



Systematic review: probiotics in the management of lower gastrointestinal symptoms – an updated evidence-based international consensus

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Summary

Background: In 2013, a systematic review and Delphi consensus reported that specific probiotics can benefit adult patients with irritable bowel syndrome (IBS) and other gastrointestinal (GI) problems.

Aim: To update the consensus with new evidence.

Methods: A systematic review identified randomised, placebo-controlled trials published between January 2012 and June 2017. Evidence was graded, previously developed statements were reassessed by an 8-expert panel, and agreement was reached via Delphi consensus.

Results: A total of 70 studies were included (IBS, 34; diarrhoea associated with antibiotics, 13; diarrhoea associated with *Helicobacter pylori* eradication therapy, 7; other conditions, 16). Of 15 studies that examined global IBS symptoms as a primary endpoint, 8 reported significant benefits of probiotics vs placebo. Consensus statements with 100% agreement and “high” evidence level indicated that specific probiotics help reduce overall symptom burden and abdominal pain in some patients with IBS and duration/intensity of diarrhoea in patients prescribed antibiotics or *H. pylori* eradication therapy, and have favourable safety. Statements with 70%-100% agreement and “moderate” evidence indicated that, in some patients with IBS, specific probiotics help reduce bloating/distension and improve bowel movement frequency/consistency.

Conclusions: This updated review indicates that specific probiotics are beneficial in certain lower GI problems, although many of the new publications did not report benefits of probiotics, possibly due to inclusion of new, less efficacious preparations. Specific probiotics can relieve lower GI symptoms in IBS, prevent diarrhoea associated with antibiotics and *H. pylori* eradication therapy, and show favourable safety. This study will help clinicians recommend/prescribe probiotics for specific symptoms.

The Handling Editor for this article was Professor Alexander Ford, and this uncommissioned review was accepted for publication after full peer-review.

Authors' complete affiliations are listed in Appendix 1.

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1 | INTRODUCTION

In 2013, the European Society for Primary Care Gastroenterology (ESPCG) published an evidence-based international guide for the use of probiotics in the management of specific lower gastrointestinal (GI) symptoms.¹ This guide was based on the results of a systematic review of evidence regarding the use of probiotics vs placebo in randomised controlled trials (RCTs). A Delphi panel assessed this evidence and developed a number of consensus statements. Since the publication of these statements, numerous relevant clinical studies of probiotics in the management of lower GI symptoms have been published. In the light of the new evidence available in this rapidly evolving field, the objectives of this publication are to update the systematic review and Delphi consensus, and to incorporate the new findings into the guidelines.

The importance of gut microbiota in health and disease is becoming increasingly evident, and there is a growing body of literature on the therapeutic potential of probiotics in GI disorders^{2,3} like irritable bowel syndrome (IBS) and many other conditions. The proposed mechanisms of action for the beneficial effects of probiotics include competitive exclusion of pathogenic microorganisms, inhibition of pathogen adhesion, production of anti-microbial substances and modulation of the immune system.⁴⁻⁶ Studies in several animal models have indicated positive therapeutic results for probiotics in a range of conditions, such as asthma,⁷ obesity,^{8,9} diabetes mellitus,¹⁰ hypertension,^{11,12} and depression and anxiety;¹³ however, definitive data from human studies are relatively sparse. There is some evidence for a beneficial effect of probiotics in humans in the prevention of hypertension¹⁴ and improvement of the symptoms of schizophrenia,¹⁵ depression¹⁶ and Alzheimer's disease,¹⁷ although further studies are needed to confirm these findings. Evaluation of the effect of probiotics in humans is complex due to differences in strains, patient populations and dosing. In addition, many clinical trials report conflicting findings, and results of meta-analyses have been published that compare non-identical probiotic strains, making the evidence difficult to interpret. A transparent and rigorous methodology is needed when evaluating the evidence because this topic remains complex.

Lower GI symptoms commonly require a visit to a physician, but the heterogeneity of symptoms presented and their underlying causes may limit the pharmacological treatment options offered because no single dominant drug therapy would be effective in all cases. Although new pharmacological treatments are emerging, challenges remain in terms of their ability to improve symptoms without incurring side effects.¹⁸⁻²¹ Current evidence suggests that probiotics in the diet may play a role in reducing uncomfortable lower GI symptoms in adults. Therefore, as before, the emphasis of the ESPCG updated evidence-based guidelines is on the potential role of probiotics in the management of lower GI symptoms in clinical practice.

2 | METHODS

2.1 | Design

The repeated consensus procedure was based on an updated systematic literature review and re-rating of statements by an expert panel.

2.2 | Systematic literature search

Placebo-controlled RCTs evaluating the effects of probiotics on lower GI symptoms were identified through a systematic literature review (based on Appraisal of Guidelines, Research and Evaluation [AGREE] II criteria²²) capturing studies published since the original searches were conducted in January 2012.¹ The same search terms were used as in the original review to search Embase, MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE (1946-present). A search was performed in July 2016 to identify publications from 1 January 2012 to 28 July 2016. To keep this publication as current as possible, an updated database search was performed in June 2017.

2.3 | Citation screening and full-text review

Identified publications were screened manually based on the title and abstract in accordance with 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines²³ against predefined eligibility criteria (Table 1). Full-text versions of all publications meeting the eligibility criteria at initial screening were reviewed to confirm eligibility.

2.4 | Data items collected and quality assessment

The same data items were collected and tabulated as in the original systematic review, including patient demographics, sample size, strain of probiotic, setting, primary and secondary endpoints, and results. Of note, the term "probiotics" has been used throughout this publication to refer to products that contain probiotics, regardless of whether these are single or multiple strains. The additional step of a quality assessment was performed for each publication (in both the original and the updated review) using a modified version of the Critical Appraisal Skills Programme (CASP) Checklist for Randomised Controlled Trials,²⁴ as recommended by the National Institute for Health and Care Excellence.²⁵

2.5 | Delphi consensus

A modified Delphi process was used to review the original consensus statements in the light of the new evidence identified in the current updated systematic review. The Delphi process uses anonymous and iterative feedback and voting to achieve consensus among a panel of independent experts by means of stepwise

TABLE 1 Eligibility criteria for inclusion of publications examining probiotics in the management of lower GI symptoms

	Inclusion criteria	Exclusion criteria
Population	<ul style="list-style-type: none"> Adults (≥ 18 y old) Patients with IBS or other FGID Patients with diarrhoea as a side effect of antibiotic treatment Patients with no specific GI diagnosis 	<ul style="list-style-type: none"> Children Disorders such as inflammatory bowel disease and diverticular disease Specialist populations (eg patients with any type of cancer)
Interventions	<ul style="list-style-type: none"> Probiotics 	<ul style="list-style-type: none"> Synbiotics Sterile preparations
Outcomes	<ul style="list-style-type: none"> IBS (global symptoms) Abdominal pain Bloating/distension Flatus Diarrhoea (treatment) Diarrhoea (prevention) Constipation Bowel habit Health-related quality of life Adverse events 	<ul style="list-style-type: none"> No symptom scores or clearly defined response rates for specific symptoms Symptom clusters not reported as pre-specified primary or secondary endpoints
Study design	<ul style="list-style-type: none"> RCTs Placebo-controlled trials Studies with a clear sample size calculation 	<ul style="list-style-type: none"> Meta-analysis Systematic review Studies lasting <4 wks with <80% follow-up Pooled data analyses
Date restrictions	January 2012-June 2017	
Language restrictions	English language and foreign language publications with an English abstract	
Country	Not restricted by country	

FGID, functional gastrointestinal disorders; GI, gastrointestinal; IBS, irritable bowel syndrome; RCT, randomised controlled trial.

refinement of responses. The Consensus Group consisted of 10 primary care physicians with an interest in gastroenterology drawn from the ESPCG, with the addition of 2 members from secondary care; 7 of these individuals had taken part in the original consensus. The Group was advised by a nonvoting Chair (APSH) who, in common with the members of the Consensus Group, has experience of systematic reviews and guideline development. For this update, the Steering Committee (APSH, CRM, PW and NdW) reviewed the original statements in the light of the new evidence, and agreed to keep them unchanged for the voting.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system²⁶ was used by the Chair and Steering Committee to rate the level of supporting evidence and the strength

of each statement. Using the GRADE system, each statement was rated as follows: high—further research is unlikely to change our confidence in the estimate of effect; moderate—further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low—further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low—any estimate of effect is very uncertain.

