Treating vaginitis with probiotics in non-pregnant females: A systematic review and meta-analysis

HUEY-SHENG JENG^{1,2}, TSONG-RONG YAN¹ and JING-YI CHEN³

¹Department of Chemical Engineering and Biotechnology, Institute of Chemical Engineering and Biotechnology, Tatung University, Taipei 10452; ²Department of Urology, Zhong-Xing Branch, Taipei City Hospital, Taipei 10341; ³School of Medicine for International Students, College of Medicine, I-Shou University, Kaohsiung 82445, Taiwan, R.O.C.

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Abstract. Vaginitis, also known as vulvovaginitis, is an inflammation of the vagina and vulva and a common disease in females. It is thought to be caused by vaginal dysbiosis and improved by probiotics. Bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC) are the major types of vaginal infections. The present systematic review and meta-analysis aimed to clarify the efficacy of probiotics in the treatment of common vaginal infections in non-pregnant females. Literature on randomized controlled trials and two-armed prospective studies on any intervention with probiotics published until December 24th, 2018 was searched in the PubMed, Cochrane and EMBASE databases. The outcomes of interest were recurrence rate, cure rate, remission rate and normal vaginal flora restoration. Finally, a total of 30 studies on bacterial vaginosis (BV) and/or VVC were included and stratified into 3 study types based on treatment design as follows: Type I, antibiotic/probiotics vs. antibiotics/antifungals (22 studies); Type II, probiotics vs. placebo (5 studies); Type III, probiotics vs. antibiotics (3 studies). The type I studies comprised 1,788 non-pregnant females and had the highest inter-study comparability in post-treatment follow-up design and meta-analysis outcome data. Probiotics interventions were significantly associated with a lower recurrence rate of vaginitis [pooled odds ratio (OR)=0.27, 95% CI: 0.18-0.41, P<0.001] and higher cure/remission rate (pooled OR=2.28, 95% CI: 1.20-4.32, P=0.011). However, a significant increase in normal vaginal flora after probiotic treatment was observed only in BV (pooled OR=4.55, 95% CI: 1.44-14.35, P=0.01). In addition, supportive but heterogeneous results were obtained from the 6-month follow-up data of Type-I studies, different infection types and supplementary analysis of Type-II studies. In conclusion, probiotics have a significant short-term effect in the treatment of common vaginal infections in non-pregnant females. In order to evaluate the long-term effects of probiotics in common vaginal infections, it is worthwhile to perform higher-quality clinical trials in the future.

Introduction

Vaginal infections of bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC) are common in females, accounting for almost 80% of all cases of vaginitis also known as vulvovaginitis, is an inflammation of the vagina and vulva. Symptoms may include itching, burning, pain, discharge and a bad odor (1,2). While BV is generally regarded as a mild disease, it has been indicated to be associated with the occurrence of endometritis and pelvic inflammatory disease in females without clinical symptoms of BV and may lead to spontaneous abortion, premature rupture of the membranes, and premature delivery during pregnancy (2,3). VVC results from overgrowth of one or more types of yeast organism (e.g., Candida albicans) that normally inhabit the vaginal mucosa in small numbers, and symptoms include external dysuria, pruritus, redness and flocculant vaginal discharge (2,4). In most cases, standard treatments with antibiotics or anti-fungals are effective for BV and VVC. However, the use of antibiotics may cause physiological and non-physiological changes in patients, and interfere with the balance of the normal vaginal microbiota. Thus, the common side-effects of antibiotic treatment are characterized by reduction or depletion of the Lactobacillus species and the excessive growth of Candida species. In addition, excessive use of antibiotics frequently causes the emergence of resistant strains.

Probiotics are defined as 'live microorganisms when administered in adequate amounts confer a health benefit to the host' (5). Over the past 2 decades, accumulating evidence has indicated that the intestinal and urogenital microflora has a central role in maintaining the health of human beings (5). In addition, the use of beneficial bacteria to improve dysbiosis by replacing pathogenic bacteria or augmenting normal microflora

Correspondence to: Professor Tsong-Rong Yan, Department of Chemical Engineering and Biotechnology, Institute of Chemical Engineering and Biotechnology, Tatung University, Number 40, Section 3, Zhongshan North Road, Taipei 10452, Taiwan, R.O.C. E-mail: tryan@gm.ttu.edu.tw

Abbreviations: BV, bacterial vaginosis; VVC, vulvovaginal candidiasis; UTI, urinary tract infection

Key words: probiotics, *Lactobacillus*, vaginitis, bacterial vaginosis, vulvovaginal candidiasis, meta-analysis

has been gradually accepted and proven useful in conditions including necrotizing enterocolitis and antibiotic-resistant infections (5). The intestinal, vaginal and urethral microflora have an important role in maintaining health and preventing gynecologic infections in females, and the use of probiotics has been extended to the treatment of refractory cases of female urogenital infections (5).

The use of probiotics has been examined in a number of studies over the past 2 decades as a method of treating and reducing the risk and recurrence rate of gynecologic infections in females, particularly in whom standard treatments are not effective. Probiotics may protect the vagina from pathogen colonization through a number of mechanisms, including blocking potential sites of attachment, production of microbiocidal substances, e.g. hydrogen peroxide, maintenance of a low pH and induction of anti-inflammatory cytokine responses in epithelial cells (3-5). The most common probiotics used in female patients are of the *Lactobacillus* species (3-5).

While numerous clinical trials have been performed to determine the effectiveness of probiotics for the treatment of vaginal infections, the results have generally been inconsistent, with certain studies suggesting an excellent response and other indicating no effect. Meta-analyses have also provided inconsistent results. A meta-analysis by Huang et al (3) from 2014 indicated that probiotic supplementation improves the cure rate for BV. Other previously published systematic reviews have suggested that the use of probiotics remains controversial in preventing BV and VVC in adult females due to evidence limitations (4,6,7). Potential bias on the benefits of probiotics cannot be ruled out, as the majority of evidence came from small-scale studies, heterogeneous populations, different lengths of follow-up and inhomogeneous treatment designs among the study. Similar views were also expressed by a recently published systemic review by Hanson et al (4) from 2016 with a focus on urogenital infections in non-pregnant females, highlighting the requirement of carefully-planned study stratification upon meta-analysis.

