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REVIEW

British Dietetic Association systematic review of systematic reviews and evidence-based practice guidelines for the use of probiotics in the management of irritable bowel syndrome in adults (2016 update)

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diet, guidelines, irritable bowel syndrome, probiotics, systematic review of systematic reviews.

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Abstract

Background: Probiotics are often taken by individuals with irritable bowel syndrome (IBS). Which products are effective is unclear, despite an increasing research base. This project will systematically review which strain- and dose- specific probiotics can be recommended to adults with IBS to improve symptoms and quality of life (QoL). It is part of a broader systematic review to update British Dietetic Association guidelines for the dietary management of IBS in adults.
Methods: CINAHL, Cochrane, Embase, Medline, Scopus and Web of Science were searched for systematic reviews (SRs) of randomised controlled trial (RCT)s recruiting adults with IBS comparing probiotic intervention with placebo. AMSTAR, risk of bias and diet bias tools were used to appraise methodological quality. Symptom and QoL data were appraised to develop probiotic-specific evidence statements on clinically meaningful and marginal outcomes in various settings, graded clinical practice recommendations and practical considerations.
Results: Nine systematic reviews and 35 RCTs were included (3406 participants) using 29 dose-specific probiotic formulations. None of the RCTs were at low risk of bias. Twelve out of 29 probiotics (41%) showed no symptom or QoL benefits. Evidence indicated that no strain or dose specific probiotic was consistently effective to improve any IBS symptoms or QoL. Two general clinical practice recommendations were made.
Conclusions: Symptom outcomes for dose-specific probiotics were heterogeneous. Specific probiotic recommendations for IBS management in adults were not possible at this time. More data from high-quality RCTs treating specific symptom profiles are needed to support probiotic therapy in the management of IBS.

Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder, affecting 11% of the general population [(1)]. The Rome III diagnostic criteria for IBS are internationally recognised [(2)] and subtypes include IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D), mixed type (IBS-M) and unclassified (IBS-U) [(3)].

Medication, diet and lifestyle are the main treatment options for IBS, with numerous single and multi-strain probiotics being widely used. Individuals with IBS regularly ask healthcare professionals about which probiotic to use [4].

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host [5]. Furthermore, in IBS treatment, it is recommended that a probiotic should have its strains defined and have proof of delivery of viable strain(s) at an efficacious dose at the end of shelf-life established and, if it is a drug, then the benefit has to outweigh risk for its use [6].

This systematic review is complementary to the second British Dietetic Association (BDA) Guidelines on the dietary management of IBS [7]. The original guidelines reviewed five randomised controlled trials (RCTs) relating to only UK available probiotics [8], which limited international applicability; thus, a wider search criteria was warranted. There is increasing recognition that measurement of quality of life (QoL) in RCTs is important, considering the debilitating burden that IBS places on individuals, with associated high healthcare and socio-economic costs [9,10].

Diet affects gastrointestinal physiology, in particular in relation to functional symptoms [11,12] and the gastrointestinal microbiota [13]. Therefore, it is important to evaluate diet as a potential source of bias in IBS RCTs. Several dietary aspects should be considered. Few RCTs measure background dietary intake at baseline or endpoint. Furthermore, a placebo may contain confounding ingredients that are known dietary triggers in IBS (e.g. lactose, wheat) [14]. Tolerance to placebo and probiotic in terms of appearance, smell, taste and the ability to swallow (e.g. capsules/tablets) should be considered in relation to drop-out rate, especially in long-term studies. Adherence rates in dietary studies are important and should be defined at the outset and monitored throughout [15].

There is an increasing research base, with over 60 RCTs assessing IBS symptom and QoL benefits of probiotics compared to placebo. The aim of this systematic review of reviews and evidence-based practice guidelines was to investigate which strain- and dose-specific probiotics can be recommended to adults with IBS to improve global and/or individual symptoms and/or QoL using an integrated quality assessment process with an added focus on dietary bias.

Methods

Study selection

A systematic review of systematic reviews using previously described methodology [16] was performed to identify suitable RCTs. In brief, Population, Interventions, Comparisons, Outcome measures and Types of study (PICOT) included systematic reviews that had systematically appraised RCTs of at least one probiotic versus placebo in adults with IBS assessing symptom and/or QoL outcomes were included. Eligibility criteria using PICOT is detailed in the Supporting information (Table S1).

Literature search sources and review selection

Six electronic databases (CINAHL, Cochrane, Embase, Medline, Scopus, Web of Science) from January 1985 to October 2015 were searched to identify suitable papers using IBS and probiotic search terms (see Supporting information, Table S2). Relevant meta-analyses and guidelines were cross-checked for further systematic reviews. Three reviewers (PG, YAM, JT) independently assessed each paper and followed the methodology below. Any differences in assessment were agreed through consensus. The search results were screened for further papers for inclusion. Where it was unclear from the title and abstract whether a study was eligible, the full paper was retrieved. Only full papers limited to the English language were included. The RCT critical appraisal methodology is described elsewhere [7]. RCTs were excluded if they allowed medication that could influence gastrointestinal symptoms or motility other than low usage of rescue IBS medication (e.g. once a week).

Data extraction

Clinical outcome assessment for probiotic versus placebo at baseline and intervention endpoint and, where applicable, follow-up endpoint, were extracted from each RCT. Outcomes of interest included global symptoms, abdominal pain/discomfort, bloating/distension, flatulence and QoL, collected as intention-to-treat wherever possible. For the subtypes IBS-D and IBS-C, data were also collected on stool consistency, stool frequency, incomplete evacuation, straining, bowel habit satisfaction, time of bowel movement and colonic transit time. Statistically significant outcomes for comparisons between intervention and placebo at endpoint ($P < 0.05$) were assessed for clinical relevance. Effect size was recorded or calculated wherever possible as the numbers needed to treat (NNT) or the numbers need to harm (NNH) or estimate of change. Symptom outcomes were patient-reported in preference to physician-reported, defined as dichotomous (percentage of responders with satisfactory/adequate/considerable relief of symptoms, often referred to as the global symptom question) or continuous [severity or frequency of symptoms, using a clearly defined Likert or visual analogue scale (VAS) scoring system]. Multiple

probiotic treatments within one RCT with a common control group were analysed separately.

Currently, no validated and widely accepted outcome measures for assessing clinical endpoints in IBS are available. Food and Drug Administration (FDA) [17] recommendations on endpoint outcomes for medicinal products in the treatment of IBS were used to separate clinically meaningful benefit (improvement of at least 30% from baseline) from marginal benefit (see Supporting information, Table S3). A decrease of at least 95 points [18] in the IBS symptom severity system (IBS-SSS) tool [19] was used because this change is used in many IBS pharmaceutical RCTs and is accepted by the Rome Committee. For IBS-QoL, a decrease of at least 10 points was used [20]. Data on clinical setting and adverse events were collected and only serious effects were reported to appraise probiotic safety. Data on dietary factors (protocol and reported data) were also collected relating to the probiotic and placebo products to assess dietary bias: ingredients and quantities consumed per day, reported tolerance, adherence rate set and reported adherence, as well as any dietary intake assessments before and after the intervention (Table 1).

Table 1 Dietary bias criteria

	Risk assessment criteria
Appropriate probiotic/placebo formulation	Did the product contain only ingredients other than the probiotic strain/placebo that would be unlikely to alter gut motilityFor a product in capsule or powder form, did the product contain a desiccant that would be unlikely to alter gut motilityFor a product as a caplet/tablet were ingredient(s) that made it hard/robust described to ensure it would be unlikely to alter gut motilityIf the product contained more than 12 g day^{-1} lactose was lactose intolerance a study exclusion criteria
Probiotic/placebo tolerance	Tolerance reported for appearance, smell and taste of the product
Probiotic/placebo adherence rate	Adherence rate of at least 80% was set
Adherence to probiotic/placebo	Adherence rate was reported with any deviation from set rate explained
Dietary intake	Dietary intake at baseline/end-point of intervention/follow-up was reported (24-h recall, food frequency questionnaire or diet diary) for probiotic and placebo groups to show no difference between the groups and therefore be unlikely to alter gut motility. Relevant measurements include mean BMI and mean intake of energy, total carbohydrates, dietary fibre, alcohol, FODMAPs (fructans, GOS, polyols, excess fructose, lactose)

BMI, body mass index; FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; GOS, galacto-oligosaccharides.

Quality and validity

The AMSTAR tool was used to assess the quality of the systematic reviews [21]. To assess the validity of included RCTs, the Cochrane Risk of Bias tool was used [22] and modified to include a specific domain relating to diet adapted from previous research [23], which took into account dietary factors recommended for clinical trial design [15]. Six diet-related bias criteria were appropriate to probiotic RCTs and are presented in Table 1.

Data synthesis

The Australian Government National Health and Medical Research Council (NHMRC) methodology was used to develop two evidence statement matrices (single and multiple strains) to judge the evidence across studies and their consistency, generalisability and applicability to develop evidence statements and graded clinical recommendations [24]. Practical considerations were also developed.

Results

Nine systematic reviews met the inclusion criteria [25–33] and were appraised (see Supporting information, Tables S4 and S5); six reviewed probiotic treatment for IBS [25–28,30,32] and one for lower gastrointestinal symptoms [29], one reviewed probiotics, prebiotics and synbiotics in IBS [33] and another in IBS and chronic constipation [31]. A total of 69 RCTs were identified from the systematic reviews and 35 met the inclusion criteria (Fig. 1). Reasons for excluded systematic reviews and RCTs are provided in the Supporting information (Tables S6 and S7).