The Consensus Group members reviewed both the original and new evidence on the use of probiotics in the management of lower GI symptoms. It was anticipated that 3 rounds of anonymous voting would be required to achieve consensus. Votes were cast using an online platform (Google Forms) and the results were analysed by the nonvoting Chair. For each statement, voters indicated their level of agreement on a scale from 1 to 6 (1 = strongly disagree; 2 = disagree with major reservation; 3 = disagree with minor reservation; 4 = agree with major reservation; 5 = agree with minor reservation; and 6 = strongly agree). Consensus was defined *a priori* as agreement by at least 67% of respondents. In some cases, the consensus statement is indication-specific; however, studies in other indications that provide relevant data are also described for completeness. In the following discussion, “significant” refers to a statistically significant result ($P < 0.05$).

After the updated consensus was completed, 3 consensus statements covering general considerations related to probiotic use in daily practice which referenced no specific studies individually (Statements 14, 15 and 16 in the original consensus) were moved to Section 4.

3 | RESULTS

The updated database searches identified 3176 articles (January 2012-July 2016) and 1090 articles (July 2016-June 2017; Figure 1). After applying inclusion and exclusion criteria, 33 RCTs that reported on the effects of probiotics in the management of lower GI symptoms in clinical practice published since January 2012 were identified, and considered in conjunction with 37 RCTs included in the original systematic review. Of the 33, 6 publications were found in the June 2017 update.²⁷⁻³² These could not be included in the consensus voting process; however, they were reviewed by the Steering Committee, which decided that the new evidence provided in these studies would not alter the results of the Delphi consensus and so could be included in our publication.

Collectively, the 70 studies investigated a total of 54 different probiotic products (containing 108 strains either alone or in combination) at doses ranging from 1×10^6 to 4.5×10^{11} colony-forming units (CFU) per day, administered as 1, 2 or 3 doses. They predominantly contained bacteria (mostly lactobacilli and/or bifidobacteria); a few contained the yeast *Saccharomyces*. Of the 54 probiotic products, 28 were included in studies published since the original consensus, and the majority of these (22 of 28; 79%) were new probiotics that had not been evaluated in the original consensus.

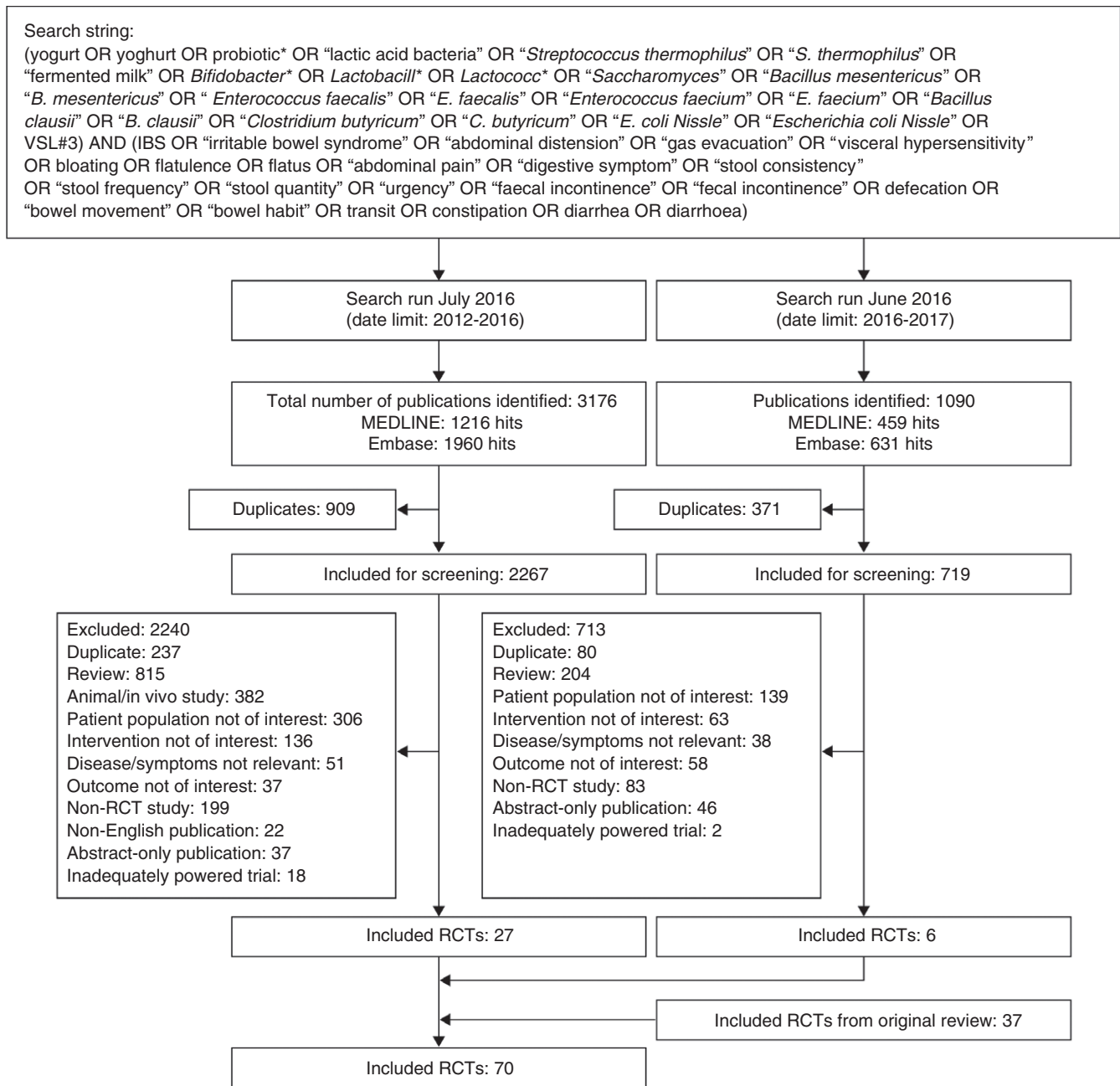


FIGURE 1 Flow diagram of literature searches. MEDLINE and Embase searches were performed in July 2016 and June 2017. RCT, randomised controlled trial

Table 2 provides a summary of the symptoms and indications examined in the 70 studies.

Product adherence was addressed in 49 of the included studies. In 42 studies, adherence to the intervention was assessed by counting empty containers or unused test substance returned at the end of the study and/or by participant self-reporting (in treatment diaries or during investigator visits). Three of these studies used faecal recovery of probiotic strains to measure adherence, and publications from 4 studies did not report the method of assessing adherence. Where adherence data were reported (38 studies), the level of adherence was generally high. In the probiotic intervention groups,

the proportion of participants who were adherent to treatment (taking >80% of doses) was >75%.