The purpose of the present study was to perform a meta-analysis of randomized controlled trials (RCTs) and two-armed prospective studies identified by a thorough systematic review and meta-analysis of adequately-selected literature to determine the effect of probiotics for the treatment of common vaginal infections in non-pregnant adult females.

Materials and methods

Literature search strategy and inclusion criteria. The present systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (8). On December 24th, 2018, the Pubmed, Cochrane and EMBASE databases were searched for all studies published previously using the following key words: 'Probiotics', 'Lactobacillus', 'urogenital infections', 'bacterial vaginosis', 'vulvovaginitis', 'vaginitis' and 'candidiasis'. The search strategy was (probiotics or Lactobacillus) and (vaginosis or vulvovaginal candidiasis or vaginitis or vulvovaginitis or urogenital infections). Articles of interest were also hand-searched for potentially relevant studies. Searches were performed by 2 independent reviewers (HSJ and JYC) and any disagreements were resolved by a third reviewer (TRY). Inclusion criteria for the analysis were as follows: i) RCTs and two-armed prospective studies; ii) studies including females with a current or history of gynecologic infections of BV and/or VCC; iii) studies that examined probiotic treatment vs. non-probiotics treatment (control) with or without antibiotics; iv) studies that provided quantitative data of the outcomes of interest; and v) full-text articles published in English or Chinese. Exclusion criteria were as follows: i) Retrospective studies, cohort studies, case series, letters, comments, editorials, case reports, proceedings, personal communications and one-arm studies; ii) studies on pediatric patients, pregnant females or males; iii) studies on healthy females with/without a history of recurrent urogenital infections. Studies designed to examine Lactobacillus treatment in combination with estriol, probiotic agents containing an unknown number of Lactobacilli or a mixture of multiple types of non-Lactobacillus bacteria were also excluded.

Data extraction. The following information/data was extracted from studies that met the inclusion criteria: Name of the first author, year of publication, study design, number of participants in each group, participants' age, type of infection, type of interventions, probiotic agents, probiotic administration, length of follow-up period and major outcomes (recurrence rate, cure/remission rate and/or the rate of restoring normal vaginal flora).

Quality assessment. The quality of the RCTs included was assessed using the Cochrane 'assessing risk of bias' table, which consists of 6 domains (random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting risk) (9). The quality of non-RCTs was assessed using a Cochrane risk of bias assessment tool for non-randomized studies of interventions (ACROBAT-NRSI) (10). This tool assesses 7 sources of bias associated with confounding, selection of participants, measurement of interventions, departures from intended interventions (10), missing data, measurement of outcomes and selection of the reported result.

Statistical analysis. Outcome measures for the meta-analysis were recurrence rate, cure and/or remission rate and restoration rate of normal flora. The odds ratios (ORs) with 95% CIs were calculated for each individual study and for all the studies combined. ORs of <1 for recurrence and ORs of >1 for cure and/or remission rate and normal flora restoration rate indicated that the probiotic group was favored. By contrast, ORs of >1 for recurrence and ORs of <1 for cure and/or remission rate and normal flora restoration rate indicated the control group was favored. OR=1 indicated that the probiotic and control groups had comparable outcomes. A χ^2 -based test of homogeneity was performed and the inconsistency index (I²) and Q-statistics were determined. A random effect model (DerSimonian-Laird method) was considered for the meta-analysis if either the Q statistic of P<0.10 or I^2 value of >50% were derived; otherwise, a fixed effect model (Mantel-Haenszel method) was considered for the meta-analysis (11). Heterogeneity determined using the I² statistic was defined as follows: 0-24%, no heterogeneity; 25-49%, moderate heterogeneity; 50-74%, high heterogeneity;

and 75-100%, extreme heterogeneity. When the number of studies included in a meta-analysis is small, heterogeneity tests have low statistical power (12) and in this situation, a random-effects model of analysis is used (13). The National Research Council recommends the use of random-effects approaches for meta-analysis and the exploration of sources of variation in study results (14). Pooled effects were calculated and a 2-sided P<0.05 was considered to indicate statistical significance. Sensitivity analysis was performed using the leave-one-out approach to test the validity and robustness of the major results (12). All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat).

Results

Literature search. A flow diagram of the study selection process is provided in Fig. 1. A total of 771 articles were identified by database- and hand-searching with duplicates removed. After screening by title and abstract, 682 articles were excluded based on inclusion and exclusion criteria. The full text of the remaining 89 articles was reviewed and 59 were further excluded for reasons presented in Fig. 1. The remaining 30 articles were included in the qualitative synthesis, including 20 studies for BV alone or with other pathogens (15-34), 10 studies for VVC alone (31,35-43) and 1 study for BV/VVC (44).

Characteristics of the reviewed studies. Studies were categorized into three types based on treatment design (Table I): Type I, antibiotics plus Lactobacillus (probiotic) vs. antibiotic with or without placebo (control; n=22) (15,17,18,20,22-26,29,31,32,35-41); type II, Lactobacillus (probiotic) vs. placebo (control; no antibiotics; n=5) (19,21,27,33,34); and type III, Lactobacillus (probiotic) vs. antibiotic (control; n=3) (16,28,30). A summary of the patients' characteristics and interventions for the treatment of BV and/or VVC is provided in Table I. The age range of the female patients included in the analysis was between 18 to 50 years. Table II presents a summary of the outcomes of the studies included. Table III provides a summary of the type of probiotic and the route and dose of administration for the treatment of vaginitis. Probiotic species included L. rhamnosus BMX54, L. fermentum, L. plantarum, L. gasseri, L. plantarum, L. acidophilus, L. brevis CD2, L. salivarius subsp. Salicinius, L. delbrueckii subsp. lactis, L. reuteri, P. acidilactici, L. casei rhamnosus, L. reuteris, B. bifidum, B. longum, L. crispatus and Lactobacillus GG either alone or in various combinations depending on the infection being treated. The route of administration included oral capsule, vaginal tablet and vaginal capsule (Table III).

Meta-analysis. The detailed treatment outcomes of all studies reviewed are summarized in Table II. The majority of studies adopted a type I treatment design for BV and/or VVC infections and those with 1- and/or 6-months follow-up data were included in the meta-analysis. These comprised of a total of 21 articles (10 articles on BV, 9 studies on VVC and 2 on BV/VVC) (15,17,18,20,22-26,29,31,32,35-41). The total number of patients evaluated in the 21 type I studies was 1,788 (probiotic test group, n=910; control group, n=878). These type I studies were the major focus of the present meta-analysis,



Figure 1. Flow diagram of study selection in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

while type II and III studies were analyzed separately for supplementation.