Quality of included randomised controlled trials

Risk of bias across RCTs was variable (Table 2) [7]. Random sequence generation carried a low risk of bias in 15 studies [36,38,39,41,45–48,52,55,57,58,62,63,68] and was high in two [64,66]. Eighteen RCTs provided inadequate information to make clear judgment. Allocation concealment was low in 17 RCTs [34,36,38,39,41,46–48,52,55,57,58,63–66,68], high in one [45] and unclear in the remaining RCTs. All RCTs stated that they were double-blind and therefore scored well for blinding of participants and researchers, although details were lacking. There was a low risk of bias for blinding of outcome assessment, with no RCT considered to have a high risk of bias and nine RCTs lacked clarity [37,42–44,51,54,56,58,68]. Incomplete outcome data, which includes an attrition bias if the drop-out rate is >20%, had a high risk of bias in five RCTs [36,43,52,53,56] and a low risk in the

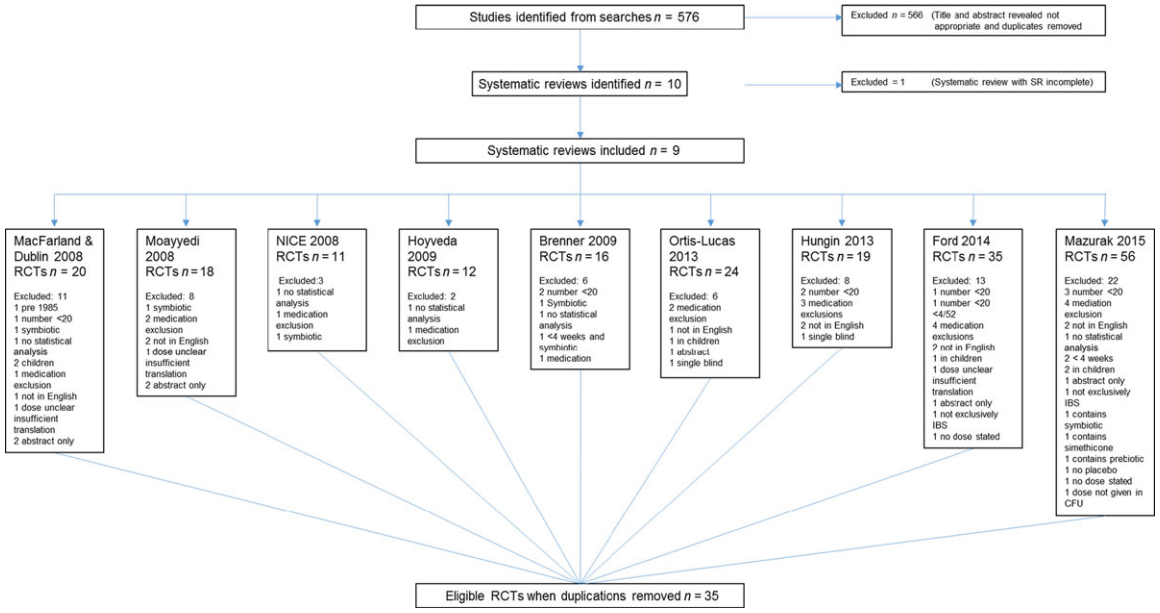

Figure 1 Flow of systematic review papers retrieved, published between 2008 and 2015, to identify eligible RCTs.

remaining RCTs. Selective reporting had a low risk of bias in 20 RCTs, being unclear in one [61] with the remaining RCTs considered to be high [36–39,41,43–46,50,52,54,55,62]. Other bias included the reported sample size calculation and medication use, which had a low risk of bias in four RCTs [47,51,65,68] and was unclear in five RCTs [41,54,62,63,66] and high in the remaining RCTs.

Only one RCT had a low risk of diet-related bias [64] and one had a high risk of diet-related bias as a result of an inappropriate ingredient (skimmed milk powder, lactose intolerance not excluded) for their study population [55] (Table 2). Appropriate probiotic formulations were reported in 77% (27/35) of the RCTs [35–38,41,45–53,55–62,64–68], whereas only 43% (15/35) gave adequate detail to judge the placebo as suitable [38,45,46,48,50–53,56,61,64–68]. Only one RCT measured patient-reported tolerance (91.7% product versus 83.3% placebo) [41] and 11 reported acceptable tolerance without any measurement or adequate details [37,39,44,46–49,58,64,66,67]. Six (17%) RCTs set an adherence rate at 80% [36,47,58,61,64,66], which was adhered to, except for two RCTs that did not provide these data [36,61]. A further six RCTs did not set a rate but reported successful probiotic adherence [43,44,51,55,59,60]. Only one RCT measured dietary intakes before and after intervention, although these data were not presented [64].

Probiotic randomised controlled trial demographics

The RCTs included 3406 adults with IBS and the studies were undertaken in Denmark, France, Germany, Holland, India, Iran, Ireland, Israel, Poland, South Africa, South Korea, Spain, Sweden, UK and the USA. All studies were parallel in design, except one cross-over study [34].

Single-strain formulations were taken by 1539 participants (45% of total participants) in 19 different single-strain doses from 16 RCTs [34–49]. Multi-strain probiotics were taken by 1867 participants in 20 different multi-strain doses/formulations from 19 RCTs [50–68].

Twelve RCTs (1831 participants) were in the primary care/community setting [38,39,41,42,44,49,51–54,63,67], 17 RCTs (1061 participants) were in the secondary care/hospital setting [34,36,43,46–48,50,55–62,64,68], three RCTs were in primary and secondary care (327 participants) [45,65,66] and the setting was not reported in three RCTs (187 participants) [35,37,40]. The details of the probiotic strains, doses and formulations are provided in Table 2.

Outcomes

Twenty-nine probiotics from 35 RCTs improved at least one outcome that had been measured (Table 3; see also the Supporting information, Tables S8–S14). No evidence was found to suggest that improved outcomes were present with an increasing number of probiotic strains.

Global symptoms

Twenty-nine RCTs assessed global symptoms, whereas the remaining six did not [34,36,37,40,46,47]. Fourteen RCTs showed statistically significant improvements for adequate symptom relief [38,39,42,54,57,58,68], a VAS [45,49,50,55,56] or the IBS-SSS [65,67]. Ten probiotics demonstrated a clinically meaningful improvement in primary care

Table 2 Risk of bias and quality assessment for 35 included randomised controlled trials

Reference	RCT risk of bias[22]					Dietary risk of bias							
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13
Agrawal 2009 [50]	?	?	+	+	+	-	-	+	+	?	?	?	?
Begtrup 2013[53]	?	?	+	+	-	+	-	+	+	?	?	?	?
Charbonneau 2013 [35]	?	?	+	+	+	+	-	+	?	?	?	+	?
Choi 2011 [36]	+	+	+	+	-	-	-	+	?	?	+	?	?
Dolin 2009[37]	?	?	+	?	+	-	-	+	?	+	?	?	?
Ducrotte 2012[38]	+	+	+	+	+	-	-	+	+	?	?	?	?
Enck 2008[54]	?	?	+	?	+	-	?	?	?	?	?	?	?
Gade & Thorn 1989[39]	+	+	+	+	+	-	-	?	?	+	?	?	?
Guyonnet 2007[51]	?	?	+	?	+	+	+	+	+	?	?	+	?
Hong 2009[55]	+	+	+	+	+	+	-	+	-	?	?	+	?
Hong 2011[56]	?	?	+	?	-	+	-	+	+	?	?	?	?
Hun 2009[40]	?	?	+	+	+	-	-	?	?	?	?	?	?
Jafari 2014[57]	+	+	+	+	+	+	-	+	?	?	?	?	?
Ki Cha 2012 [58]	+	+	+	?	+	+	-	+	?	+	+	+	?
Kim 2003[59]	?	?	+	+	+	+	-	+	?	?	?	+	?
Kim 2005[60]	?	?	+	+	+	+	-	+	?	?	?	+	?
Ko 2013[61]	?	?	+	+	+	?	-	+	+	?	+	?	?
Kruis 2012[41]	+	+	+	+	+	-	?	+	?	+	?	+	?
Lorenzo-Zúñiga 2014[62]	+	?	+	+	+	-	?	+	?	?	?	?	?
Ludidi 2014[63]	+	+	+	+	+	+	?	?	?	?	?	?	?
Neidzielin 2001[42]	?	?	+	?	+	+	-	?	?	?	?	?	?
Niv 2005[43]	?	?	+	?	-	-	-	?	?	?	?	+	?
Nobaek 2000[44]	?	?	+	?	+	-	-	?	?	+	?	+	?
O'Mahony 2005 [45]	+	-	+	+	+	-	-	+	+	?	?	?	?
O'Sullivan 2000[34]	?	+	+	+	+	+	-	?	?	?	?	?	?
Pineton de Chambrun 2015[46]	+	+	+	+	+	-	-	+	+	+	?	+	?
Roberts 2013[52]	+	+	+	+	-	-	-	+	+	?	?	?	?
Simren 2010[64] *	-	+	+	+	+	+	-	+	+	+	+	+	+
Sinn 2008[47]	+	+	+	+	+	+	+	+	?	+	+	+	?
Sisson 2014[65]	?	+	+	+	+	+	+	+	+	?	?	+	?
Sondergaard 2011[66]	-	+	+	+	+	+	?	+	+	+	+	+	?
Stevenson 2014[48]	+	+	+	+	+	+	-	+	+	+	?	+	?
Whorwell 2006[49]	?	?	+	+	+	+	-	+	?	+	?	?	?
Williams 2009[67]	?	?	+	+	+	+	-	+	+	+	?	+	?
Yoon 2014[68]	+	+	+	?	+	+	+	+	+	?	?	+	?

1, Random sequence generation; 2, Allocation concealment; 3, Blinding of participants and personnel; 4, Blinding of outcome assessment; 5, incomplete outcome data; 6, selective reporting; 7, other bias; 8, Probiotic formulation suitable; 9, Placebo suitable; 10, Well tolerated; 11, Adherence rate set; 12, Probiotic adherence; 13, Dietary intake.

Risk of bias: ■, low; ■, unclear; ■, high.

*Dietary intake assessed but results not reported. RCT, randomised controlled trial.