The majority of the 70 studies (Table S1)²⁷⁻⁹⁶ focused on IBS (based on Rome I, II or III criteria or physician diagnosis; 34 studies), antibiotic-associated diarrhoea (13 studies) or diarrhoea-associated *Helicobacter pylori* eradication therapy (7 studies). Other conditions were investigated in 16 studies. Sixty-four studies provided evidence for the Delphi consensus³³⁻⁹⁶ (6 were identified after voting was completed).²⁷⁻³² The evidence level was graded as "high" for 5 statements, "moderate" for 2, "low" for 4 and "very low" for 2. Table S2 summarises the studies and specific probiotics with evidence for

TABLE 2 Indications and symptoms examined in included studies

Symptom	Indication						Total
	IBS	Functional GI disorders	Antibiotic treatment	<i>Helicobacter pylori</i> eradication	Lactose intolerance	Healthy/minor GI symptoms	
IBS (global symptoms)	30	0	0	0	0	0	30
Abdominal pain	30	2	0	0	2	4	38
Bloating/distension	27	1	0	0	1	4	33
Flatus	15	2	0	0	2	3	22
Diarrhoea (treatment)	4	2	0	0	2	2	10
Diarrhoea (prevention)	0	0	13	7	0	0	20
Constipation	4	3	0	0	0	4	11
Bowel habit	25	2	0	0	1	8	36
Health-related quality of life	20	1	0	0	0	4	25
Total	34	3	13	7	2	11	70

GI, gastrointestinal; IBS, irritable bowel syndrome.

each consensus statement, together with an indication of whether the result was a primary or secondary endpoint. A table stating probiotic availability by country in Europe, the USA and China is available at <http://espcg.eu/>. For consistency with the original consensus, 10 experts were invited to participate in the Delphi consensus voting in the update but for logistical reasons only 8 voted. Consensus was reached for all of the 16 statements developed in the original Delphi consensus in the first round of voting (see Figure 2). For each consensus statement, the result of the first (final) vote and the grade of supporting evidence are given, followed by a discussion of the evidence. Sometimes, a particular probiotic yielded conflicting results for a symptom/problem when it was investigated in different studies (see Table S2).

3.1 | IBS (global symptom assessment)

Statement 1: specific probiotics help relieve overall symptom burden in some patients with IBS. Agreement: 100% (6, 12.5%; 5, 87.5%; grade of evidence for effect: high).

Supportive evidence: Twenty-three studies of 19 different probiotics evaluated overall symptoms in 3112 patients with IBS. Of these studies, 15 evaluated overall IBS symptoms as a primary endpoint, of which 8 reported a significant beneficial effect of 8 different probiotic products (dosed at 3.4×10^7 to 2.5×10^{10} CFU per day) compared with placebo,^{32,46,49,56,57,82,93,95} 5 reported no significant differences between 2 specific probiotic treatments and placebo,^{30,36,43,80,83} and 2 reported mixed results.^{54,88} Of the 15 studies, 6 had been published since the original consensus. Two of the new studies (33%) reported no significant difference, compared with 3 of the 9 studies (33%) in the original consensus.

Eight studies of 7 different probiotics evaluated overall IBS symptoms as a secondary endpoint only. Of these, 2 studies found a significant beneficial effect of 2 different probiotic treatments compared with placebo.^{44,55} One further dose-ranging study reported a beneficial effect of the specific probiotic treatment at the 1×10^8 CFU dose, but not at the lower and higher doses tested (1×10^6

and 1×10^{10} CFU).⁹² Four studies reported no significant differences between 4 different probiotic treatments and placebo^{37,66,85,94} and 1 study reported a negative effect of a probiotic treatment compared with placebo.⁶⁴ Of the 8 studies, 6 had been published since the original consensus. Four of the new studies (67%) reported no significant difference or a negative effect, compared with 1 of the 2 studies (50%) in the original consensus.

Statement 2: specific probiotics may help relieve overall symptom burden in some patients with IBS-C. Agreement: 100% (6, 12.5%; 5, 37.5%; 4, 50%; grade of evidence for effect: very low).

Supportive evidence: Five studies of 4 different probiotics evaluated overall IBS symptoms as a secondary endpoint in 577 patients with constipation-predominant IBS (IBS-C). Of these, 1 study reported a beneficial effect of the specific probiotic treatment (dosed at 2.5×10^{10} at CFU per day) vs placebo.³³ Another study of the same probiotic found a significant improvement from baseline in the probiotic group but not in the placebo group in a subanalysis of patients with fewer than 3 bowel movements per week.⁵⁰ In a third study with a different probiotic treatment, an improvement was observed in the composite score of IBS symptoms in the probiotic group vs the placebo group, but this just failed to reach statistical significance. However, the total area under the curve of the composite score of IBS symptoms over 12 weeks was significantly lower in the probiotic group than in the placebo group ($P = 0.03$).⁸⁵ Two studies examining 2 different probiotics reported no significant improvement in symptoms vs placebo.^{86,92} Of the 5 studies, 2 had been published since the original consensus. Of the 2 new studies, 1 reported no significant improvement, compared with 1 of the 3 studies in the original consensus.

Statement 3: specific probiotics help to relieve overall symptom burden in some patients with IBS-D. Agreement: 100% (6, 12.5%; 5, 37.5%; 4, 50%; grade of evidence for effect: low).

Supportive evidence: Seven studies examining different probiotics evaluated overall IBS symptoms in 495 patients with diarrhoea-predominant IBS (IBS-D). Two studies (both included in the original