With respect to recurrence at 1 month after treatment, 9 studies [2 on BV alone (15,26), 5 on VVC alone (37,38,40,42,43) and 2 on BV/VVC (31,44)] with complete quantitative data were included in the present meta-analysis. A total of 1,220 patients were evaluated (probiotic test group, n=631; control group, n=589). There was no heterogeneity present among all 9 studies or those on either BV or VVC (total: Q=11.82, I²=24%; BV: Q=2.14, I²=7%; VVC: Q=1.86, I²=0%; Fig. 2A). The analysis indicated that patients in the probiotic group had a significantly lower recurrence rate than those in the control group (pooled OR=0.27, 95% CI: 0.18-0.41; Fig. 2A). A favorable outcome associated with the probiotics group was also observed when analyzing BV and VVC individually (BV: Pooled OR=0.10, 95% CI: 0.04-0.26; VVC: Pooled OR=0.27, 95% CI: 0.16-0.45; all P<0.001; Fig. 2A). However, there was no significant difference in the recurrence rate between the probiotic and control groups at 6 months after treatment (Fig. 2A).

With respect to cure or remission after treatments, a total of 12 studies were included. These comprised 12 studies with 1-month follow-up results [6 for BV alone (15,18,23,24,26,29), 4 for VVC alone (37,38,40,42) and 2 for BV/VVC (31,44)] and 2 studies (22,24) with 6-month follow-up for BV alone. In the 12 studies with 1-month follow-up outcomes, 1,643 patients in total were evaluated (probiotic test group, n=836; control group, n=807). There was moderate to high heterogeneity among the 12 studies with 1-month follow-up (total: Q=52.69, I²=77%; BV: Q=47.02, I²=87. %; VVC: Q=5.45, I²=27%), as well as between studies with 6-month follow-up (Q=1.70, I²=40%).

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First autnor (publication year)	Study design	Grouping	of patients	Age (years)	Diagnosis	Diagnostic standard	Intervention	Follow-up time	(Refs.)
Laue (2018)	RCT	Probiotic Control	18 18	32.6 39	BV	Amsel criteria	Metronidazole plus <i>Lactobacillus</i> Metronidazole plus placebo	4 weeks	(23)
Davar (2016)	RCT	Probiotic Control	28 31	32.3 31.1	VVC	Symptoms and positive culture	Fluconazole plus probiotic tablet Fluconazole plus placebo	6 months	(36)
Recine (2016)	Prospective	Probiotic Control	125 125	29.3 29.5	BV	≥3 of Amsel criteria ^ª	MTZ plus <i>Lactobacillus</i> MTZ plus placebo	9 months	(32)
Heczko (2015)	RCT	Probiotic Control	73 81	18-50	BV/AV	Clinical signs, NS ^b	MTZ plus <i>Lactobacillus</i> MTZ plus placebo	NA	(20)
Bradshaw (2012)	RCT	Probiotic Control	140	27° 27°	BV	NS 7-10 or ≥3 of Amsel criteria and NS 4-10	MTZ plus clindamycin cream MTZ plus vaginal pessary containing <i>Lactobacillus</i>	6 months	(17)
Nouraei (2012)	RCT	Clindamycin Probiotic	135 45	27° 18-40	VVC	Symptoms and culture	M1Z plus placebo vagınal pessary Fluconazole plus probiotic	5-7 days	(41)
		Control	45				Fluconazole plus placebo		
Ehrström (2010)	RCT	Probiotic Control	60 35	18-45	BV/VVC	≥3 Amsel criteria	Antibiotics plus vaginal capsule containing <i>Lactobacillus</i> Antibiotics plus placebo vaginal capsule	1 menstruation	(44)
Marcone (2010)	RCT	Probiotic Control	24 25	N/A	ΒV	Fulfilled all Amsel criteria	MTZ plus <i>Lactobacillus</i> tablet MTZ plus placebo tablet	12 months	(25)
Anukam (2009)	RCT	Probiotic Control	19 7	18-50	VVC	Positive culture	Fluconazole plus <i>L. rhamnosus</i> GR-1 Fluconazole plus placebo capsule	3 months	(35)
Martinez (2009a)	RCT	Probiotic Control	32 32	N/A	ΒV	≥3 Amsel criteria or NS 7-10	Tinidazole plus <i>Lactobacillus</i> Tinidazole plus placebo capsule	28 days	(26)
Martinez (2009b)	RCT	Probiotic Control	29 26	29.1±7.5 26.9±7.8	VVC	Symptoms and positive culture	Fluconazole plus <i>L. rhamnosus</i> GR-1 and <i>L. reuteri</i> RC-14 Fluconazole plus placebo	4 wks	(43)
Yang (2009)	RCT	Probiotic Control	44 24	36 (range: 25-48)	VVC	Symptoms and microscopy	Clotrimazole plus Lactobacillus Clotrimazole	30 days	(42)
Hua (2008)	RCT	Probiotic Control	118 117	28.45	VVC	Symptoms and microscopy	Miconazole plus Lactobacillus Miconazole	33-37 days	(38)
Larsson (2008)	RCT	Probiotic Control	50 50	34.3	BV	Amsel criteria	Clindamycin plus Lactobacillus Clindamycin plus placebo	6 months	(22)