[38,39,42,54,65,67], secondary care [55,57,58,68] or both [65]. These improvements were with *Lactobacillus plantarum* 299v (DSM 9843) at a dose of 1×10^9 [38] and 2×10^{10} [42], *Streptococcus faecium* [39], a four-strain probiotic: *Bifidobacterium animalis* subsp. actisBB-12, *L. acidophilus* LA-5, *L. delbrueckii* subsp. *bulgaricus* LBY-27 and *S. thermophilus* STY-31 [57] and a six-strain probiotic: *B. longum*, *B. bifidum*, *B. lactis*, *L. acidophilus*, *L. rhamnosus* and *Streptococcus thermophilus* [68] all at 4 weeks, a two-strain probiotic: *Enterococcus faecalis* (DSM 16440)

and *Escherichia coli* (DSM 17252) [54] and a four-strain probiotic: *B. bifidum* BGN4, *B. lactis* AD011; *L. acidophilus* AD031 and *L. casei* IBS041 [67] at 8 weeks and a four-strain probiotic: *L. rhamnosus* NCIMB 30174, *L. plantarum* NCIMB 30173, *L. acidophilus* NCIMB 30175 and *Enterococcus faecium* NCIMB 30176 at 12 weeks [65]. In IBS-D, global symptom improvement was seen with a seven-strain probiotic: *L. acidophilus*, *L. plantarum*, *L. rhamnosus*, *B. breve*, *B. lactis*, *B. longum* and *S. thermophilus* [58] and a four-strain probiotic: *B. bifidum*

Table 3 Outcomes for included probiotic randomised controlled trials

Probiotic	Study			Total N	Intervention	Control	Drop out rate <20%	Pre-intervention	Intervention duration	Follow-up	Global	Pain	Bloating	Flatulence	QOL	Adverse events
B. infantis 35624 (1x10^9) capsule	Charbonneau 2013 [35]	IBS Rome	Ireland setting: unclear	76	39	37	✓	2w	8w	2w						NS
B. infantis 35624 (1x10^{10}) malted milk	O'Mahony 2005 [45]	IBS Rome II	Ireland primary/secondary	77	25	25	✓	4w	8w	4w						NS
B. infantis 35624 (1x10^6) capsule	Whorwell 2006[49]	IBS all F Rome II	UK primary care	362	90	90	✓	2w	4w	2w						NS
B. infantis 35624 (1x10^8) capsule	Whorwell 2006[49]	IBS all F Rome II	UK primary care	362	90	90	✓	2w	4w	2w	+IBS-D	+IBS-C				NS
B. infantis 35624 (1x10^{10}) capsule	Whorwell 2006[49]	IBS all F Rome II	UK primary care	362	90	90	✓	2w	4w	2w						NS
B. coagulans GB-1-30, 6068[a] (2x10^9) capsule	Dolin 2009[37]	IBS-D Rome II	USA setting: unclear	61	26	29	✓	2w	8w	0						NS
B. coagulans GB-1-30, 6068 (8x10^8) capsule	Hun 2009[40]	IBS-D Rome III	USA setting: unclear	50	25	25	✓	0	8w	0						NS
E. coli Nissle 1917[b] (2.5-25x10^9, to 5-50x10^9) capsule	Kruis 2012[41]	IBS Rome II	Germany primary care	120	60	60	✓	0	12w	0						NS
L. casei GG[c] (1x10^{10}) tablet	O'Sullivan 2000[34]	IBS Rome I	Ireland secondary care	48	24	24	✓	2w	8w	2w						NS
L.plantarum 299v[d] (1x10^9) capsule	Ducrotte 2012[38]	IBS Rome III	India primary care	214	108	106	✓	0	4w	0						NS
L.plantarum 299v[e] (2x10^{10}) liquid rosehip drink	Niedzielin 2001[42]	IBS Manning	Poland primary care	40	20	20	✓	0	4	0						NS
L.plantarum 299v[d] (2x10^{10}) liquid rosehip drink	Nobaek 2000[44]	IBS Rome I	Sweden primary care	60	25	27	✓	2w	4w	12 m						NS
L.plantarum 299v (1x10^{10}) capsule	Stevenson 2014[48]	IBS-D and IBS-C Rome II	South Africa secondary care	81	27	27	✓	2w	8w	2w						NS
L. reuteri ATCC 55730 (1x10^8) tablet	Niv 2005[43]	IBS Rome II	Israel secondary care	54	21	18	×	1w	6m	0						NS
L. salivarius (1x10^{10}) malted milk	O'Mahony 2005[45]	IBS Rome II	Ireland primary/secondary	77	26	25	✓	4w	8w	4w						NS
S. boulardii[f] (4x10^{11}) capsule	Choi 2011 [36]	IBS-D and IBS-M	South Korea secondary care	67	34	33	×	1w	4w	0						NS
S. cerevisiae[g] (4x10^9) capsule	Pineton De Chambrun 2015 [46]	IBS Rome III	France secondary care	179	93	86	NR	2w	8w	3w						NS
Streptococcus faecium[h] (6.4x10^7) tablet	Gade & Thorn 1989[39]	IBS physician Δ	Denmark primary care	58	32	22	✓	0	4w	0						NS
2-strain[i] (1.5-4.5x10^7) liquid	Enck 2008[54]	IBS Kruis score	Gernany primary care	297	149	148	✓	0	8w	0						GI
2-strain[j] (2.0x10^9) capsule	Sinn 2008[47]	IBS-mild Rome II	South Korea secondary care	40	20	20	✓	0	4w	0						NS
3-strain[k] (4.0x10^9) fermented milk	Hong 2011[56]	IBS, Rome III	South Korea secondary care	72	37	36	✓	0	8w	0						NS
3-strain[l] (3.6x10^9) capsule	Lorenzo-Zúñiga 2014[62]	IBS-D Rome III	Spain secondary care	84	29	27	✓	0w	6w	0w						NR
3-strain[l] (1.3x10^{10}) capsule	Lorenzo-Zúñiga 2014[62]	IBS-D Rome III	Spain secondary care	84	28	27	✓	0w	6w	0w						NR
3-strain[m] (5.2x 10^{10}) capsule	Begtrup 2013[53]	IBS Rome III	Denmark primary care	131	67	64	×	0	6m	6m						NS
3-strain[n] (1.25x10^{10} + 1.2x10^9) natural yoghurt	Agrawal 2009 [50]	IBS-C , all F Rome III	UK secondary care	34	17	17	✓	11d	4w	0						NS
3-strain[n] (1.25x10^{10} + 1.2x10^9) natural yoghurt	Guyonnet 2007[51]	IBS-C Rome II	France primary care	274	135	132	✓	2w	4w	2w						NS
3-strain[n] (1.25x10^{10} + 1.2x10^9) natural yoghurt	Roberts 2013[52]	IBS-C, M Rome III	UK primary care	179	91	88	×	0	12w	0						NR

Table 3. Continued

Probiotic	Study			Total N	Intervention	Control	Drop out rate <20%	Pre-intervention	Intervention duration	Follow-up	Global	Pain	Bloating	Flatulence	QOL	Adverse events
3-strain[o] (5x10^7) fermented milk	Simren 2010[64]	IBS-D,C,M Rome II	Sweden secondary care	74	37	37	✓	2w	8w	8w						NS
3-strain[o] (7.5x10^{10}) fermented milk	Sondergaard 2011[66]	IBS Rome II	Denmark & Sweden primary/secondary	64	32	32	✓	2w	8w	8w						NS
4-strain[p] (4x10^9) capsule	Jafari 2014[57]	IBS with bloating Rome II	Iran secondary care	108	54	54	✓	0w	4w	4w						NS
4-strain[q] (4x10^{10}) powder	Hong 2009[55]	IBS-D,C,M,U Rome III	South Korea secondary care	70	36	34	✓	1w	8w	0	IBS-D	IBS-D				NS
4-strain[r] (2.5x10^{10}) capsule	Williams 2009[67]	IBS Rome II	UK primary care	56	28	28	✓	0	8w	2w						NS
4-strain[s] (1x10^{10} at 1ml/kg) water based suspension	Sisson 2014[65]	IBS Rome III	UK Primary/secondary	186	124	62	NR	0w	12w	4w						NS
6-strain[t] (5x10^9) powder	Ludidi 2014[63]	IBS Rome III	Holland primary care	40	22	19	NR	2w	6w	2w						NR
6-strain[u] (1x10^{10}) capsule	Yoon 2014[68]	IBS Rome III	South Korea secondary care	49	25	24	NR	2w	4w	0						NS
7-strain[v] (1x10^{10}) capsule	Ko 2013[61]	IBS-D Rome III	South Korea secondary care	26	14	12	✓	2w	8w	2w						NS
7-strain[w] (1x10^{10}) capsule	Ki Cha 2012 [58]	IBS-D	South Korea secondary care	50	25	25	✓	1w	8w	2w						NS
8-strain[x] (4.5x10^{11}) powder	Kim 2003[59]	IBS-D Rome II	USA secondary care	25	12	13	✓	2w	8w	0						NS
8-strain[x] (9x10^{11}) powder	Kim 2005[60]	IBS with bloating Rome II	USA secondary care	48	24	24	✓	0	4w	2w						NS

■, benefit; ■, marginal benefit; ■, no improvement; ■, not measured/reported.

IBS-C significant in subtype IBS-C, IBS-D significant in subtype IBS-D, IBS-M significant in IBS-M, +IBS-C significant for IBS and subtype IBS-C, +IBS-D significant for IBS and subtype IBS-D.

IBS, irritable bowel syndrome; IBS-C, IBS – constipation-predominant; IBS-D, IBS – diarrhoea-predominant; IBS-M, IBS involving both diarrhoea and constipation; NS, no serious; NK, not reported; GI, gastrointestinal; QoL, quality of life; w, weeks.

[a]*Bifidobacterium coagulans* GB-1-30, 6068 (GanedenBC^{30}).

[b]*Escherichia coli* Nissle 1917 (Mutaflor).

[c]*Lactobacillus casei* GG (Culturelle).

[d]*Lactobacillus plantarum* 299v (DSM 9843).

[e]*Lactobacillus plantarum* 299v (Proviva).

[f]*Saccharomyces boulardii* (Bioflor).

[g]*Saccharomyces cerevisiae* (Lesaffre).

[h]*Streptococcus faecium* (Paragut).

[i]*Enterococcus faecalis* (DSM 16440) with *E. coli* (DSM 17252) (ProSymbioflor).

[j]*Lactobacillus acidophilus*-SDC 2012, 2013.

[k]*Lactobacillus* sp. HY7801, *B. longum* HY8004, *L. brevis* HY7401.

[l]*Lactobacillus plantarum* CECT7484 and CECT7485 *Pediococcus acidilactici* CECT7483.

[m]*Lactobacillus paracasei* subsp. *paracasei* F19, *L. acidophilus* La5 and *B.* Bb1.

[n]*Bacterium lactis* CNCM I-2494 (previously DN 173010), *L. delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus* (Activia).

[o]*Lactobacillus paracasei* subsp *paracasei* F19, *L. acidophilus* La5 and *B. animalis* subsp. *lactis* Bb12 (Cultura).

[p]*Bifidobacterium animalis* subsp *actis* BB-12®, *L. acidophilus* LA-5®, *L. delbrueckii* subsp *bulgaricus* LBY-27, *S. thermophilus* STY-31 (Probio-Tec).