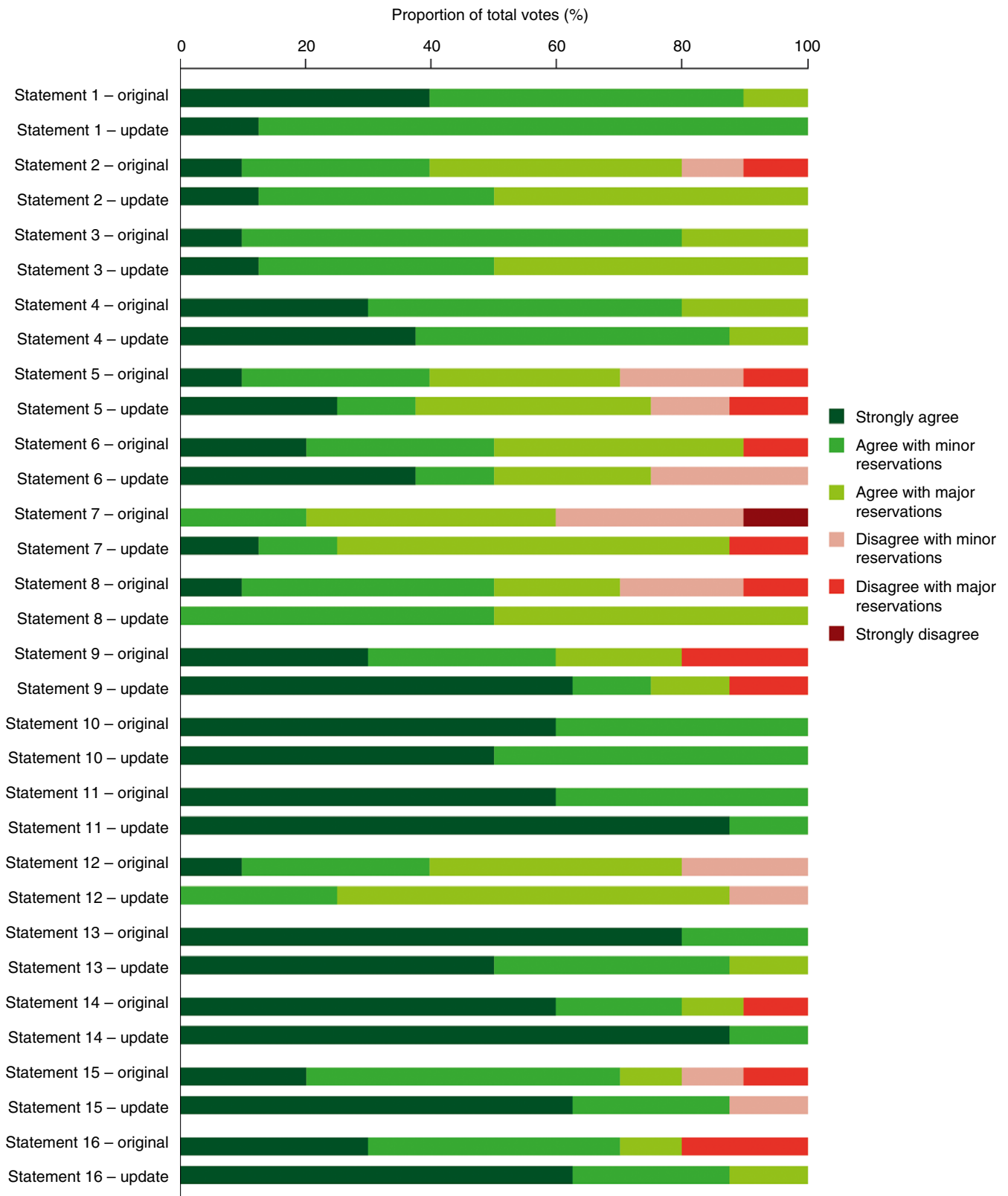


FIGURE 2 Breakdown of voting agreement for each individual statement in the original and updated Delphi consensus

consensus) evaluated overall IBS symptoms as a primary endpoint, with 1 study reporting a significant beneficial effect of the specific probiotic treatment (dose of 1×10^{10} CFU per day) compared with placebo⁵⁹ and the other reporting no significant difference.⁶⁰ Five

studies evaluated overall IBS symptoms as a secondary endpoint only. Of these, 2 (both included in the original consensus) found a significant beneficial effect of the specific probiotic treatments,^{92,96} and 3 (all published since the original consensus) found no significant

difference in the composite IBS symptom score between the probiotic group and the placebo group.^{65,85,86}

3.2 | Abdominal pain

Statement 4: specific probiotics help reduce abdominal pain in some patients with IBS. Agreement: 100% (6, 37.5%; 5, 50%; 4, 12.5%; grade of evidence for effect: high).

Supportive evidence: Thirty studies examining 23 different probiotics evaluated abdominal pain in 3771 patients with IBS. Of these studies, 9 (examining 8 probiotic treatments dosed at 1×10^6 to 1×10^{10} CFU per day) evaluated abdominal pain as a primary endpoint, of which 7 (4 from the original consensus and 3 new studies) showed a significant beneficial effect of specific probiotic treatments compared with placebo.^{44,46,54,74,81,85,92} One of these found no statistically significant difference in abdominal pain/discomfort between probiotic and placebo in the overall population but a significantly greater improvement in the subgroup of patients with IBS-C.⁸⁵ Two studies (both included in the original consensus) had mixed results: 1 showed a trend towards a beneficial effect in the weekly symptom score for abdominal pain (and, in a secondary analysis, abdominal pain was reduced in a significantly greater proportion of the probiotic group than of the placebo group)⁵⁶ and the other showed no significant increase in the proportion of patients reporting symptom relief, but a significantly greater decrease in the abdominal pain score in the probiotic group than in the placebo group.⁴³

Abdominal pain was evaluated as a secondary endpoint only in 21 studies. Of these, 5 reported a significant beneficial effect of 5 different probiotics^{33,49,55,82,96} (1 of which³³ also showed no significant effect in another study⁵⁰), 15 (examining 11 different probiotics) reported no significant effect^{30,36,37,50,57,59-61,66,80,83,88,93-95} (of which 1 reported a nonsignificant trend in favour of probiotics vs placebo),⁹⁵ and another reported a negative effect of the specific probiotic treatment.⁶⁴ Of the 21 studies, 9 had been published since the original consensus. Seven of the new studies (78%) reported no significant difference or a negative effect, compared with 9 of the 12 studies (75%) in the original consensus.

Abdominal pain was examined in indications other than IBS in 8 studies, each investigating a different probiotic. Of these, 1 study (included in the original consensus) investigated abdominal pain as a primary endpoint in individuals with symptoms related to post-prandial intestinal gas, and found a significant improvement in the probiotic group compared with the placebo group.⁵⁸ Seven studies examined abdominal pain as a secondary endpoint only, with 4 of these reporting no significant difference among 4 different probiotic treatments and placebo.^{47,51,62,69} Another 3 studies (2 examining 2 different probiotics in lactose-intolerant individuals^{71,73} and another reporting on a different probiotic in patients with functional GI symptoms⁹⁰) found significantly improved abdominal pain from baseline in the probiotic group, but not in the placebo group. Of the 7 studies, 3 had been published since the original consensus. Of the 3 new studies, 2 (67%) reported no significant difference, compared with 2 of the 4 studies (50%) in the original consensus.

3.3 | Bloating/distension

Statement 5: specific probiotics help reduce bloating/distension in some patients with IBS. Agreement: 75% (6, 25%; 5, 12.5%; 4, 37.5%; 3, 12.5%; 2, 12.5%; grade of evidence for effect: moderate).

Supportive evidence: The treatment of bloating/distension in 3561 patients with IBS was evaluated in 27 studies examining 20 different probiotics. Of these studies, 4 (examining 4 different probiotics, dosed between 1×10^6 and 2.5×10^{10} CFU per day) evaluated bloating/distension as a primary endpoint. Two studies (including 1 published since the original consensus) reported a significant beneficial effect of the specific probiotic treatment vs placebo,^{33,55} whereas a further 2 (both included in the original consensus) reported no significant differences.^{56,61} Bloating/distension was evaluated as a secondary endpoint only in 23 studies. Of these, 8 reported a significant beneficial effect of 8 different probiotic treatments^{44,46,49,50,57,85,92,93} (1 of which⁵⁰ also showed a beneficial effect as a primary endpoint in another study³³). Of these studies, some found a significant effect only at one time point,⁵⁰ after a single dose⁹² or only in patients with IBS-C.^{85,92} Fifteen studies reported no significant difference between 12 different probiotic treatments and placebo^{30,36,37,59,60,64,66,74,80,82,83,88,94-96} (1 of these probiotics⁶⁰ also showed no significant effect on the primary endpoint).⁶¹ Of the 23 studies, 11 had been published since the original consensus. Of the 11 new studies, 9 (82%) reported no significant difference, compared with 6 of the 12 studies (50%) in the original consensus.