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publication year)	Study design	Grouping	of patients	Age (years)	Diagnosis	Diagnostic standard	Intervention	Follow-up time	(Refs.)
Marcone (2008)	RCT	Probiotics Control	42 42	18-40	BV	Fulfilled all Amsel criteria	MTZ plus <i>Lactobacillus</i> tablet MTZ plus placebo tablet	1 month	(24)
Petricevic (2008)	RCT	Probiotics Control	83 88	32.6	ΒV	NS 7-10	Clindamycin plus <i>Lactobacillus</i> Clindamycin plus placebo	1 month	(29)
Ma (2007)	RCT	Probiotics Control	54 54	26	VVC	Symptoms and microscopy	Miconazole plus <i>Lactobacillus</i> Miconazole	NA	(39)
Mai (2007)	RCT	Probiotics Control	85 84	30.1 (range: 20-47)	VVC	Symptoms and microscopy	Clotrimazole plus <i>Lactobacillus</i> Clotrimazole	30 days	(40)
Anukam (2006a)	RCT	Probiotic	65	18-44	BV	NS 7-10 and positive BV Blue test	MTZ plus Lactobacillus tablet	30 days	(15)
		Control	60				MTZ plus placebo tablet		
Han (2006)	RCT	Probiotic Control	86 90	37 (range: 19-48)	VVC	Symptoms and microscopy	Clotrimazole plus <i>lactobacillus</i> capsule Clotrimazole	30 days	(37)
Lin (2006)	RCT	Probiotic Control	32 30	30 (range: 20-44)	Trichomonial Vaginitis	Microscopy	MNZ plus lactobacillus capsule	30 days	(31)
		Probiotic Control	53		VVC	Microscopy	Cretrozole plus lactobacillus capsule		
		Probiotic	59 51		ΒV	Amsel criteria	MNZ plus Lactobacillus capsule		
Eriksson (2005)	RCT	Probiotics	91	32°	BV	≥3 Amsel criteria	Clindamycin plus tampons containing	NA	(18)
		Control	96	32°			Lacrobactuus Clindamycin plus placebo tampons		
B, Type II studies:	Lactobacillus (p	robiotic) vs. p	lacebo (contre	ol)					
First author			Number	Φue		Disease			
(publication year)	Study design	Grouping	of patients	(years)	Diagnosis	Diagnostic standard	Intervention	Follow-up time	(Refs.)
Vicariotto (2014)	RCT	Probiotic Control	24 10	34.7	BV	≥3 of Amsel criteria or NS 7-10	Lactobacillus Placebo tablet	56 days	(33)
Vujic (2013)	RCT	Probiotic Control	395 149	N/A	BV and Other vaginal infections	≥3 Amsel criteria or NS 7-10	<i>Lactobacillus</i> capsule Placebo capsule	44.16 days	(34)

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			NT			Disease			
rurst author (publication year)	Study design	Grouping	of patients	Age (years)	Diagnosis	Diagnostic standard	Intervention	Follow-up time	(Refs.)
Hemalatha (2012)	RCT	Probiotic Control	34 27	N/A	BV	NS 7-10	Lactobacillus Placebo tablet	9 days	(21)
Mastromarino (2009)	RCT	Probiotics Control	18 16	33 35	BV	NS 7-10	Vaginal tablets containing Lactobacillus Placebo vaginal tablets	2 weeks	(27)
Hallen (1992)	RCT	Probiotics Control	28 29	24	BV	≥3 Amsel criteria	Vaginal tablets containing <i>Lactobacillus</i> Placebo vaginal tablets	7-10 days; 20-40 days	(19)
C, 1) pe III audica. Lat	vid) common			form		Disease			
First author (publication year)	Study design	Grouping	Number of patients	Age (years)	Diagnosis	Diagnostic standard	Intervention	Follow-up time	(Refs.)
Ling (2013)	RCT	Probiotic Control	25 30	N/A	BV	Amsel criteria and NS	Intravaginal <i>Lactobacillus</i> MTZ	30 days	(30)
Anukam (2006b)	RCT	Probiotic Control	20 20	N/A	BV (Symptomatic)	NS7-10 and positive BV Blue test	Lactobacillus capsule MTZ	30 days	(16)
Parent (1996)	RCT	Probiotics Control	16 16	31.1 34.4	BV	≥3 Amsel criteria	<i>Lactobacillus</i> tablet MTZ plus placebo tablet	28 days	(28)

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Table I. Continued.

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Table II Niimmary	of the olifcomes	in the meta-analysis	2
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А,	Type I	
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First author (year)	Disease type	Patients (n)	Intervention	Recurrence	Cure/remission	Restored normal flora	(Refs.)
Laue (2018)	BV	18 18	Probiotic Control		16 (100) 13 (76.5)		(23)
Davar (2016)	VVC	28 31	Probiotic Control	2 (7.2) 11 (35.5)			(36)
Recine (2016)	BV	125 125	Probiotic			2 mo: 113 (90.4) 6 mo: 106 (74.6) 9 mo: 118 (79.7) 2 mo: 99 (79.2)	(32)
						6 mo: 36 (25.4) 9 mo: 30 (20.3)	
Heczko (2015)	BV/AV	73 81	Probiotic Control	33 (45.2) 38 (47.0)			(20)
Bradshaw (2012)	BV	140 133 135	Clindamycin Probiotic Control	42 (30) 37 (27.8) 36 (26.7)		92 (65.7) 63 (47.4) 63 (46.7)	(17)
Nouraei (2012)	VVC	45 45	Probiotic Control		42 (93.3) 37 (82.2)		(41)
Ehrström (2010)	BV/VVC	60	Probiotic	1 mo: 13 (22.4) 2 mo: 23 (38.1) 6 mo: 35 (58.4)	1 mo: 47 (78)		(44)
		35	Control	1 mo: 10 (29.4) 2 mo: 13 (38.1) 6 mo: 20 (56.6)	1 mo: 25 (71)		
Marcone (2010)	BV	24 25	Probiotic Control			6 mo: 18 (74) 12 mo: 16 (69) 6 mo: 24 (96)	(25)
			connor			12 mo: 23 (91)	
Anukam (2009)	VVC	19 7	Probiotic Control		15 (79) 3 (43)		(35)
Martinez (2009a)	BV	32 32	Probiotic Control	4 (12.5) 15 (46.9)	28 (87.5) 16 (50)	24 (75) 11 (34.4)	(26)
Martinez (2009b)	VVC	29 26	Probiotic Control	3 (10.3) 10 (38.5)			(43)
Yang (2009)	VVC	44 42	Probiotic Control	3 (7.1) 7 (16.7)	42 (92.86) 38 (83.33)		(42)
Hua (2008)	VVC	118 117	Probiotic Control	4 (4.8) 11 (13.9)	83 (70.34) 79 (67.52)		(38)
Larsson (2008)	BV	50 50	Probiotics Control		24 (64.9) 18 (46.2)		(22)
Marcone (2008)	BV	42	Probiotics		1 mon: 22 (96) 6 mon: 23 (98)	30 d: 37 (88) 90 d: 37 (88) 180 d: 35 (83)	(24)
		42	Control		1 mon: 21 (91) 6 mo: 17 (74)	30 d: 34 (81) 90 d: 30 (71) 180 d: 28 (67)	
Petricevic (2008)	BV	83 88	Probiotics Control		1 mon: 83 (100) 1 mon: 35 (39.8)	69 (83.1) 31(35.2)	(29)
Ma (2007)	VVC	54 54	Probiotics Control		46 (85.2) 38 (70.4)		(39)
Mai (2007)	VVC	85 84	Probiotics Control	5 (5.9) 13 (15.5)	80 (94.1) 70 (83.3)		(40)

Table II. Continued.