[q]*Bifidobacterium bifidum* BGN4, *B. lactis* AD011, *L. acidophilus* AD031 and *L. casei* IBS041.

[r]*Lactobacillus acidophilus* CUL60 (NCIMB 30157), *L. acidophilus* CUL21(NCIMB 30156), *B. animalis* subsp. *lactis* CUL34 (NCIMB 30172), *B. bifium* (LAB4).

[s]*Lactobacillus rhamnosus* NCIMB 30174, *L. plantarum* NCIMB 30173, *L. acidophilus* NCIMB 30175 and *Enterococcus faecium* NCIMB 30176 (Symprove).

[t]*Bifidobacterium lactis* W52, *L. casei* W56, *L. salivarius* W57, *Lactococcus lactis* W58, *L. acidophilus* NCFM and *L. rhamnosus* W71.

[u]*Bifidobacterium bifidum* KCTC 12 199BP, *B. lactis* KCTC 11 904BP, *B. longum* KCTC 12 200BP, *L. acidophilus* KCTC 11 906BP, *L. rhamnosus* KCTC 12 202BP and *S. thermophilus* KCTC 11 870BP.

[v]*Lactobacillus acidophilus, L. plantarum, L. rhamnosus, B. breve, B. lactis, B. longum, S. thermophilus* (Duolac 7S).

[w]*Lactobacillus acidophilus, L. plantarum, L. rhamnosus, B. breve, B. lactis, B. longum, S. thermophilus* (Duolac 7).

[x]*Bifidobacterium longum, B. infantis, B. breve, L. acidiphilus, L. casei, L. bulgaricus, L. plantarum, Streptococcus salivarius* subsp. *thermophilus* (VSL#3).

BGN4, *B. lactis* AD011, *L. acidophilus* AD031 and *L. casei* IBS041 [55]. In IBS-C, no probiotics provided clinically meaningful global symptom improvement. Marginal improvements were found with *B. infantis* 35624 at a dose of 1×10^8 [49] at 4 weeks, *B. infantis* 35624 at a dose of 1×10^{10} at 8 weeks [45] and a three-strain probiotic: *L.* sp. *HY7801, B. longum HY8004* and *L. brevis HY7401* [56] at 8 weeks and, in subgroup analysis of IBS-D ($n = 201$), *B. infantis* 35624 at a dose of 1×10^8 at 4 weeks [49], and IBS-C, a three-strain probiotic: *B. lactis DN73010, S. thermophilus* and *L. bulgaricus* at 4 weeks [50].

Abdominal pain

All RCTs except one [62] assessed abdominal pain. Thirteen RCTs showed improvement between the 4- and 12-week endpoints [38,40,42,46,47,49,50,54,55,57,61,65,68], four assessed adequate relief [42,46,54,61], seven used a five-point Likert or VAS scoring system [38,40,47,50,55,57,68], one used the IBS-SSS (pain severity and frequency) [65] and one used least squares mean scoring [49]. Clinically meaningful improvements in abdominal pain were shown for eight probiotics: at 4 weeks using *L. plantarum* 299v (DSM 9843) at a dose of 1×10^9 [38] and 2×10^{10} [42], a four-strain probiotic: *B. animalis* subsp. Actis BB-12®, *L. acidophilus* LA-5®, *L. delbrueckii* subsp. *bulgaricus* LBY-27 and *S. thermophilus* STY-31 [57], a six-strain probiotic: *B. longum*, *B. bifidum*, *B. lactis*, *L. acidophilus*, *L. rhamnosus* and *S. thermophilus* [68], at 8 weeks using and *S. cerevisiae* CNCM I-3856 [46] and a two-strain probiotic: *E. faecalis* (DSM 16440) and *E. coli* (DSM 17252) [54], and in IBS-D, using a seven-strain probiotic: *L. acidophilus, L. plantarum, L. rhamnosus, B. breve, B. lactis, B. longum* and *S. thermophilus* [61] and, in subgroup analysis, at 8 weeks using a four-strain probiotic: *B. bifidum* BGN4, *B. lactis* AD011, *L. acidophilus* AD031 and *L. casei* IBS041 [55]. Marginal improvements in abdominal pain were found for five probiotics: at 4 weeks using *L. acidophilus*-SDC 2012, 2013 [47], *B. infantis* 35624 at a dose of 1×10^8 [49] at 12 weeks using a four-strain probiotic: *L. rhamnosus* NCIMB 30174, *L. plantarum* NCIMB 30173, *L. acidophilus* NCIMB 30175 and *E. faecium* NCIMB 30176 [65], in IBS-D, for pain severity at 8 weeks using *Bacillus coagulans* GB1-30, 6068 [40], and IBS-C at 4 weeks using a three-strain probiotic: *B. lactis DN73010, S. thermophilus* and *L. bulgaricus* [50] and also *B. infantis* 35624 at a dose of 1×10^8 (sub-group analysis) [49].

Abdominal pain did not statistically significantly improve using 22 dose-specific probiotics in 21 RCTs [34–36,39,41,43–45,48,49,51–53,56,58–60,63,64,66,67]. One RCT did not present these data [37].

Bloating

All RCTs except six [37,39,44,48,55,62] assessed bloating/distension. Five showed improvement in bloating [38,40,49,57,59], all measured severity scores and one also measured frequency [38]. Two probiotics provided a clinically meaningful improvement at 4 weeks: a four-strain probiotic: *B. animalis* subsp. Actis BB-12®, *L. acidophilus* LA-5®, *L. delbrueckii* subsp. *bulgaricus* LBY-27 and *S. thermophilus* STY-31 [57] and *L. plantarum* 299v (DSM 9843) at a dose of 1×10^9 [38]. Marginal improvements were found for *B. infantis* 35624 at a dose of 1×10^8 at 4 weeks [49] and in IBS-D using an eight-strain probiotic: *B. longum, B. infantis, B. breve, L. acidiphilus, L. casei, L. bulgaricus, L. plantarum* and *Streptococcus salivarius* subsp. *thermophilus* at 4 weeks [59] and *B. coagulans* GB1-30, 6068 at 8 weeks [40]. All other 27 dose-specific probiotics showed no improvement.

Flatulence

Nineteen RCTs used a Likert or VAS scoring system to measure flatulence [36,40,41,43–45,49–53,55,58,60,61,63–66]. A clinically meaningful improvement in flatulence was shown with *L. plantarum* 299v, at a dose of 2×10^{10} at 4 weeks [44] and marginal improvement was found for *B. infantis* 35624 at a dose of 1×10^8 [49] and an eight-strain probiotic: *B. longum, B. infantis, B. breve, L. acidiphilus, L. casei, L. bulgaricus, L. plantarum* and *S. salivarius* subsp. *thermophilus*, where bloating was the predominant symptom [60] at 4 weeks. No probiotics improved flatulence in any IBS subtypes. Twenty-four probiotics did not improve flatulence [36,40,41,43,45,49–53,55,58,61,63–66]. Sixteen RCTs did not report [39,42] or measure this outcome [34,38,45–48,54,56,57,62,65,67,68] or present these data [37].

Diarrhoea

Six RCTs measured stool consistency and urgency in IBS-D (Bristol stool form scale 1 to 7) [37,55,58,59,61] or IBS-D and IBS-M [36]. Two further studies assessed bowel habit satisfaction and urgency in sub-analysis [37,49] and stool frequency in another [38].

A clinically meaningful improvement in bowel habit or stool consistency was not shown after using any dose-specific probiotic. Stool frequency (and incomplete evacuation) substantially improved for *L. plantarum* 299v (DSM 9843) at a dose of 1×10^9 [38] at 4 weeks. Marginal improvements were found in three RCTs for satisfaction in bowel habit using *B. infantis* 35624 at a dose of 1×10^8 at 4 weeks [49], stool consistency using a seven-strain probiotic: *L. acidophilus, L. plantarum, L. rhamnosus, B. breve, B. lactis, B. longum* and *S. thermophilus* [58] at 8 weeks and stool frequency for *B. coagulans* GB1-30, 6068 [37] at 8 weeks.

Constipation

Ten RCTs measured frequency of bowel movements, reported as daily [34,36,44,46,49–52] or weekly [42,68], although only three studies subtyped for IBS-C to determine clinically relevant outcomes for constipation [49–51]. These RCTs assessed bowel habit satisfaction in sub-analysis [49], stool consistency and frequency [51] and stool consistency, time of bowel movement, straining during evacuation, incomplete evacuation using a daily symptom diary and objective measurement of gut transit time [50]. No probiotic provided a clinically meaningful improvement in constipation. Marginal improvements were shown for *B. infantis* 35624 at a dose of 1×10^8 in bowel habit satisfaction at 4 weeks [49], and for a three-strain probiotic *B. lactis* DN73010, *S. thermophilus* and *L. bulgaricus* at a dose of $1.25 \times 10^{10} + 1.2 \times 10^9$ [50]. Colonic transit time improved from 56 h down to 12 h (21%; $P = 0.026$). The same dose-specific probiotic used in two large RCTs [51,52] did not show benefit compared to placebo.

Quality of life

Sixteen RCTs measured QoL using a validated tool [19,69–71] for nineteen probiotic dose-specific probiotics and strains; using the IBS-QoL tool [36,43,45,48,49,52,53,58,61,62,64], the QoL domain in the IBS-SSS score [65–67], the Rand 36 [55] and a HRQOL tool [51].

Clinically meaningful improvements were found using two probiotics, one with two different doses, a three-strain probiotic: *L. plantarum* CECT7484 and CECT7485 and *Pediococcus acidilactici* CECT7483 taken at a daily dose of 3.6×10^9 and 1×10^{10} for 6 weeks in IBS-D patients [62], and a four-strain probiotic: *B. bifidum* BGN4, *B. lactis* AD011; *L. acidophilus* AD031 and *L. casei* IBS041 for 8 weeks in IBS [67]. A marginal improvement was observed using two probiotics: a seven-strain probiotic: *L. acidophilus, L. plantarum, L. rhamnosus, B. breve, B. lactis, B. longum* and *S. thermophilus* for 8 weeks in IBS-D [58] and *Saccharomyces boulardii* for 4 weeks in IBS-D and IBS-M [36]. No RCTs showed any improvement in any QoL measures for IBS-C.

Fifteen probiotic doses in 12 RCTs showed no QoL improvements after treatment [43,45,48,49,51–53,55,61,64–66]. Two RCTs gave inadequate data to assess QoL [41,45].