Six studies investigated the effect of 6 different probiotics on distension/bloating in indications other than IBS. One of these studies (included in the original consensus) evaluated symptoms related to post-prandial intestinal gas as a primary endpoint in healthy individuals and reported no significant differences between the probiotic and placebo groups.⁵⁸ The remaining 5 studies (examining 5 different probiotics) evaluated distension/bloating as a secondary endpoint. Single studies reported no significant differences between the probiotic and control groups in women with mild digestive symptoms,⁵¹ patients with functional GI disorders (FGID),⁶² healthy individuals with low defecation frequency and abdominal discomfort,⁴⁷ and healthy patients with hard or lumpy stools in the past 2 years.⁶⁹ The fifth study, in individuals with lactose intolerance undergoing a hydrogen breath test, reported significantly reduced bloating in the group receiving the specific probiotic treatment but no significant improvement in the placebo group.⁷¹ Of the 5 studies, 2 had been published since the original consensus; both of the new studies reported no significant difference between probiotic and control groups.

3.4 | Flatus

Statement 6: probiotics tested to date do not help reduce flatus in patients with IBS. Agreement: 75% (6, 37.5%; 5, 12.5%; 4, 25%; 3, 25%; grade of evidence for effect: low).

Supportive evidence: Overall, 15 studies examining 12 different probiotics evaluated flatus in 1478 patients with IBS. All 3 studies

that examined flatus as a primary endpoint (all included in the original consensus) showed no significant difference between 3 specific probiotic treatments and control.^{54,56,79} Twelve studies examined flatus as a secondary endpoint only. Of these, 8 showed no significant difference between 8 specific probiotic treatments and control.^{33,37,57,59,60,66,85,94} Four studies reported a significant beneficial effect of 4 different probiotic treatments^{61,88,92,96} (1 of which⁶¹ also showed no significant effect in another study⁶⁰); the significant effect was seen at 1 dose only in 1 of these studies,⁹² and at week 16 (after follow-up) but not week 8 (end of treatment) in another study.⁸⁸ Of the 12 studies, 5 had been published since the original consensus. Of the 5 new studies, 4 (80%) reported no significant difference, compared with 4 of the 7 studies (57%) in the original consensus.

Seven studies examined the effect of 7 different probiotics on flatus in indications other than IBS. Four of these studies reported no significant effects on flatus (primary endpoint for 1 probiotic⁵⁸ and secondary endpoint for 3 other probiotics^{62,69,73}). Three studies reported a significant benefit of 3 different probiotic treatments on flatus (secondary endpoint) in women with mild digestive symptoms,⁵¹ patients with functional GI symptoms⁹⁰ and individuals with lactose intolerance undergoing a lactose breath test.⁷¹ Of the 7 studies, 2 had been published since the original consensus; both of the new studies reported no significant effect on flatus as a secondary endpoint.

3.5 | Constipation

Statement 7: specific probiotics may help reduce constipation in some patients with IBS. Agreement: 87.5% (6, 12.5%; 5, 12.5%; 4, 62.5%; 2, 12.5%; grade of evidence for effect: low).

Supportive evidence: Four studies of 4 different probiotics examined the treatment of constipation as a secondary endpoint in 487 patients with IBS. One study (in patients with IBS-C) reported significant improvements with the specific probiotic treatment (administered at 1.25×10^{10} CFU twice daily) vs control for some of the endpoints (orocecal transit time, colonic transit time and urgency), but not others (stool frequency and consistency, straining during evacuation and feelings of incomplete evacuation).³³ The 3 remaining studies did not detect any statistically significant effects of 3 different probiotic treatments on the relief of constipation.^{36,49,74} Of the 4 studies, 2 had been published since the original consensus; both of the new studies reported no significant effect on constipation.

Seven studies of 7 different probiotics examined constipation in patients with broader FGID. Of these, 3 studies reported significant improvements in the relief of constipation, with 1 reporting an increase in defecation frequency⁴⁷ and another reporting a significant effect of the probiotic on stool consistency vs placebo (although this study did not show a significant effect of the probiotic on stool frequency vs placebo).⁸⁹ The third study did not provide a between-group statistical analysis; however, the decrease in constipation frequency score was approximately twofold greater in the probiotic groups than in the placebo group.⁹⁰ Four studies reported

no significant effect of 4 different probiotic treatments;^{31,62,68,69} however, 1 of these studies showed a nonsignificant trend in favour of probiotics.⁶⁸ Of the 7 studies, 5 had been published since the original consensus. Of the 5 new studies, 3 (60%) reported no significant effect, compared with 1 of the 2 studies (50%) in the original consensus.

3.6 | Bowel habit

Statement 8: specific probiotics help improve frequency and/or consistency of bowel movements in some patients with IBS. Agreement: 100% (5, 50%; 4, 50%; grade of evidence for effect: moderate).

Supportive evidence: Twenty-five studies examining 20 different probiotics evaluated bowel habit in 3069 patients with IBS. Two studies of 2 different probiotics (administered at doses of between 1.3×10^8 and 9×10^9 CFU per day) evaluated bowel habit as a primary endpoint, with 1 study (included in the original consensus) reporting no significant difference in weekly defecation frequency between the probiotic and placebo groups, although a significant positive effect of the specific probiotic treatment vs placebo was observed on the secondary endpoints of urgency and feelings of incomplete evacuation.⁵⁶ The second study (published since the original consensus) found that the number of bowel movements changed favourably in the probiotic group compared with the placebo group.³² Of the 25 studies in patients with IBS, 22 evaluated bowel habit as a secondary endpoint only. Seventeen studies used 1 or more of 3 main endpoints: stool frequency, stool consistency and satisfaction with bowel habits. Eleven reported significant beneficial effects of 11 different probiotics,^{43,44,46,49,50,55,59,81,82,92,93} 1 of these studies reported a significant improvement in the feeling of incomplete defecation on completion of 4 weeks of treatment that was not significant 1 month later.⁵⁵ Nine studies reported no significant effects of 7 different probiotics^{37,54,57,61,74,80,83,85,95} (1 of which⁶¹ showed no significant benefit on the primary endpoint in another study⁶⁰). One found a trend to normalisation of stool consistency ($P = 0.058$); however, no significant effects on straining and feelings of incomplete evacuation were observed.³³ Another study reported a significant negative effect of the specific probiotic treatment.⁶⁴ Of the 22 studies, 7 had been published since the original consensus. Of the 7 new studies, 4 (57%) reported no significant effect or a negative effect, compared with 6 of the 15 studies (40%) in the original consensus.

Two studies (both included in the original consensus) examined the effects of probiotics on GI transit times. This was assessed as a primary endpoint in 1 study that reported no difference in GI transit times between the probiotic and placebo groups.⁶⁰ A second study showed significant improvements in the secondary endpoints of colonic and small bowel transit times in the probiotics vs placebo groups.³³

Eleven studies examining 10 different probiotic treatments assessed bowel habit in indications other than IBS. Of these, 8 studies of 8 different probiotics reported that probiotics produced significant improvements in measures of bowel habit vs

placebo,^{31,47,51,63,75,87,89,90} whereas 3 reported no difference between 3 different probiotics and placebo.^{68,69,73} Of the 11 studies, 7 had been published since the original consensus. Of the 7 new studies, 3 (43%) reported no significant difference, compared with none of the 4 studies in the original consensus.

3.7 | Diarrhoea

Statement 9: probiotics tested to date do not reduce diarrhoea in patients with IBS. Agreement: 87.5% (6, 62.5%; 5, 12.5%; 4, 12.5%; 2, 12.5%; grade of evidence for effect: very low).