Α.	Type	I
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	Disease					Restored	
First author (year)	type	Patients (n)	Intervention	Recurrence	Cure/remission	normal flora	(Refs.)
Anukam (2006a)	BV	65	Probiotic	0 (0)	8 (12)	57 (88)	(15)
		60	Control	17 (28)	19 (32)	24 (40)	
Han (2006)	VVC	86	Probiotic	3 (3.9)	74 (96.10)		(37)
		90	Control	9 (13.0)	60 (86.96)		
Lin (2006)	VVC	53	Probiotic	2 (3.8)	52 (98.1)		(31)
		52	Control	13 (25.0)	49 (94.2)		
Lin (2006)	BV	59	Probiotic	1 (1.7)	58 (98.3)		(31)
		51	Control	12 (23.5)	47 (92.2)		
Eriksson (2005)	BV	91	Probiotics		52 (56.8)		(18)
		96	Control		58 (60.2)		

B, Type II

First author (year)	Disease type	Patients (n)	Intervention	Recurrence	Cure/remission	Restored normal flora	(Refs.)
Vicariotto (2014)	BV	24	Probiotic	Day 28: 2 (8.3) Day 56: 4 (16.7)	Day 28: 22 (91.7) Day 56: 20 (83.3)		(33)
		10	Control	Day 28: 8 (80) Day 56: 9 (90)	Day 28: 2 (20) Day 56: 1 (10)		
Vujic (2013)	BV and other infection	395	Probiotic			1.5 mo: 243 (61.5) 3 mo: 202 (51.1)	(34)
		149	Control			1.5 mo: 40 (26.8) 3 mo: 31 (20.8)	
Hemalatha (2012)	BV	34	Probiotic	7 (21)		11 (32)	(21)
Mastromarino (2009)	BV	27 18 16	Probiotics Control	7 (26)	11 (61) 3 (18.75)	9 (50) 1 (6.25)	(27)
Hallen (1992)	BV	28	Probiotics		7-10 d: 16 (57.1) 20-40 d: 0 (0)		(19)
		29	Control		7-10 d: 3 (10.3) 20-40 d: 0 (0)		

C, Type III

First author (year)	Disease type	Patients (n)	Intervention	Recurrence	Cure/remission	Restored normal flora	(Refs.)
Ling (2013)	BV	25 30	Probiotic Control				(30)
Anukam (2006b)	BV	20 20	Probiotic Control	2 (10) 9 (45)	15 (75) 9 (45)	11 (55) 6 (30)	(16)
Parent (1996)	BV	16 16	Probiotics Control		14 (87.5) 4 (22.2)		(28)

Values are expressed as n for patients' number, n (%) for recurrence, cure/remission, and restored normal flora. mo, months; d, days; BV, bacterial vaginosis; VVC, vulvovaginal candidiasis; AV, aerobic vaginitis; Ref., reference.

The analysis indicated that probiotic treatment was favorable among all studies and those focusing on VVC alone 1 month after treatment (total: Pooled OR=2.28, 95% CI: 1.21-4.32,

P=0.011; VVC: Pooled OR=1.72, 95% CI: 1.13-2.64, P=0.012), as well as 6 months after treatment of BV (pooled OR=2.58, 95% CI: 1.07-6.23, P=0.036; Fig. 2B). However, there was

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A, Disease type, BV

First author (year)	Probiotic regimen	Brand	Dosage and duration	Route of administration	Length of follow-up period	(Refs.)
Laue (2018)	Lactobacillus	Verum	125 g yoghurt containing (besides <i>L. delbrueckii</i> ssp. bulgaricus and <i>S. thermophilus</i>) living strains <i>L. crispatus</i> LbV 88, <i>L. gasseri</i> LbV 150N, <i>L. jensenii</i> LbV 116 and <i>L. rhannosus</i> LbV96, each 1x10 ⁷ cfu/ml; placebo was 125 g chemically acidified milk. Twice daily for 4wks	Oral	4 wks	(23)
Recine (2016)	L. rhannosus BMX54	NORMOGIN	Once a day for 10 d, twice a week for 15 d and once every 5 d for 7 mo as maintenance therapy	Vaginal tablet	9 mo	(32)
Heczko (2015)	L. fermentum, L. plantarum, and L. gasseri	prOVag	One capsule daily for 10 d perimenstrually	Oral	Approximately 4 menstrual periods	(20)
Vicariotto (2014)	L.fermentum plus L. plantarum	N/A	Once a day for 7 nights, followed by 1 tablet every 3 nights for 3 wks and 1 tablet per wk	Vaginal tablet	56 d	(33)
Bradshaw (2012)	L. acidophilus	N/A	12 nights	Vaginal tablet	6 mo	(17)
Hemalatha (2012)	L. brevis CD2, L. salivarius subsp. Salicinius, L. plantarum	Florisia	8 nights	Vaginal tablet	9 d	(21)
Ling (2013)	L. delbrueckii subsp. lactis	N/A	10 d	Vaginal capsule	30 d	(30)
Vujic (2013)	L. rhannosus and L. reuteri	Lactogyn	Twice daily	Oral	6 mo	(34)
Ehrström (2010)	L gasseri, L. fermentum, L. casei subsp. rhannosus and P. acidilactici	N/A	2 capsules daily for 5 d	Vaginal capsule	6 то	(44)
Marcone (2010)	L. rhannosus	Normogin	Once a week for 6 mo of a capsule containing 40 mg of <i>L. rhamnosus</i> (N40000 CFU; Normogin), beginning 8 d after MTZ discontinued	Oral	12 mo	(25)
Martinez (2009a)	GR-1, RC-14		2 Capsule daily for the following 4 wks	Vaginal capsule	28 d	(26)
Mastromarino (2009)	L. brevis, L. salivarius subsp. salicinius, and L. plantarum	N/A	Daily for 7 d	Vaginal tablet	2 wks	(27)
Larsson (2008)	L. gasseri and L. rhannosus	$\mathrm{EcoVag}^{\circledast}$	10 d during 3 menstrual cycles	Vaginal capsule	6 mo	(22)
Marcone (2008)	L. rhannosus	N/A	Once a week at bedtime for 2 mo starting 1 wk after the last antibiotic administration	Vaginal tablet		(24)
Petricevic (2008)	L. caseirhannosus	N/A	7 d	Vaginal capsule	1 mo	(29)
Anukam (2006a)	L. rhannosus and L. reuteri	N/A	1-30 d	Vaginal tablet	30 d	(15)
Anukam (2006b)	L. rhamnosus and L. reuteri	N/A	2 capsules for 5 d	Vaginal tablet	30 d	(16)