Adverse events

No RCTs reported any serious adverse events and therefore all included probiotic products were considered safe. Gastrointestinal adverse events were reported in one RCT using a two-strain probiotic: *E. faecalis* (DSM 16440) with *E. coli* (DSM 17252) [54]. Twenty-nine events (vomiting, heartburn or diarrhoea) in the probiotic group and 20 events (abdominal pain) in the placebo group led to study discontinuation. Three RCTs did not report on adverse events [52,62,63]. All remaining RCTs reported no or minor adverse events.

Long-term effects

Evidence is lacking to demonstrate longer-term sustained symptom improvement. Follow-up duration in nine RCTs that showed clinical or marginal symptom or QoL improvements were no longer than 4 weeks [45,46,49,57,58,60,61,65,67]. Only one RCT showed clinical improvement at 12 months follow-up [44]. A high drop-out rate (>20%) was found in six RCTs, one of only 4 weeks in duration [36] and the remaining five, of 6 weeks to 6 months in duration (Table 3) [43,48,52,53,65].

Evidence statements

Eighteen evidence statements were developed demonstrating clinically useful efficacy for dose-specific probiotics (Table 4). One further evidence statement lists 12 dose-specific probiotics found to be ineffective in IBS treatment.

Recommendations for clinical practice

No strain- and dose-specific probiotic demonstrated efficacy from more than two RCTs. Therefore, no specific recommendations were made. Two general recommendations have been updated (Table 5) [7].

Practical considerations

Individuals with IBS can be advised that, despite numerous probiotic RCTs, there is insufficient good evidence to recommend any specific probiotic product and, independent of IBS-subtype, improvement in all symptoms is unlikely.

There are many probiotics available with different preparations, bacterial strains and doses. Individuals with IBS who choose to try probiotics should be aware that some products contain ingredients that may increase IBS symptoms [dietary fibre, fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs)]. If an individual finds a probiotic beneficial after 4 weeks, he/she can be advised that the long-term effects of continued use are unknown.

For individuals with co-morbidities that may modulate immune function, healthcare professionals should use these recommendations assessing each individual on a case by case basis.

Probiotics are often expensive, and so individuals may wish to weigh up benefit against ongoing cost.

Table 4 Evidence statements

Probiotics used in various healthcare settings
Bifidobacterium infantis 35624 at a dose of 1 × 10^8 CFU 1 capsule per day for 4 weeks marginally improved global symptoms, abdominal pain, bloating and flatulence, bowel habit satisfaction in IBS, IBS-D and IBS-C but not QoL in primary care [49]
Bacillus coagulans GB-1-30, 6068 at a dose of 2.0 × 10^9 CFU 1 capsule per day for 8 weeks marginally improved bowel frequency in IBS-D [37] but not abdominal pain or flatulence and, at a dose of 8 × 10^8 CFU 1 capsule per day, it marginally improved abdominal pain and bloating but not flatulence in IBS [40] (unknown setting)
A 4-strain probiotic barley extract liquid containing *Lactobacillus rhamnosus* NCIMB 30174, *Lactobacillus plantarum* NCIMB 30173, *Lactobacillus acidophilus* NCIMB 30175 and *Enterococcus faecium* NCIMB 30176 at a dose of 1 × 10^{10} CFU at 1 mL kg^{-1} per day for 12 weeks improved global symptoms and marginally improved pain but not bloating or QoL **in IBS in primary and secondary care** [65]
Primary care/GP diagnosed
***Streptococcus faecium* at a dose of 6.4 3 107 CFU 4 tablets twice daily for 4 weeks improved global symptoms (NNT = 2.4) in IBS** but not abdominal pain or flatulence [39]
A 2-strain probiotic *Enterococcus faecalis* [DSM 16440] and *Escherichia coli* [DSM 17252] at a dose of 3.0–9.0 × 10^7 CFU in 1.5 mL (20 drops) taken at 10 drops per day for 1 week, 20 drops per day for 2 weeks and 30 drops per day for 5 weeks improved global symptoms (NNT = 3.3) and abdominal pain (NNT = 3.6) but not bloating **in IBS in primary care** [54]. Adverse events included vomiting, heartburn, diarrhoea (NNH = 9)
A 4-strain probiotic containing *Lactobacillus acidophilus* CUL60 [NCIMB 30157], *Lactobacillus acidophilus* CUL21 [NCIMB 30156], *Bifidobacterium animalis* subsp. *lactis* CUL34 [NCIMB 30172] and *Bifidobacterium bifidum* CUL20 at a dose of 2.5 × 10^{10} CFU 1 capsule per day for 8 weeks improved global symptoms and QoL but not abdominal pain or bloating **in IBS in primary care** [67]
Secondary care/diagnosed by a gastroenterologist
Saccharomyces boulardii at a dose of 4 × 10^{11} CFU 1 capsule per day for 4 weeks marginally improved QoL but not abdominal pain, bloating or flatulence in IBS-D and IBS-M [36]
***Saccharomyces cerevisiae* at a dose of 4 × 10^9 CFU 500 mg capsule per day for 8 weeks improved abdominal pain (NNT = 6.4)** but not bloating **in IBS**[46]
A 2-strain probiotic *Lactobacillus acidophilus*-SDC 2012 and 2013 at a dose of 2 × 10^9 CFU 1 capsule twice daily for 4 weeks marginally improved abdominal pain but not bloating in IBS [47]
A 3-strain probiotic containing *Lactobacillus plantarum* CECT7484 and CECT7485 and *Pediococcus acidilactici* CECT7483 at a dose of 3.6 × 10^9 and 1.3 × 10^{10} CFU 1 capsule per day for 6 weeks improved QoL but not global symptoms **in IBS-D** [62]
A 3-strain probiotic containing *Lactobacillus* sp. HY7801, *Bifidobacterium longum* HY8004 and *Lactobacillus brevis* HY7401 at a dose of 4 × 10^{10} CFU 150 mL fermented milk tds for 8 weeks marginally improved global symptoms (NNT = 6) but not abdominal pain or bloating in IBS in secondary care [56]
A 4-strain probiotic *Bifidobacterium animalis* subsp. actisBB-12®, *Lactobacillus acidophilus* LA-5®, *Lactobacillus delbrueckii* subsp. bulgaricus LBY-27 and *Streptococcus thermophilus* STY-31 at a dose of 4 × 10^9 CFU 1 capsule twice daily for 4 weeks improved global symptoms, abdominal pain and bloating in IBS [57]
A 4-strain probiotic *Bifidobacterium bifidum* BGN4, *Bifidobacterium lactis* AD011, *Lactobacillus acidophilus* AD031 and *Lactobacillus casei* IBS041 at a dose of 4 × 10^{10} CFU 1 sachet (powder) twice daily for 8 weeks improved global symptoms and abdominal pain but not flatulence or QoL **in IBS** [55]
A 6-strain probiotic *Bifidobacterium longum*, *Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus* and *Streptococcus thermophilus* at a dose of 1 × 10^{10} CFU 1 capsule twice daily for 4 weeks improved global symptoms (NNT = 3.3) and abdominal pain but not bloating **in IBS** [68]
An 8-strain probiotic *Bifidobacterium longum, Bifidobacterium infantis, Bifidobacterium breve, Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus delbrueckii* subsp. *bulgaricus, Lactobacillus plantarum* and *Streptococcus salivarius* subsp. *thermophilus* at a dose of 9 × 10^{11} lyophilised bacteria at 2 sachets per day for 4 weeks marginally improved flatulence but not abdominal pain in IBS with bloating [60]. At a dose of 4.5 × 10^{11} lyophilised bacteria at 2 sachets per day for 8 weeks, it marginally improved bloating but not global symptoms, abdominal pain or flatulence in IBS-D [59]
Probiotics where evidence was inconsistent across RCTs
***Lactobacillus plantarum* 299v (DSM 9843) at a dose of 1 × 10^9 CFU 1 capsule per day for 4 weeks substantially improved global symptoms, abdominal pain and bloating,** and marginally reduced high stool frequency **in IBS in primary care** [38]. At a dose of 1 × 10^{10} CFU 1 capsule per day for 8 weeks in secondary care, there was no benefit on global symptoms, abdominal pain or QoL in IBS-C and IBS-D [48]. At a dose of 2 × 10^{10} CFU 400 mL per day rosehip drink for 4 weeks, global symptoms and abdominal pain substantially improved (5% oatmeal) in one study [42] and flatulence substantially improved in another [44]
Bifidobacterium infantis 35624 at a dose of 1 × 10^{10} CFU in malted milk for 8 weeks marginally improved global symptoms but not abdominal pain, bloating or quality of life in IBS (lactose intolerance excluded) in primary and secondary care [45]. Evidence was lacking for *B. infantis* 35264 at a dose of 1 × 10^{10} CFU 1 capsule per day for 4 weeks in primary care [49]
A 3-strain probiotic *Bifidobacterium lactis* CNCM I-2494, with *Streptococcus thermophilus* and *Lactobacillus bulgaricus* (2 starters) at a dose of 1.25 × 10^{10} + 1.2 × 10^9 CFU in two 125 g pots per day (natural yoghurt; unflavoured) for 4 weeks marginally improved IBS-C (NNT = 13), abdominal pain and bowel frequency in secondary care [50] but it did not improve IBS-C or IBS-M at 4 weeks [52] or 6 weeks [51] in primary care

