-blinding (patient-caregiver)	Equal follow-up	Blind assessment	Final Rating
Heimberger 1994[2]	N. R. ?	N.R. ?	Yes +	Yes +	Unclear ?	C
Plummer 2004[3]	N.R. ?	N.R. ?	Yes +	N.R. ?	Unclear ?	C
Beausoleil 2007[4]	N.R. ?	N.R. ?	Yes +	Yes +	Unclear ?	C
Hickson 2007[5]	Yes +	N.R. ?	Yes +	Yes +	Yes +	A
Safdar 2008[6]	Yes +	Yes +	Yes +	Yes +	N.R. ?	B
Sampalis 2010[7]	N.R. ?	N.R. ?	Yes +	Yes +	Unclear ?	C
Gao 2010[1]	Yes +	Yes +	Yes +	Yes +	Yes +	A
Allen 2013[8]	Yes +	Yes +	Yes +	Yes +	Yes +	A
Selinger 2013[9]	Yes +	Yes +	Yes +	Yes +	Unclear ?	B
Ouwehand 2014[10]	Yes +	Yes +	Yes +	Yes +	Yes +	A

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References

1. Gao XW, Mubasher M, Fang CY, Reifer C, Miller LE. Dose-response efficacy of a proprietary probiotic formula of Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC80R for antibiotic-associated diarrhea and Clostridium difficile-associated diarrhea prophylaxis in adult patients. The American journal of gastroenterology. 2010 Jul;105(7):1636-41.
2. Heimburger DC, Sockwell DG, Geels WJ. Diarrhea with enteral feeding: prospective reappraisal of putative causes. Nutrition. 1994 Sep-Oct;10(5):392-6.
3. Plummer S, Weaver MA, Harris JC, Dee P, Hunter J. Clostridium difficile pilot study: effects of probiotic supplementation on the incidence of C. difficile diarrhoea. International microbiology : the official journal of the Spanish Society for Microbiology. 2004 Mar;7(1):59-62.
4. Beausoleil M, Fortier N, Guenette S, L'Ecuyer A, Savoie M, Franco M, et al. Effect of a fermented milk combining Lactobacillus acidophilus Cl1285 and Lactobacillus casei in the prevention of antibiotic-associated diarrhea: a randomized, double-blind, placebo-controlled trial. Canadian journal of gastroenterology = Journal canadien de gastroenterologie. 2007 Nov;21(11):732-6.
5. Hickson M, D'Souza AL, Muthu N, Rogers TR, Want S, Rajkumar C, et al. Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. BMJ (Clinical research ed). 2007 Jul 14;335(7610):80.
6. Safdar N, Barigala R, Said A, McKinley L. Feasibility and tolerability of probiotics for prevention of antibiotic-associated diarrhoea in hospitalized US military veterans. Journal of clinical pharmacy and therapeutics. 2008 Dec;33(6):663-8.
7. Sampalis J, Psaradellis E, Rampakakis E. Efficacy of BIO K+ CL1285 in the reduction of antibiotic-associated diarrhea - a placebo controlled double-blind randomized, multi-center study. Archives of medical science : AMS. 2010 Mar 1;6(1):56-64.
8. Allen SJ, Wareham K, Bradley C, Harris W, Dhar A, Brown H, et al. A multicentre randomised controlled trial evaluating lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea in older people admitted to hospital: the PLACIDE study protocol. BMC infectious diseases. 2012;12:108.
9. Selinger CP, Bell A, Cairns A, Lockett M, Sebastian S, Haslam N. Probiotic VSL#3 prevents antibiotic-associated diarrhoea in a double-blind, randomized, placebo-controlled clinical trial. The Journal of hospital infection. 2013 Jun;84(2):159-65.
10. Ouwehand AC, DongLian C, Weijian X, Stewart M, Ni J, Stewart T, et al. Probiotics reduce symptoms of antibiotic use in a hospital setting: a randomized dose response study. Vaccine. 2014 Jan 16;32(4):458-63.