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A, Disease type, BV						
⁷ irst author (year)	Probiotic regimen	Brand	Dosage and duration	Route of administration	Length of follow-up period	(Refs.)
Eriksson (2005)	L. gasseri, L. caseivarrhamnosus and L. fermentum	Medipharm AB	During the following menstruation	Tampon containing lactobacilli	After the second menstrual period (~1 mo)	(18)
arent (1996)	L. acidophilus	Gynoflor	1-2 tablets daily for 6 d	Vaginal tablet	28 d	(28)
Hallen (1992)	L. acidophilus (Vivag)	Vigag	Twice daily for 6 d	Vaginal capsule	7-10 d, 20-40 d	(19)
in (2006)	Lactobacillus capsule		Once daily for 7 d	Vaginal capsule	30 d	(31)
3, Disease type, VVC	()					
⁷ irst author (year)	Probiotic regimen	Brand	Dosage and duration	Route of administration	Length of follow-up period	(Refs.)
)avar (2016)	L. acidophilus, B. bifidum and B. longum	Pro-Digest	Twice daily for 10 d	Oral	6 mo	(36)
Anukam (2009)	L. rhamnosus and L. reuteri	N/A	Once daily for 3 mo	Oral	3 mo	(35)
Martinez (2009b)	L. rhamnosus and L. reuteri	N/A	Once daily for 28 d	Oral	4 wks	(43)
Vouraei (2012)		protexin	20 capsules within an interval of 72 h (3 d)	Oral	5-7 d	(41)
Yang (2009)	Lactobacillus capsule	Ding-jun-sheng	Once daily for 10 d	Vaginal capsule	30 d	(42)
Hua (2008)	Lactobacillus capsule	Ding-jun-sheng	Once daily for 10 d	Vaginal capsule	33-37 d	(38)
Aa (2007)	Lactobacillus capsule	N/A	0.5 g once daily for 7 d	Vaginal capsule	N/A	(39)
Mai (2007)	Lactobacillus capsule	Ding-jun-sheng	0.25 g capsule, once daily for 10 d	Vaginal capsule	30 d	(40)
Han (2006)	Lactobacillus capsule	Ding-jun-sheng	Once daily for 10 d	Vaginal capsule	30 d	(37)
in (2006)	Lactobacillus capsule	N/A	Once daily for 7 d	Vaginal capsule	30 d	(31)
l, day; mo, month; wk,	week; N/A, not available; Ref., reference.					

Table III. Continued.