Table 4. Continued

A 7-strain probiotic *Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus rhamnosus, Bifidobacterium breve, Bifidobacterium lactis, Bifidobacterium longum* and *Streptococcus thermophilus* at a dose of 1×10^{10} CFU 1 capsule bd for 8 weeks in IBS-D in secondary care substantially improved overall symptoms (adequate relief) (NNT = 3) and marginally improved diarrhoea and QoL in one RCT [36] but improvement was substantial for only abdominal pain (NNT = 1.9) [61] and global symptoms, bloating, flatulence or QoL did not improve in a further small pilot study
Ineffective probiotics
Evidence is lacking to show any symptom or QoL improvements after the use of 12/29 (41%) dose-specific probiotics:
Bifidobacterium infantis 35264 at a dose of 1×10^6 CFU and 1×10^{10} CFU 1 capsule per day for 4 weeks in primary care [49] and at dose 1×10^9 1 capsule per day for 8 weeks (unclear setting) [35]
Escherichia coli Nissle 1917 at a dose of 2.5×10^9 to 5×10^{10} CFU 1–2 capsule per day for 12 weeks in primary care [41]
Lactobacillus casei GG at a dose of 1×10^{10} CFU 1 tablet per day for 8 weeks in secondary care [34]
Lactobacillus plantarum 299V at a dose of 1×10^{10} CFU 1 capsule per day for 8 weeks in secondary care [48]
Lactobacillus reuteri ATCC 55730 at a dose of 1×10^8 CFU 1 tablet per day for 25 weeks in secondary care [43]
Lactobacillus salvarius subsp. *salvarius* UCC4331 at a dose of 1×10^{10} CFU malted milk for 8 weeks in primary and secondary care [45]
A 3-strain probiotic *Lactobacillus paracasei* subsp. *paracasei* F19, *Lactobacillus acidophilus* La5, B. Bb12 at a dose of 1.3×10^{10} CFU 1 capsule per day for 6 months in primary care [53] and at a dose of 5×10^7 CFU 400 mL day^{-1} fermented milk [64] or 7.5×10^{10} CFU 500 mL day^{-1} fermented milk [66] for 8 weeks in primary and secondary care
A 6-strain probiotic *B. lactis* W52, *Lactobacillus casei* W56, *Lactobacillus salivarius* W57, *Lactococcus lactis* W58, *Lactobacillus acidophilus* NCFM and *Lactobacillus rhamnosus* W715 $\times 10^9$ CFU one sachet per day for 6 weeks in secondary care [63]

Clinically meaningful improvements are shown in bold. CFU, colony forming unit; NNT, number needed to treat; NNH, number needed to harm; IBS, irritable bowel syndrome; IBS-C, IBS – constipation-predominant; IBS-D, IBS – diarrhoea-predominant; IBS-M, IBS involving both diarrhoea and constipation; QoL, quality of life.

Table 5 Clinical practice recommendations for probiotics

Recommendation	Grade
Advise that probiotics are unlikely to provide substantial benefit to IBS symptoms. However, individuals choosing to try probiotics are advised to select one product at a time and monitor the effects. They should try it for a minimum of 4 weeks at the dose recommended by the manufacturer (2016)	B
For individuals with IBS, taking a probiotic product is considered safe in IBS (2016)	B

Republished with permission [7]. IBS, irritable bowel syndrome.

Probiotic fermented milks and yoghurts are a good source of calcium.

Discussion

This systematic review of 35 probiotic RCTs from nine systematic reviews shows that the evidence for using specific probiotics to improve IBS symptoms is inadequate, probably as a result of the heterogeneity of IBS and probiotics and a limited amount of research that has investigated IBS subtypes, as well as the same dose-specific probiotic and formulation. There was no consistency of efficacy between different probiotics and no product specific recommendations can be made for use in clinical practice.

These recommendations are applicable to primary and secondary care and, to our knowledge, detail on setting has not previously been presented. The recommendations are consistent with other guidelines [33,72] and eight of the included systematic reviews [25–28,30–33]. The other systematic review was published by a European expert consensus group and was based on primary outcomes for each RCT [29]; however, over half of the included RCTs were in secondary care and included studies with less than 20 participants [73,74]. Recommendations for symptom-specific probiotics were made without accounting for effect size.

It has been argued that meta-analysis may be superior to systematic review in the assessment of probiotic RCTs in IBS management [25,27,30,31,33]. However, a meta-analysis should only compare like with like and the underlying differences between probiotic products may explain some of the heterogeneity when the results are pooled. Added ingredients may obscure the true probiotic benefit when (i) the dose only differs [49,62]; (ii) doses and formulations of the same strain differ [38,42,44,48]; or (iii) symptom severity and setting differ [50–52].

In seeking to establish what was a clinically meaningful outcome, criteria were extrapolated from the FDA recommendations for abdominal pain with an improvement score of at least 30% compared to baseline [17], despite knowing that the placebo effect is 37.5% in pharmaceutical RCTs in IBS [26,31]. This means that the clinically meaningful outcomes presented here may overestimate patient-perceived benefit and justify using a decrease of at least 95 points in the IBS-SSS as a response [75] as opposed to 50 points as originally described [19]. The 95-point reduction correlates well with a 30% pain

improvement over time [75]. The European Medicines Agency recommendation is that a clinically meaningful response for a five- or seven-point scale is the highest or two highest improvement grades, respectively, and where abdominal pain score has improved by at least 30% compared to baseline [76]. If these two critical symptom outcomes are combined, then only six included studies [38,42,54,55,57,68] showed clinically meaningful effectiveness. It is difficult to achieve statistically significant clinically meaningful benefit in dietary RCTs where the total sample size is less than 100, as shown for two RCTs with a seven-strain probiotic [58,61], and especially because dietary variability and pre- and probiotic intake are confounding factors [28]. Only three RCTs had at least 100 participants [38,51,54] and six had 50–99 [41,46,49,52,53,57], which means that almost three-quarters of the RCTs were potentially pilot studies with a sample size too small to develop any probiotic-specific clinical recommendations.

All RCTs reported no serious adverse events, although one lacked clarity on whether study discontinuation as a result of vomiting, heartburn or diarrhoea could have been serious [54]. Therefore, clarity is needed for definitions of minor and serious events, as described elsewhere [77].

The current recommendations are general, providing unsurprising but clinically useful information on safety and the evidence-base. It is disappointing that the more recent RCTs cannot be translated into symptom and QoL specific IBS treatment options. These findings remain consistent with other national guidelines [33], although some strongly recommend probiotic use in general [78], or for pain, bloating, diarrhoea and constipation [72], being relatively low in cost and safe to use. Probiotics are readily accessible and are considered to have a role in IBS management for mild to moderate symptoms [79]. Therefore, healthcare professionals and individuals with IBS should be advised that the current evidence does not support any specific probiotics to have a significant benefit on symptoms or QoL and probiotics can be expensive for the patient over time.

This is the first systematic review of probiotics in IBS to consider diet-related bias for uncertainty in outcomes and specific criteria were developed. Appropriateness of the ingredients in the vehicles used to carry the probiotic dose or as a placebo is of paramount importance to minimise their effect on outcomes. Over one-fifth of the included RCTs did not adequately describe these [34,39,40,42–44,54,63] and yet all studies should report on all of the ingredients used for both probiotic and placebo. One RCT used a lactose-containing milk-based product and did not exclude IBS participants with known lactose intolerance [55]. Exclusion of participants with known lactose intolerance should be considered in populations where there is a high prevalence [80].

Diet can influence the microbiota composition [81,82] and particular dietary components (e.g. dietary fibre and FODMAPs) influence IBS symptoms [11,83–86] and the colonic microbiota [83,84]. Alterations in the colonic microbiota in IBS may explain a reduction in anti-inflammatory cytokine levels (interleukin-10) [45] and visceral hypersensitivity [87], increasing IBS symptoms [85]. Only one RCT measured dietary intake at baseline and endpoint using a 3-day food diary [64]. Recognition that diet can influence outcomes was considered in eight RCTs because participants were advised not to change eating habits [35,38,43,48,50–52,60], although background diet was rarely reported. One RCT checked for dietary habits that might interfere with the assessment of the study product, although this was not quantified [38]. Thus, dietary intake should be measured at baseline and endpoint to (i) determine whether there has been any change to dietary intake during the RCT and, if this is the case, (ii) whether this may have had an impact on the clinical outcomes.

Reporting on product tolerance, adherence and adherence rate was limited, with 13 RCTs (37%) not reporting on any of these aspects [34,38,40,42,45,50,52–54,56,57,62,63]. An 80% adherence rate was provided in six RCTs but no justification for this rate was provided [36,47,58,61,64,66], it and may have been too low compared to validated standards for other dietary studies [15]. One RCT reported that natural yoghurt impacted its high drop-out rate [52] and another made no direct association with adherence, despite six out of 24 (32%) participants reporting tablet aftertaste in both groups [34]. These factors should be included in protocol design.

With wide variation in the number of probiotic species, strains and suitable vehicles to carry a viable dose to the colon, the study of probiotics and their application to this heterogeneous disorder is challenging. The task of one or several strains substantially impacting on an individual's microbial ecosystem appears to be unlikely when the true extent of its biodiversity is unknown. Considering how IBS symptoms fluctuate over time, there may be a net benefit for some individuals to trial a probiotic because there is a high placebo response [26]. It may also offer nutritional benefit, if provided in a milk- or fibre-based form, or offset pharmacotherapy.

Future probiotic RCTs should ensure that diet-related bias is included in protocol development and intervention and that placebo products are appropriate for an IBS population through appropriate feasibility work. Non-gastrointestinal health status, such as somatic, mental and social domains, is also important [88], which may impact on food choice and dietary intake; these factors were not assessed but were also not identified as relevant outcomes in the nine systematic reviews.

Limitations

Several limitations were identified during the appraisal process. First, the heterogeneity of IBS makes outcome judgement complex and internationally agreed validated symptom and QoL outcome measures are lacking. Cut-off points to measure participant-reported IBS symptom efficacy were developed from three sources [17,20,75] so that all symptoms were independently presented and not combined as recommended for medicines [17,76]. Second, a small sample size and high risk of bias were also likely to contribute. Third, in clinical practice, size of effect (e.g. NNT and NNH) is useful; however, the data were limited and so future studies should be designed to easily measure these by including a binary yes/no clinical response endpoint for adequate relief of symptoms [31]. Fourth, only three systematic reviews provided adequate detail regarding RCT exclusion [25,28,33]; for the remaining six systematic reviews, it was difficult to identify why RCTs had been excluded, adding complexity to quality assessment across the reviews. Finally, in the present review, four RCTs included in other systematic reviews were excluded as a result of medication usage and concern over the potential impact on IBS symptoms during the study [89–92]. Three of these studies had 86 [92], 103 [91] and 122 [90] participants each where medication was allowed throughout the intervention for constipation and diarrhoea [90–92] and, additionally, abdominal pain and flatulence [91,92].

Research recommendations

High-quality RCTs of probiotics should consider IBS subtype and predominant symptom profile, validated symptom and QoL assessment, meet low risk established bias criteria and low diet-related bias criteria, and standardise baseline and outcome assessment. Multicentre collaborative research is desirable to develop probiotic therapy so that it is individualised to the IBS symptom profile, with equality from the local to international level.