Supportive evidence: Four studies of 4 different probiotics (dosed at between 4×10^7 and 5.2×10^{10} CFU per day) evaluated the treatment of diarrhoea as a secondary endpoint in 283 patients with IBS. Of these, 3 studies (including 1 published since the previous consensus) reported no difference between specific probiotic treatments and placebo,^{36,57,59} and another found significant worsening of diarrhoea with the specific probiotic treatment compared with placebo.⁶⁴ Six studies of 6 different probiotics (including 2 studies published since the previous consensus) evaluated diarrhoea as a secondary endpoint in indications other than IBS. Specific probiotic treatment had no significant effect on diarrhoea in elderly nursing home residents,⁷⁵ patients with a functional bowel disorder,⁶² individuals with functional GI symptoms⁹⁰ or individuals with hard or lumpy stools in the past 2 years.⁶⁹ Two studies (including 1 published since the previous consensus) showed a beneficial effect of 2 different probiotics vs placebo on symptoms of diarrhoea, both of which were in patients with lactose intolerance.^{71,73}

Statement 10: in patients receiving antibiotic therapy, specific probiotics are helpful as adjuvant therapy to prevent or reduce the duration of associated diarrhoea. Agreement: 100% (6, 50%; 5, 50%; grade of evidence for effect: high).

Supportive evidence: Thirteen studies of 10 different probiotics examined the prevention of antibiotic-associated diarrhoea and/or reduction in antibiotic-associated diarrhoea in 6091 patients who received antibiotics (although they were initiated in a hospital setting, these studies were included because of the relevance of antibiotic-associated diarrhoea to primary care). Of these, 11 studies examined antibiotic-associated diarrhoea as a primary endpoint. Six studies of 4 different probiotics administered at doses of 2×10^9 to 5×10^{10} CFU per day^{35,38,48,53,72,78} (3 of which tested the same probiotic treatment)^{35,48,78} showed a significant reduction in antibiotic-associated diarrhoea compared with placebo. One study reported a significant benefit of the probiotic vs placebo on the duration of antibiotic-associated diarrhoea only.²⁸ In contrast, 4 studies of 4 other probiotics reported no evidence that probiotics were effective in the prevention of antibiotic-associated diarrhoea vs placebo,^{34,45,77,84} although 1 of these (an underpowered study) showed a nonsignificant reduction in antibiotic-associated diarrhoea.⁸⁴ Of the 11 studies, 6 had been published since the original consensus. Of the 6 new studies, 3 (43%) reported no significant effect compared with 1 of the 5 studies (20%) in the original consensus. The 2 studies that assessed antibiotic-associated diarrhoea as only a

secondary endpoint (1 study from the original consensus and 1 new study) found no difference between the probiotic and placebo groups.^{29,76}

Statement 11: in patients receiving H. pylori eradication therapy, specific probiotics are helpful as adjuvant therapy to prevent or reduce the duration/intensity of associated diarrhoea. Agreement: 100% (6, 87.5%; 5, 12.5%; grade of evidence for effect: high).

Supportive evidence: Seven studies evaluated the effect of 9 different probiotics (at doses of between 2×10^6 and 2×10^{10} CFU per day) on diarrhoea as a side effect of *H. pylori* eradication therapy in 1480 patients. All the 5 studies examining *H. pylori* eradication therapy-associated diarrhoea as a primary endpoint (including 1 study published since the original consensus) reported a significant benefit of specific probiotic treatments compared with placebo.^{39-42,70} However, the results for 2 of the studies were mixed, with a significant benefit of the specific probiotic treatment seen after 1 week, but not 2 weeks, in 1 study,⁷⁰ and significantly fewer days with diarrhoea and a shorter mean duration of diarrhoea episodes, but no significant difference in the frequency of diarrhoea episodes, in the probiotic group compared with the placebo group in another study.⁴² Two studies (both published since the original consensus) were identified that assessed the occurrence of diarrhoea as a secondary endpoint, and both reported that the addition of probiotics to *H. pylori* eradication therapy significantly decreased diarrhoea as a side effect of treatment.^{27,52}

3.8 | Health-related quality of life

Statement 12: with specific probiotics, improvement of symptoms has been shown to lead to improvement in some aspects of health-related quality of life. Agreement: 87.5% (5, 25%; 4, 62.5%; 3, 12.5%; grade of evidence for effect: low).

Supportive evidence: Health-related quality of life (HRQoL) was assessed as a primary endpoint in 6 studies with 4 different probiotics (administered at doses of between 5×10^7 and 3×10^{10} CFU per day). Two studies of 2 different probiotics reported a significantly greater improvement in HRQoL with probiotics, as measured by an improvement in GI well-being in women with minor GI symptoms⁵¹ and improvements in scores using the Irritable Bowel Syndrome Quality of Life (IBS-QoL) instrument in patients with IBS,⁶⁵ compared with placebo. One study in patients with IBS-C reported no significant difference between the probiotic and placebo groups for the change from baseline in the discomfort dimension score of the Functional Digestive Disorders Quality of Life (FDDQL) questionnaire after 3 and 6 weeks of treatment; however, the probiotic group had a significantly greater proportion of responders for the discomfort dimension score than the placebo group at week 3.⁵⁰ Another study assessed 2 different probiotics in patients with FGID and found no significant differences between the probiotic and control groups for the Gastrointestinal Quality of Life Index (GIQLI) total score and well-being subscales (physical, social and mental; primary endpoint); however, use of the 36-item Short-Form Health Survey (SF-36; secondary endpoint) revealed significant improvements in

physical functioning and/or “role-physical” domains with probiotics, but no significant changes in the control groups.⁶² In 1 study, a significant reduction in “health-related worry” was observed in patients with IBS receiving the probiotic treatment vs placebo, but not in other domains of the IBS-QOL.³² The remaining study in women with minor GI symptoms found no significant difference in the percentage of women reporting an improvement in GI well-being with probiotics vs placebo.⁶⁷ Nineteen studies assessed aspects of HRQoL as secondary endpoints only. Fourteen of these (evaluating 12 different probiotics) found no difference between treatment groups in measures of HRQoL,^{30,31,36,54,56-58,80,82,83,85,86,88,92} whereas 5 studies (all in patients with IBS) reported significant benefits of 5 different probiotic treatments for some aspects of HRQoL.^{43,46,49,59,93}

3.9 | Adverse events

Statement 13: probiotics have a favourable safety profile in patients with a range of lower GI symptoms typically managed in primary care or general practice. Agreement: 100% (6, 50%; 5, 37.5%; 4, 12.5%; grade of evidence for effect: high).

Supportive evidence: Safety data were reported in 50 studies. The majority of studies revealed no meaningful treatment-emergent adverse events that were attributed to probiotic use. Forty-three studies found no relevant differences in safety between 37 specific probiotic treatments and placebo.^{30,31,34,35,37,39-42,44,45,47-50,53-57,59-63,65,68,69,72,74,77,78,80-84,90,92-96} Findings of the remaining 7 studies (examining 7 probiotic strains) are summarised below.