Study name Extern (10a) Study name Study name Study name Extern (10a) Study name Study name Study name Extern (10a) Study name Study name Study name Extern (10a) Study name Study name Stud		Diagnosis		Lower	Upper	-		F	Relative
Followspin Environ Difference Difference <thdifference< th=""> <thdifference< th=""></thdifference<></thdifference<>	Study name	disease	Odds ratio	limit	limit	Z-value	p-value	Odds ratio (95%CI)	weight
Enterior 2010) BVVC 0.058 0.269 1.777 - 0.758 0.448 0.449 1.567 - 4.35 0.448 0.449 1.567 - 4.35 0.448 0.449 1.567 - 4.35 0.056 0.457 0.457 - 4.35 0.056 0.457 0.457 - 4.35 0.056 0.457 0.457 - 4.35 0.056 0.457 0.457 - 4.35 0.056 0.457	Follow-up time=1 mo	onth							
Sector Disprosi Disprosi <thdisprosi< th=""> <thdisprosi< th=""> <th< td=""><td>Ehrström (2010)</td><td>BV/VVC</td><td>0.693</td><td>0.269</td><td>1.787</td><td>-0.758</td><td>0.448</td><td></td><td>19.48</td></th<></thdisprosi<></thdisprosi<>	Ehrström (2010)	BV/VVC	0.693	0.269	1.787	-0.758	0.448		19.48
Starting 2000 molection VVC 0.038 0.039 1.997 -1.393 0.058 Mail (2007) VVC 0.342 0.161 0.056 -1.991 0.051 Mail (2007) VVC 0.324 0.161 0.056 -2.972 0.000 Mail (2007) VVC 0.317 0.027 0.027 0.047 -2.945 0.001 Lin (2006) VVC 0.117 0.027 0.487 -2.945 0.000 0.01 0.01 0.027 0.026 0.247 -2.945 0.000 0.01 0.01 0.027 0.026 0.017 0.000 0.01 0.01 0.000 0.01	Martinez (2009a) Martinez (2009b)	VVC	0.162	0.046	0.568	-2.841	0.004		8.49
Hull (2007) VVC 0.313 0.055 1.029 -1.913 0.056 Andwar (2006) VVC 0.224 0.116 1.005 0.057 0.051 Andwar (2006) VVC 0.227 0.005 0.059 0.007 0.444 -2.72 0.006 In (2006) BV 0.028 0.007 0.454 -2.712 0.006 Continued (BV) 0.287 0.158 0.007 0.454 -2.712 0.006 Continued (BV) 0.287 0.158 0.451 -4.583 0.000 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.001 0.01 <	Yang (2009)	VVC	0.384	0.094	1.567	-1.333	0.182		8.85
Ma (207) WVC 0.342 0.116 1.005 -1.951 0.051 Hav (2000) WV 0.221 0.077 0.447 -2.44 0.041 Hav (2000) WV 0.221 0.077 0.447 -2.44 0.041 Hav (2000) WV 0.228 0.177 0.498 -2.174 0.000 Combined (FW) Combined (FW)	Hua (2008)	VVC	0.313	0.095	1.029	-1.913	0.056		12.36
Ankar (2006) BV 0.019 0.001 0.329 -2.27 0.006 Har (2006) BV 0.028 0.007 0.44 -2.718 0.007 Continue (BV) 0.028 0.008 0.451 -4.829 0.000 D1 0.1 0.1 0.1 0.1 0.1 0.000 Favors probidic group Forescentral group Favors control group Favors probidic group Favors probidic group Favors control group Favors probidic group Favors probidic group Favors probidic group Favors control group Favors probidic group Favors pr	Mai (2007)	VVC	0.342	0.116	1.005	-1.951	0.051		15.03
Har (2000) VVC 0.21 0.077 0.447 -2.448 0.041 In (2000) VVC 0.288 0.177 0.448 -2.418 0.001 Contributed (FVVC) 0.288 0.177 0.448 -4.553 0.001 Contributed (FVVC) 0.288 0.177 0.448 -4.553 0.000 Contributed (FVVC) 0.287 0.158 0.451 -4.929 0.000 Contributed (FVVC) 0.288 0.177 0.448 -4.533 0.001 0.1 1 10 10 Struct -value-118, 26, 0+9, p-value-0.224, 1-squared-23.44%; XV-value-18, 26, 0 0.11 0.1 1 10 10 Struct -value-118, 21, 0+124, 0+24, 0+24, 0+24, 1-574; VVC 0.147 0.208 0.017 1 10	Anukam (2006a)	BV	0.019	0.001	0.329	-2.727	0.006		2.17
$ \begin{array}{c} \text{In} (2030) & \text{EV} & 0.085 & 0.007 & 0.448 & -2.716 & 0.007 \\ \text{continued} (WC & 0.187 & 0.056 & 0.284 & -4.553 & 0.000 \\ \text{Continued} (WC & 0.087 & 0.056 & 0.284 & -4.553 & 0.000 \\ \text{Continued} (WC & 0.087 & 0.056 & 0.481 & -4.829 & 0.000 \\ \text{Continued} (WC & 0.087 & 0.058 & 0.481 & -4.829 & 0.000 \\ \text{Continued} (WC & 0.287 & 0.158 & 0.481 & -4.829 & 0.000 \\ \text{Continued} (WC & 0.287 & 0.158 & 0.481 & -4.829 & 0.000 \\ \text{Continued} (WC & 0.287 & 0.058 & 0.481 & -4.829 & 0.000 \\ \text{Continued} (WC & 0.287 & 0.011 & 0.028 & 0.706 & -2.384 & 0.917 \\ \text{Continued} (WC & 0.141 & 0.028 & 0.706 & -2.384 & 0.917 \\ \text{Continued} (VC & 0.287 & 0.487 & 1.80 & 0.202 & 0.486 \\ \text{Enterting 2010 } & \text{BVV} & 0.76 & 0.483 & 2.50 & 0.171 & 0.844 \\ \text{Continued} (Data) & 0.722 & 0.303 & 1.734 & -0.722 & 0.476 \\ \text{Continued} (Data) & 0.722 & 0.303 & 1.734 & -0.722 & 0.476 \\ \text{Continued} (Data) & 0.728 & 0.303 & 1.734 & -0.722 & 0.476 \\ \text{Continued} (Data) & 0.728 & 0.303 & 1.734 & -0.722 & 0.476 \\ \text{Continued} (Data) & 0.728 & 0.303 & 1.734 & -0.722 & 0.476 \\ \text{Continued} (Data) & 0.728 & 0.583 & 1.768 & 0.483 & 0.407 \\ \text{Favors probiotic group} & \text{Favors control group} \\ \text{Favors control group} & \text{Favors control group} \\ \text{Favors control group} & 0.004 & \text{ratio} (95\%CI) & \text{Fit} \\ \text{Continued} (Data) & 0.728 & 0.583 & 1.738 & 0.427 & 0.446 \\ \text{Martinez} (2006) & \text{EV} & 2.747 & 0.189 & 2.4581 & 3.038 & 0.002 \\ \text{Martinez} (2006) & \text{EV} & 2.747 & 0.189 & 0.425 & 2.257 & 0.011 \\ \text{In} (2006) & \text{EV} & 2.577 & 1.185 & 2.484 & 1.559 & 0.722 & 0.446 \\ \text{Martinez} (2006) & \text{EV} & 2.576 & 1.066 & 0.232 & 2.525 & 0.011 \\ \text{In} (2006) & \text{EV} & 2.576 & 1.068 & 0.433 & 0.182 \\ \text{Martinez} (2006) & \text{EV} & 2.576 & 1.068 & 0.433 & 0.182 \\ \text{Martinez} (2006) & \text{EV} & 2.576 & 1.066 & 0.625 & 2.571 & 0.010 \\ \text{Martinez} (2006) & \text{EV} & 2.176 & 0.852 & 2.477.86 & 1.866 & 0.033 \\ \text{Marcone} (2006) & \text{EV} & 2.176 & 0.852 & 2.477.86 & 1.866 & 0.033 \\ \text{Marcone} (2006) & \text{EV} & 2.1756 & 0.852 & 2.477 & 0.859 \\ \text{Marcone} (2006) & \text{EV}$	Han (2006)	VVC	0.271	0.077	0.947	-2.046	0.041		11.15