Conclusions

This systematic review of systematic reviews focused on dose-specific probiotics from the highest quality of evidence available to determine clinically meaningful efficacy. The probiotic evidence statements and recommendations provide health professionals with the most accurate evidence-based answers that are currently available for adults with IBS within each clinical setting. Individual probiotics for specific IBS symptom profiles cannot be recommended at this time. More data from high-quality RCTs in IBS and its subtypes taking into consideration all types of bias, including diet-related bias, are needed to determine the effectiveness of probiotic therapy in IBS.

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Conflicts of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
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YAM, JT and PG undertook the data analysis. YAM developed the evidence statements, which were approved through critical appraisal with JT, PG and MCEL. Clinical practice recommendations and practical considerations were agreed by all members of the IBS-DGRG. YAM and JT wrote the first draft of the manuscript and MCEL completed the corrections and developed the final draft tables, which were approved by all authors prior to submission. All authors critically reviewed the manuscript and approved the final version submitted for publication.

References

1. Lovell RM & Ford AC (2012) Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol* **10**, 712–721. e4
2. Drossman DA (2006) The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* **130**, 1377–1390.
3. Longstreth GF, Thompson WG, Chey WD *et al.* (2006) Functional bowel disorders. *Gastroenterology* **130**, 1480–1491.
4. Mercer M, Brinich MA, Geller G *et al.* (2012) How patients view probiotics: findings from a multicenter study of patients with inflammatory bowel disease and irritable bowel syndrome. *J Clin Gastroenterol* **46**, 138–144.
5. Organisation FaAOWH (2001) Evaluation of health and nutritional properties of probiotics in food, including

powder milk with the live lactic acid bacteria. Report of a Joint FAO/WHO Expert Consultation.Geneva: World Health Organization.
6. Hill C, Guarner F, Reid G *et al.* (2014) Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* **11**, 506–514.
7. McKenzie Y, Bowyer R, Leach H *et al.* (2016) British Dietetic Association systematic review and evidence-based practice guidelines for the dietary management of irritable bowel syndrome in adults (2016 update). *J Hum Nutr Diet*. under review.
8. McKenzie YA, Alder A, Anderson W *et al.* (2012) British Dietetic Association evidence-based guidelines for the dietary management of irritable bowel syndrome in adults. *J Hum Nutr Diet* **25**, 260–274.
9. Canavan C, West J & Card T (2014) Review article: the economic impact of the irritable bowel syndrome. *Aliment Pharmacol Ther* **40**, 1023–1034.
10. Agarwal N & Spiegel BM (2011) The effect of irritable bowel syndrome on health-related quality of life and health care expenditures. *Gastroenterol Clin North Am* **40**, 11–19.
11. Staudacher HM, Irving PM, Lomer MC *et al.* (2014) Mechanisms and efficacy of dietary FODMAP restriction in IBS. *Nat Rev Gastroenterol Hepatol* **11**, 256–266.
12. Chey WD (2013) The role of food in the functional gastrointestinal disorders: introduction to a manuscript series. *Am J Gastroenterol* **108**, 694–697.
13. Manichanh C, Eck A, Varela E *et al.* (2014) Anal gas evacuation and colonic microbiota in patients with flatulence: effect of diet. *Gut* **63**, 401–408.
14. Monsbakken K, Vandvik P & Farup P (2006) Perceived food intolerance in subjects with irritable bowel syndrome – aetiology, prevalence and consequences. *Eur J Clin Nutr* **60**, 667–672.
15. Yao CK, Gibson PR & Shepherd SJ (2013) Design of clinical trials evaluating dietary interventions in patients with functional gastrointestinal disorders. *Am J Gastroenterol* **108**, 748–758.
16. Smith V, Devane D, Begley CM *et al.* (2011) Methodology in conducting a systematic review of systematic reviews of healthcare interventions. *BMC Med Res Methodol* **11**, 15.
17. Food and Drug Administration (2012) Guidance for industry: Irritable bowel syndrome – clinical evaluation of drugs for treatment. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
18. Irvine EJ, Whitehead WE, Chey WD *et al.* (2006) Design of treatment trials for functional gastrointestinal disorders. *Gastroenterology* **130**, 1538–1551.
19. Francis CY, Morris J & Whorwell PJ (1997) The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther* **11**, 395–402.
20. Passos MC, Lembo AJ, Conboy LA *et al.* (2009) Adequate relief in a treatment trial with IBS patients: a prospective assessment. *Am J Gastroenterol* **104**, 912–919.
21. Shea BJ, Grimshaw JM, Wells GA *et al.* (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* **7**, 10.
22. Higgins JP, Altman DG, Gøtzsche PC *et al.* (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**, d5928.
23. Hooper L, Abdelhamid A, Moore HJ *et al.* (2012) Effect of reducing total fat intake on body weight: systematic review and meta-analysis of randomised controlled trials and cohort studies. *BMJ* **345**, e7666.
24. Australia Government: National Health and Medical Research Council (2009) NHMRC additional levels of evidence and grades for recommendations for developers of guidelinesAvailable at: http://www.nhmrc.gov.au/guidelines-publications/cp65 (accessed 6 January 2016).
25. Ortiz-Lucas M, Tobias A, Saz P *et al.* (2013) Effect of probiotic species on irritable bowel syndrome symptoms: a bring up to date meta-analysis. *Rev Esp Enferm Dig* **105**, 19–36.
26. Moayyedi P, Ford AC, Talley NJ *et al.* (2010) The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Gut* **59**, 325–332.
27. McFarland LV & Dublin S (2008) Meta-analysis of probiotics for the treatment of irritable bowel syndrome. *World J Gastroenterol* **14**, 2650–2661.
28. Mazurak N, Broelz E, Storr M *et al.* (2015) Probiotic therapy of the irritable bowel syndrome: why is the evidence still poor and what can be done about it? *J Neurogastroenterol Motil* **21**, 471–485.
29. Hungin AP, Mulligan C, Pot B *et al.* (2013) Systematic review: probiotics in the management of lower gastrointestinal symptoms in clinical practice – an evidence-based international guide. *Aliment Pharmacol Ther* **38**, 864–886.
30. Hoveyda N, Heneghan C, Mahtani KR *et al.* (2009) A systematic review and meta-analysis: probiotics in the treatment of irritable bowel syndrome. *BMC Gastroenterol* **9**, 15.
31. Ford AC, Quigley EM, Lacy BE *et al.* (2014) Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. *Am J Gastroenterol* **109**, 1547–1561.
32. Brenner DM, Moeller MJ, Chey WD *et al.* (2009) The utility of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Am J Gastroenterol* **104**, 1033–1049.
33. National Institute for Health and Clinical Excellence (2015) Irritable bowel syndrome in adults. Diagnosis and management of irritable bowel syndrome in primary care.

Clinical guideline 61 Update 2015. Available at: http://www.nice.org.uk/Guidance/CG61 (accessed 6 January 2016).
34. O'Sullivan MA & O'Morain CA (2000) Bacterial supplementation in the irritable bowel syndrome. A randomised double-blind placebo-controlled crossover study. *Dig Liver Dis* **32**, 294–301.
35. Charbonneau D, Gibb RD & Quigley EM (2013) Fecal excretion of *Bifidobacterium infantis* 35624 and changes in fecal microbiota after eight weeks of oral supplementation with encapsulated probiotic. *Gut Microbes* **4**, 201–211.
36. Choi CH, Jo SY, Park HJ *et al.* (2011) A randomized, double-blind, placebo-controlled multicenter trial of *Saccharomyces boulardii* in irritable bowel syndrome: effect on quality of life. *J Clin Gastroenterol* **45**, 679–683.
37. Dolin BJ (2009) Effects of a proprietary Bacillus coagulans preparation on symptoms of diarrhea-predominant irritable bowel syndrome. *Methods Find Exp Clin Pharmacol* **31**, 655–659.
38. Ducrotte P, Sawant P & Jayanthi V (2012) Clinical trial: *Lactobacillus plantarum* 299v (DSM 9843) improves symptoms of irritable bowel syndrome. *World J Gastroenterol* **18**, 4012–4018.
39. Gade J & Thorn P (1989) Paraghurt for patients with irritable bowel syndrome. A controlled clinical investigation from general practice. *Scand J Prim Health Care* **7**, 23–26.
40. Hun L (2009) Bacillus coagulans significantly improved abdominal pain and bloating in patients with IBS. *Postgrad Med* **121**, 119–124.
41. Kruis W, Chrubasik S, Boehm S *et al.* (2012) A double-blind placebo-controlled trial to study therapeutic effects of probiotic Escherichia coli Nissle 1917 in subgroups of patients with irritable bowel syndrome. *Int J Colorectal Dis* **27**, 467–474.
42. Niedzielin K, Kordecki H & Birkenfeld B (2001) A controlled, double-blind, randomized study on the efficacy of *Lactobacillus plantarum* 299V in patients with irritable bowel syndrome. *Eur J Gastroenterol Hepatol* **13**, 1143–1147.
43. Niv E, Naftali T, Hallak R *et al.* (2005) The efficacy of *Lactobacillus reuteri* ATCC 55730 in the treatment of patients with irritable bowel syndrome – A double blind, placebo-controlled, randomized study. *Clin Nutr* **24**, 925–931.
44. Nobaek S, Johansson ML, Molin G *et al.* (2000) Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. *Am J Gastroenterol* **95**, 1231–1238.
45. O'Mahony L, McCarthy J, Kelly P *et al.* (2005) *Lactobacillus* and *Bifidobacterium* in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology* **128**, 541–551.
46. Pineton de Chambrun G, Neut C, Chau A *et al.* (2015) A randomized clinical trial of *Saccharomyces cerevisiae* versus placebo in the irritable bowel syndrome. *Dig Liver Dis* **47**, 119–124.
47. Sinn DH, Song JH, Kim HJ *et al.* (2008) Therapeutic effect of *Lactobacillus acidophilus*-SDC 2012, 2013 in patients with irritable bowel syndrome. *Dig Dis Sci* **53**, 2714–2718.
48. Stevenson C, Blaauw R, Fredericks E *et al.* (2014) Randomized clinical trial: effect of *Lactobacillus plantarum* 299 v on symptoms of irritable bowel syndrome. *Nutrition* **30**, 1151–1157.
49. Whorwell PJ, Altringer L, Morel J *et al.* (2006) Efficacy of an encapsulated probiotic *Bifidobacterium infantis* 35624 in women with irritable bowel syndrome. *Am J Gastroenterol* **101**, 1581–1590.
50. Agrawal A, Houghton LA, Morris J *et al.* (2009) Clinical trial: the effects of a fermented milk product containing *Bifidobacterium lactis* DN-173 010 on abdominal distension and gastrointestinal transit in irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* **29**, 104–114.
51. Guyonnet D, Chassany O, Ducrotte P *et al.* (2007) Effect of a fermented milk containing *Bifidobacterium animalis* DN-173 010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized, double-blind, controlled trial. *Aliment Pharmacol Ther* **26**, 475–486.
52. Roberts LM, McCahon D, Holder R *et al.* (2013) A randomised controlled trial of a probiotic 'functional food' in the management of irritable bowel syndrome. *BMC Gastroenterol* **13**, 45.
53. Begtrup LM, de Muckadell OB, Kjeldsen J *et al.* (2013) Long-term treatment with probiotics in primary care patients with irritable bowel syndrome–a randomised, double-blind, placebo controlled trial. *Scand J Gastroenterol* **48**, 1127–1135.
54. Enck P, Zimmermann K, Menke G *et al.* (2008) A mixture of *Escherichia coli* (DSM 17252) and *Enterococcus faecalis* (DSM 16440) for treatment of the irritable bowel syndrome – a randomized controlled trial with primary care physicians. *Neurogastroenterol Motil* **20**, 1103–1109.
55. Hong KS, Kang HW, Im JP *et al.* (2009) Effect of probiotics on symptoms in korean adults with irritable bowel syndrome. *Gut Liv* **3**, 101–107.
56. Hong YS, Hong KS, Park MH *et al.* (2011) Metabonomic understanding of probiotic effects in humans with irritable bowel syndrome. *J Clin Gastroenterol* **45**, 415–425.
57. Jafari E, Vahedi H, Merat S *et al.* (2014) Therapeutic effects, tolerability and safety of a multi-strain probiotic in Iranian adults with irritable bowel syndrome and bloating. *Arch Iran Med* **17**, 466–470.
58. Ki Cha B, Mun Jung S, Hwan Choi C *et al.* (2012) The effect of a multispecies probiotic mixture on the symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. *J Clin Gastroenterol* **46**, 220–227.
59. Kim HJ, Camilleri M, McKinzie S *et al.* (2003) A randomized controlled trial of a probiotic, VSL#3, on gut