In 1 study of patients with IBS, 2 patients in the probiotic group discontinued involvement because of adverse events (moderate nausea and severe exanthema). However, the most frequent adverse events (fatigue, pruritus and diarrhoea) occurred equally often in the probiotic and placebo groups.⁴⁶ In another study of patients with IBS, 1 participant had a short stay in hospital for cervicobrachialgia 2 weeks after the end of the specific probiotic treatment; however, there was no organic explanation for this, and the patient continued in the trial.⁶⁴ Two patients with IBS treated with probiotics in a third study reported an itching rash, causing one patient to drop out.³⁶ A study of patients with IBS-C reported 16 adverse events, which were judged to be possibly linked to the research or to the study product by the investigators (10 events were reported in the active comparator group and 4 in the placebo group).⁸⁵ The dropout rate was significantly higher in the probiotic group than in the placebo group in the final study in patients with IBS ($P = 0.048$); however, most of the dropouts were due to noncompliance ($n = 5$), the requirement for an antibiotic ($n = 5$) or worsening of IBS symptoms ($n = 2$).⁸⁶ In a study of healthy athletes, there was a twofold increase in the number and duration of mild GI symptoms in the probiotic group compared with the placebo group, although the severity of these symptoms tended to be lower in the probiotic group than in the placebo group.⁹¹ In a study examining the effects of probiotics on antibiotic-associated diarrhoea, the incidence of nonserious adverse events in the probiotic group was 2.0% compared with 0%

in the placebo group. A causality assessment was carried out for all adverse events, and all were found to be of either probable or possible association.³⁸

4 | DISCUSSION

This is an update to the evidence-based ESPCG consensus published in 2013 on the role of probiotics in the management of lower GI symptoms in adults consulting in primary care. It aims to provide an overview of the role of probiotics in dealing with patients with a variety of abdominal problems, and the practical implications of consensus statements for physicians are shown in Table 3.

Data from the 33 newly identified publications, in addition to those in the original 37, significantly strengthened the evidence base on the role of probiotics in GI care in just over 5 years. In addition to information from new RCTs performed in patients with IBS, more data were identified in patient populations with other GI conditions (healthy individuals with minor GI complaints, patients with lactose intolerance and those receiving antibiotics or undergoing *H. pylori* eradication therapy). The number of probiotics included in the consensus increased from 32 to 54. After assessment of the evidence, no new statements were developed, and the wording of the original statements remained unaltered. The strength of evidence assessed using the GRADE system was graded as “high” for 5 statements, “moderate” for 2, “low” for 4 and “very low” for 2. It was maintained for all 5 statements previously rated as having a high level of evidence and 100% agreement, but reduced for 2 of the 4 statements previously rated as having moderate evidence and 70%-100% agreement, and 1 of the 3 statements previously rated as having low

TABLE 3 Practical implications of consensus statements for physicians

Grade of evidence for effect	Symptoms/indications	Meaning for physicians
High	Overall symptoms and abdominal pain in IBS Prevention or reduction of diarrhoea in patients receiving antibiotics Prevention or reduction of diarrhoea in patients receiving <i>Helicobacter pylori</i> eradication therapy	Probiotics with supportive evidence for benefit should be tried
Moderate	Bowel movements and bloating/distension in IBS	Probiotics with supportive evidence for benefit could be tried
Low	Overall symptoms in IBS-D Flatus in IBS Constipation in IBS	Probiotics with supportive evidence for benefit could be considered
Very low	Overall symptoms in IBS-C Diarrhoea in IBS	Currently no evidence to support use of probiotics

IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhoea-predominant IBS.

evidence and 60%–90% agreement reflecting the more heterogeneous evidence among the studies identified in the updated review.

There may be several explanations for the more diverse results reflected in the reduced grading of evidence in this review. The field is challenging owing to the varied nature of bowel symptoms and abdominal complaints, combined with the relatively undefined mode of action of the wide range of individual probiotic strains studied. As well as including a wider range of patients, different probiotics were assessed in the original and the updated review; of the 32 probiotics evaluated in the original manuscript, only 6 were assessed in publications from 2012 onwards. It may be that the 22 new probiotics evaluated in the updated review were less efficacious in producing a beneficial response than those assessed in the original manuscript. In addition, the more recent studies in this review included a larger number of secondary endpoints than the older studies. Because the studies were not powered to detect statistical significance in these endpoints, they may show false negative results.

The reduced strength of evidence for the beneficial effect of probiotics was reflected in the levels of agreement reached for several statements during the wider Delphi voting process. For example, although consensus was achieved for Statement 1 (“Specific probiotics help to relieve overall symptom burden in some patients with IBS”), the individual levels of agreement were lower in the updated consensus (“strongly agree”, 12.5%; “agree with minor reservation”, 87.5%) than in the original consensus (“strongly agree”, 40%; “agree with minor reservation”, 50%; “agree with major reservation”, 10%). There was a reduction in the number of voters choosing to “strongly agree” with Statement 13 (“Probiotics have a favourable safety profile in patients with a range of lower GI symptoms typically managed in primary care or general practice”), despite the updated review providing no additional evidence for an adverse safety profile of probiotics. This may reflect an awareness of the limited data on long-term safety in the GI community, despite a lack of published evidence suggesting safety issues in general populations.

There are, however, statements for which the new evidence appears to have improved the experts' confidence in the statements (Figure 2). For example, the proportion of the voting panel that “strongly agreed” with Statement 11 (“In patients receiving *H. pylori* eradication therapy, specific probiotics are helpful as adjuvant therapy to prevent or to reduce the duration/intensity of associated diarrhoea”) increased from 60% in the original Delphi consensus to 87.5% in the update. This reflects the results of 2 additional RCTs identified in the updated systematic review that increased to 7 the number of RCTs showing a significant beneficial effect of a probiotic on treatment-induced diarrhoea vs placebo. For Statement 9 (“Probiotics tested to date do not reduce diarrhoea in patients with IBS”), confidence increased for a negligible effect of the probiotic vs placebo.

When focusing on primary endpoint data, the overall evidence for the beneficial effect of probiotics was strong. For example, 30 publications reported the effects of specific probiotics vs placebo on overall lower GI symptoms as a primary or secondary endpoint (23 in patients with IBS in general [included in Statement 1]); 14 of

these studies reported a significant improvement with probiotics vs placebo (61%). When publications which reported overall lower GI symptoms in patients with IBS as a primary endpoint were assessed (15 studies), 10 found a significant benefit of probiotics vs placebo (67%). A similar pattern was observed for other symptoms, with a significant benefit of probiotics compared with placebo being observed in a greater proportion of studies evaluating the symptom as a primary endpoint than as any endpoint (abdominal pain: 40% any endpoint, 78% primary endpoint; constipation: 36% any endpoint, 50% primary endpoint; bowel habit: 56% any endpoint, 63% primary endpoint; HRQoL: 40% any endpoint, 83% primary endpoint).

Although there is an abundance of data supporting the use of multiple strains of probiotics for the relief of lower GI symptoms, large meta-analyses are difficult to carry out owing to the lack of comparable data available on single specific probiotic strains. Strictly speaking, they should only be performed on data for the same organism at comparable doses. There are inherent problems with meta-analyses that compare combinations of multiple probiotic strains because they make it difficult to establish the exact role of individual strains in the management of IBS symptoms and the extent of their contribution to the efficacy of the composite probiotics. Comparisons of different strains may also dilute any positive effect of individual probiotics; however, many of these analyses have shown a beneficial effect of probiotic products.^{97–102}