transit and symptoms in diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* **17**, 895–904.
60. Kim HJ, Vazquez Roque MI, Camilleri M *et al.* (2005) A randomized controlled trial of a probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating. *Neurogastroenterol Motil* **17**, 687–696.
61. Ko SJ, Han G, Kim SK *et al.* (2013) Effect of korean herbal medicine combined with a probiotic mixture on diarrhea-dominant irritable bowel syndrome: a double-blind, randomized, placebo-controlled trial. *Evid Based Complement Alternat Med* **2013**, 824605.
62. Lorenzo-Zuniga V, Llop E, Suarez C *et al.* (2014) I.31, a new combination of probiotics, improves irritable bowel syndrome-related quality of life. *World J Gastroenterol* **20**, 8709–8716.
63. Ludidi S, Jonkers DM, Koning CJ *et al.* (2014) Randomized clinical trial on the effect of a multispecies probiotic on visceroperception in hypersensitive IBS patients. *Neurogastroenterol Motil* **26**, 705–714.
64. Simren M, Ohman L, Olsson J *et al.* (2010) Clinical trial: the effects of a fermented milk containing three probiotic bacteria in patients with irritable bowel syndrome – a randomized, double-blind, controlled study. *Aliment Pharmacol Ther* **31**, 218–227.
65. Sisson G, Ayis S, Sherwood RA *et al.* (2014) Randomised clinical trial: a liquid multi-strain probiotic vs. placebo in the irritable bowel syndrome–a 12 week double-blind study. *Aliment Pharmacol Ther* **40**, 51–62.
66. Sondergaard B, Olsson J, Ohlson K *et al.* (2011) Effects of probiotic fermented milk on symptoms and intestinal flora in patients with irritable bowel syndrome: a randomized, placebo-controlled trial. *Scand J Gastroenterol* **46**, 663–672.
67. Williams EA, Stimpson J, Wang D *et al.* (2009) Clinical trial: a multistrain probiotic preparation significantly reduces symptoms of irritable bowel syndrome in a double-blind placebo-controlled study. *Aliment Pharmacol Ther* **29**, 97–103.
68. Yoon JS, Sohn W, Lee OY *et al.* (2014) Effect of multispecies probiotics on irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. *J Gastroenterol Hepatol* **29**, 52–59.
69. Chassany O, Marquis P, Scherrer B *et al.* (1999) Validation of a specific quality of life questionnaire for functional digestive disorders. *Gut* **44**, 527–533.
70. Drossman DA, Patrick DL, Whitehead WE *et al.* (2000) Further validation of the IBS-QOL: a disease-specific quality-of-life questionnaire. *Am J Gastroenterol* **95**, 999–1007.
71. Hays RD, Sherbourne CD & Mazel RM (1993) The RAND 36-Item Health Survey 1.0. *Health Econ* **2**, 217–227.
72. Andresen V, Keller J, Pehl C *et al.* (2011) Clinical practice guideline: Irritable bowel syndrome – the main recommendations. Dtsch Arztebl Int in full it is: Deutsches Ärzteblatt International **108**, 751–760.
73. Ligaarden SC, Axelsson L, Naterstad K *et al.* (2010) A candidate probiotic with unfavourable effects in subjects with irritable bowel syndrome: a randomised controlled trial. *BMC Gastroenterol* **10**, 16.
74. Sen S, Mullan MM, Parker TJ *et al.* (2002) Effect of *Lactobacillus plantarum* 299v on colonic fermentation and symptoms of irritable bowel syndrome. *Dig Dis Sci* **47**, 2615–2620.
75. Spiegel B, Camilleri M, Bolus R *et al.* (2009) Psychometric evaluation of patient-reported outcomes in irritable bowel syndrome randomized controlled trials: a Rome Foundation report. *Gastroenterology* **137**, 1944–1953. e1-3
76. European Medicines Agency (2014) Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndromeAvailable at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500173457.pdf (accessed 30 March 2016).
77. Agency for Healthcare Research and Quality (2011) Safety of Probiotics to Reduce Risk and Prevent or Treat DiseaseAvailable at: http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/evidence-based-reports/probiotic-evidence-report.pdf (accessed 30 March 2016).
78. Fukudo S, Kaneko H, Akiho H *et al.* (2015) Evidence-based clinical practice guidelines for irritable bowel syndrome. *J Gastroenterol* **50**, 11–30.
79. Khan S & Chang L (2010) Diagnosis and management of IBS. *Nat Rev Gastroenterol Hepatol* **7**, 565–581.
80. Lomer MCE, Parkes GC & Sanderson JD (2008) Review article: lactose intolerance in clinical practice – myths and realities. *Aliment Pharmacol Ther* **27**, 93–103.
81. David LA, Maurice CF, Carmody RN *et al.* (2014) Diet rapidly and reproducibly alters the human gut microbiome. *Nature* **505**, 559–563.
82. Wu GD, Chen J, Hoffmann C *et al.* (2011) Linking long-term dietary patterns with gut microbial enterotypes. *Science* **334**, 105–108.
83. Halmos EP, Power VA, Shepherd SJ *et al.* (2014) A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology* **146**, 67–75. e5
84. Staudacher HM, Lomer MC, Anderson JL *et al.* (2012) Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. *J Nutr* **142**, 1510–1518.
85. Simren M, Barbara G, Flint HJ *et al.* (2013) Intestinal microbiota in functional bowel disorders: a Rome foundation report. *Gut* **62**, 159–176.
86. Eswaran S, Muir J & Chey WD (2013) Fiber and functional gastrointestinal disorders. *Am J Gastroenterol* **108**, 718–727.
87. Rajilic-Stojanovic M, Jonkers DM, Salonen A *et al.* (2015) Intestinal microbiota and diet in IBS: causes, consequences, or epiphenomena? *Am J Gastroenterol* **110**, 278–287.
88. Lackner JM, Gudleski GD, Thakur ER *et al.* (2014) The impact of physical complaints, social environment, and

psychological functioning on IBS patients' health perceptions: looking beyond GI symptom severity. *Am J Gastroenterol* **109**, 224–233.
89. Dapoigny M, Piche T, Ducrotte P *et al.* (2012) Efficacy and safety profile of LCR35 complete freeze-dried culture in irritable bowel syndrome: a randomized, double-blind study. *World J Gastroenterol* **18**, 2067–2075.
90. Guglielmetti S, Mora D, Gschwender M *et al.* (2011) Randomised clinical trial: Bifidobacterium bifidum MIMBb75 significantly alleviates irritable bowel syndrome and improves quality of life – a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* **33**, 1123–1132.
91. Kajander K, Hatakka K, Poussa T *et al.* (2005) A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention. *Aliment Pharmacol Ther* **22**, 387–394.
92. Kajander K, Myllyluoma E, Rajilic-Stojanovic M *et al.* (2008) Clinical trial: multispecies probiotic supplementation alleviates the symptoms of irritable bowel syndrome and stabilizes intestinal microbiota. *Aliment Pharmacol Ther* **27**, 48–57.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article:
Table S1. Population, Interventions, Comparisons, Outcome measures and Types of study (PICOT) criteria.
Table S2. Search terms.
Table S3. Clinically meaningful and marginal criteria for statistically significant symptom improvement.
Table S4. Quality assessment of included systematic reviews using the AMSTAR tool.
Table S5. Main outcomes, recommendations and implications of included systematic reviews.
Table S6. Reasons for exclusion of probiotic reviews.
Table S7. Reasons for randomised controlled trial exclusion.
Table S8. Randomised controlled trials showing statistically significant improvements for global symptom outcomes.
Table S9. Randomised controlled trials showing statistically significant improvements for abdominal pain.
Table S10. Randomised controlled trials showing statistically significant improvements in bloating.
Table S11. Randomised controlled trials showing statistically significant improvements for flatulence.
Table S12. Randomised controlled trials showing statistically significant improvements for diarrhoea.
Table S13. Randomised controlled trials showing statistically significant improvements for constipation.
Table S14. Randomised controlled trials showing statistically significant improvements for quality of life.