For meta-analysis, it is more scientifically valid to include RCTs in which participants are allocated the same single-strain probiotic and compared with a placebo. Several recent small meta-analyses have been performed that examine the effects of specific individual probiotics on lower GI symptoms using data from the studies identified in our systematic review, with results showing a beneficial effect of probiotics over placebo. A systematic review and meta-analysis evaluated the effects of fermented milk with *Bifidobacterium animalis* subsp. *lactis* CNCM I-2494 (DN-173 010) and lactic acid bacteria on GI discomfort in the general adult population.¹⁰³ The systematic review identified 3 RCTs (2 of which were eligible for inclusion in our review).^{51,67} Individual data from 598 participants were evaluated in meta-analyses using random-effects models. Results from the analyses showed that consumption of the specific probiotic was associated with a significant improvement in overall GI discomfort (based on responder/nonresponder status) compared with placebo (odds ratio [OR]: 1.48; 95% confidence interval [CI]: 1.07–2.05). The study also found that the probiotic was superior to placebo in terms of reducing digestive symptoms, as measured using a composite score. A meta-analysis of the effect of *Saccharomyces cerevisiae* CNCM I-3856 on GI symptoms in patients with IBS used data from 2 trials^{74,85} (both of which are included in our review). The authors reported that patients consuming the probiotic had a significantly higher chance of reduction in abdominal pain/discomfort ($P = 0.0134$) and improvement in stool consistency ($P = 0.0003$) than those consuming placebo.¹⁰⁴ Another recent meta-analysis examined the effects of the probiotic *Bifidobacterium longum* subsp. *infantis* 35624 in patients with IBS.¹⁰⁵ Analysis of data from the 5 studies that met the inclusion criteria (3 of which are included in our

review)^{37,61,92} showed that consumption of single probiotic *B. infantis* did not impact on GI symptoms, whereas patients who received composite probiotics containing *B. infantis* had significantly reduced abdominal pain and bloating/distention. Other recently published meta-analyses have examined whether probiotics are of benefit in the prevention of *Clostridium difficile* infection, reporting both positive¹⁰⁶ and negative^{107,108} results.

The current systematic review found strong evidence for the beneficial effect of probiotics in the prevention of diarrhoea in *H. pylori* eradication therapy. All the 6 identified studies showed a reduction in diarrhoea with probiotic consumption vs placebo. This is supported by the results of 2 recent meta-analyses that each examined the effects of a variety of probiotics on *H. pylori* eradication rates (primary endpoint) and diarrhoea associated with *H. pylori* eradication therapy (secondary endpoint).^{109,110} The first, a meta-analysis of 13 studies (1 of which is included in the current review)⁵² involving a total of 2306 patients, found a reduced risk of diarrhoea in the probiotic group compared with the placebo group (risk ratio [RR]: 0.51; 95% confidence interval [CI]: 0.31-0.84; $P = 0.008$).¹¹⁰ *Lactobacillus* alone (RR: 1.24; 95% CI: 1.12-1.38; $P < 0.0001$) and multi-strain probiotics (RR: 1.12; 95% CI: 1.07-1.18; $P < 0.00001$) were effective at improving *H. pylori* eradication rates compared with placebo. Similarly, the second meta-analysis, which involved 4515 patients from 30 RCTs (5 of which are included in this systematic review),^{40,41,52,70,84} found a significant reduction in the risk of diarrhoea with the addition of probiotics to standard triple therapy compared with triple therapy alone (RR: 0.549; 95% CI: 0.391-0.771; $P = 0.001$). The addition of probiotics to standard triple therapy also significantly increased *H. pylori* eradication rates compared with triple therapy alone ($P < 0.001$).¹⁰⁹

Our expert consensus panel made 3 general recommendations for practising clinicians. We recommend that specific probiotics have a role in the management of some IBS symptoms and can also be used as an adjunct to conventional treatment. We also recommend that probiotic strains should be selected based on the patient's symptoms, the clinical indication and the available evidence; no probiotic alleviates the full range of symptoms in IBS. Finally, we recommend that, when trying a probiotic therapy for a chronic GI problem, the product should be taken for 1 month; dose selection should be based on available evidence and manufacturers' recommendations. These general, pragmatic recommendations for daily practice were included in the original consensus as Statements 14, 15 and 16, respectively; when the updated evidence was presented to the voting panel for the current consensus, the level of agreement with these 3 statements increased from that obtained in the original consensus, in terms of both overall agreement (which reached 100% for Statements 14 and 16) and the proportion of respondents voting to "strongly agree" with the statements (Figure 2 and Table S2).

To enable the current publication to be as up to date as possible and to avoid a time lag, 6 publications identified in the updated June 2017 database search did not undergo the Delphi consensus process. This could have had an impact on the levels of agreement of the voting panel. However, these publications were reviewed by the

Steering Committee, members of which judged that the new evidence was in line with that previously reported and concluded that exclusion of the more recent publications would make little or no difference to the levels of agreement within the Delphi consensus. As in the original systematic review, only studies that were randomised, placebo-controlled clinical trials of probiotics with suitable follow-up periods were included in the analysis in an attempt to obtain the highest quality data. Publications included in both the original and updated systematic reviews were subjected to quality assessment using the CASP checklist for RCTs.²⁴ This was carried out at the suggestion of the Steering Committee to allow the wider Delphi voting panel to judge the quality of the presented evidence and to use this to aid their decision-making. The majority of the publications (67%) were classified as being of "high quality" or above. Despite the inclusion of adequately powered, high-quality studies, the results remain diverse. Variations in probiotic strain(s), doses and modes of administration, the health status of patients, and diet and concomitant medications (eg antibiotics and antacids) make comparisons between probiotics difficult.

Studies that did not strictly fit into the statement categories were excluded from those statements. For example, 1 study reported that *B. lactis* CNCM I-2494 (DN-173 010) produced a significant reduction in the "composite score of digestive symptoms" when it was administered to healthy women reporting minor digestive symptoms compared with those receiving a control dairy product ($P < 0.05$; secondary endpoint).⁶⁷ However, this study was not included in the evidence base for Statement 1 because the statement focused on patients with IBS only. Only a small subset of the studies identified in the systematic review examined probiotics in healthy individuals, or patients with lactose malabsorption, other functional GI problems or mild lower GI symptoms; hence, specific statements were not prepared for these groups.

Other limitations of the current update that also applied to the original consensus¹ are as follows: the potential for publication bias; the potential for chance findings in secondary endpoints; the focus on adults (statements cannot be extended to children); and the presentation of physicians' rather than patients' perspectives. Overall, the studies identified in this systematic review, which were powered for specific primary endpoints, reported evidence supporting the effectiveness of probiotics for the relief of lower GI symptoms (especially overall GI symptom score, abdominal pain and bowel habit), improvement of HRQoL, and prevention of both antibiotic-associated diarrhoea and diarrhoea associated with *H. pylori* eradication therapy. For safety outcomes, probiotics were comparable to placebo. When this evidence was presented to clinical experts, the panel reached consensus.

In the past 5 years, since the original review, the evidence for the effects of probiotics on lower GI symptoms has doubled. After evaluation of this evidence using the same rigorous methodology as before, the statements remain the same, and consensus was reached. This demonstrates that clinicians can remain confident that specific probiotics have a role in the management of lower GI symptoms.

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AUTHORSHIP

Guarantor of the article: APSH initiated the project.

Author contributions: APSH, CRM, CM, OC, PW, CW and NdW performed the updated literature searches. APSH, BF, CM, CRM, OC, PW, LA, PF, CL, JM, J-MPdF, CW, K-AW and NdW took part in the screening and analysis of the retrieved references. APSH, CRM, PW and NdW reviewed the original wording of statements in the light of new evidence. BF, PW, PF, CL, JM, J-MPdF, K-AW and NdW voted on the statements. CRM and OC were involved in the execution and collation of results from the Delphi voting process. CRM and CW prepared an outline and revised subsequent drafts of the paper. APSH, BF, CM, CRM, OC, PW, LA, PF, CL, JM, J-MPdF, CW, K-AW and NdW revised the outline and subsequent drafts of the paper. All authors have approved the final version of the article, including the authorship list.

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

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APPENDIX 1

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