In (Local) VVC 0.118 0.007 0.258 -2.61.7 0.000 Conclined (BV) 0.267 0.158 0.451 -4.329 0.000 Conclined (BV) 0.267 0.158 0.451 -4.329 0.000 Status 0.261 0.11 0.1 1 10 10 Status 0.261 0.11 0.1 1 10 10 Status 0.11 0.224 Legarand-22.484 0.017 Favors probletic group 1 10 100 Status 0.216 0.11 0.224 Legarand-22.484 0.017 Favors probletic group 1 10 100 Status 0.226 0.610 0.222 0.642 1 1 10 100 Status 0.021 0.11 0.11 1 1 10 100 Status 0.228 0.470 0.472 0.303 1.734 0.722 0.470 Status 0.228 0.472 0.470 1.984 0.552 722 0.470 0.470 1.984 </td <td>Lin (2006)</td> <td>BV</td> <td>0.056</td> <td>0.007</td> <td>0.449</td> <td>-2.715</td> <td>0.007</td> <td></td> <td>4.05</td>	Lin (2006)	BV	0.056	0.007	0.449	-2.715	0.007		4.05
Contained (WVC) 0.287 0.158 0.451 -4.929 0.000 eterogeneity test: 600 Conduined (WVC) 0.287 0.158 0.451 -4.929 0.000 eterogeneity test: 600 Conduined 186; de:4, p-value-0.224, t-squared-27.284; WC C-value-1.58; de:4, p-value-0.224, t-squared-67.56; WC C-value-1.58; de:4, p-value-0.244, t-squared-67.56; WC C-value-1.58; de:4, p-value-0.061, t-squared-64.285; Contineed (Intal) 0.725 0.303 1.734 -0.722 0.470 eterogeneity test: 610 Conduined 199; WVC 1.046 0.542 222.634 1.551 0.119 Enviros probletic group 1, p-value-0.061, t-squared-64.285; Conduined (State) WVC 1.448 0.559 3.752 0.762 0.446 Martinez (2006) BV VVC 1.448 0.559 3.752 0.762 0.446 Martinez (2006) BV VC 1.448 0.559 3.752 0.762 0.446 Martinez (2006) BV VC 1.410 0.565 1.333 0.102 Martinez (2006) BV VC 1.410 0.565 1.333 0.102 Martinez (2006) BV VC 3.695 1.056 12.926 2.246 0.041 LI (2006) BV VC 3.695 1.056 12.926 2.251 0.012 Martinez (2008) BV 2.550 0.756 1.286 0.470 1.620 Martinez (2008) BV 2.550 0.756 1.286 0.470 1.620 Martinez (2008) BV 2.576 1.066 0.225 2.101 0.036 Marcone (2008) BV 1.215 0.855 5.420 1.528 0.103 Marcone (2008) BV 1.216 0.552 9.1778 0.1360 0.012 Marcone (2008) BV 1.216 0.552 9.1778 0.1360 0.012 Marcone (2008) BV 1.216 0.552 9.1778 0.1360 0.037 Pavors control group Teroprobiolic group Marcone (2008) BV 1.216 0.528 1.1374 1.347 7.358 0.0002 Marcone (2008) BV 1.216 0.453 9.1563	Lin (2006) Combined (Total)	VVC	0.119	0.025	0.554	-2./12	0.007		7.35
Contained (VVC) 0.287 0.158 0.451 4.929 0.000 0.1 0.1 0.1 0.01 <th0.01< th=""> 0.01 0.01</th0.01<>	Combined (RV)		0.209	0.035	0.409	-4 553	0.000		
^{Alder} Constantial 11, 2, 45, 9, value-0.224, leguared-23, 84%, WC Constantial Compared Vision, VC Constanter Construlis Compared Vision, VC Constant	Combined (VVC)		0.267	0.158	0.451	-4.929	0.000		
Intercognently fast: serie 0liuber 1 B2, de-5, p-value-0.224, l-equared-22.04% WC - Analue-0.224, l-equared-0.256 Favors probiolic group Favors probiolic group Favors control group WC - Order 2.158, de-5, p-value-0.224, l-equared-0.256 Follow-get time-6 montris Pavors probiolic group Favors probiolic group Favors control group Sendamic 2016) WV - Content of the control group 0.01 0.01	. ,							0.01 0.1 1 10 100	
Follow-up time=6 months V/VC 0.141 0.028 0.706 -2.384 0.017 Berdshav (2012) BV 1.067 0.817 1.101 0.220 0.440 Combined (10ai) 0.725 0.303 1.734 -0.722 0.470 Intercomment (2010) BV/VVC 1.067 0.617 0.684 Study name Diagnosis 0.0151 1	leterogeneity test: fotal: Q-value=11.82, 3V: Q-value=2.14, df: /VC: Q-value=1.859,	df=9, p-valu =2, p-value= df=5, p-valu	ue=0.224, I-s 0.342, I-squa ue=0.868, I-su	quared=2 ared=6.74 quared=0	23.84% 4% 0%			Favors probiotic group Favors control group	
Follow-up time-6 months UVC 0.141 0.028 0.076 -2.384 0.017 Bradshav (2012) BV 1.057 0.617 1.1810 0.202 0.440 Endshav (2012) BV 1.057 0.617 1.1810 0.202 0.440 Endshave, (2012) BV 0.725 0.303 1.734 -0.722 0.470 Endshave, (2012) BV 0.776 0.463 2.00 1.170 0.664 Endershave, (2012) BV 0.61 1.squared=64.28% 0.611 1.0 1.0 1.0 Study name Diagnosis Odds ratio 0.533 3.752 0.752 0.446 0.442 V/V 1.484 0.542 5.752 0.446 Harinez (2006) V/VC 1.484 0.563 3.752 0.752 0.446 0.442 0.442 0.442 0.442 0.442 0.442 0.442 0.442 0.444 0.4208 0.441 0.444 0.442 0.444 0.442 0.444									_
Davar (2016) V/C 0.414 0.028 0.706 -2.384 0.017 Berdahav (2012) BV/V/C 1.076 0.453 2.500 0.171 0.864 Enstein (2010) BV/V/C 1.076 0.453 2.500 0.171 0.864 Enstein (2010) BV/V/C 1.076 0.453 2.500 0.171 0.864 Hearcogneity test: Total: Q-value-5.599, df-2, p-value-0.061, I-squared-64.29% B Cure/remission B V 10.984 0.542 222.634 1.561 0.119 B V 10.984 0.542 222.634 1.561 0.119 Cure/remission B V 10.984 0.542 222.634 1.561 0.119 Cure/remission B V 10.984 0.542 222.634 1.561 0.119 Cure/remission B V 2.002 0.932 24.581 3.033 0.002 V/C 2.002 0.638 0.002 V/C 2.002 0.638 0.002 V/C 3.179 0.089 0.322 0.758 0.000 D 2.217 0.685 0.2465 0.000 D 2.217 0.685 0.2465 0.000 D 2.228 1.205 0.206 0.012 Combined (CVC) 1.724 1.125 0.435 2.263 0.001 Combined (CVC) 1.724 1.255 0.455 5.420 1.628 0.103 Combined (CVC) 1.724 1.255 0.455 0.425 0.456 0.003 Combined (CVC) 1.724 0.435 2.256 0.458 0.000 Cure and a formal flora B C Pestoration of normal flora B Cure/remission B C Avalue=1.679, df=1, p-value=0.041, 1.357 0.256 0.000 Cure and a formal flora B Cure/remissin and and B Cure/remission and and B Cure/remission and and	Follow-up time=6 m	onths							
Bindshaw (2012) BV 10.57 0.617 1.810 0.202 0.440 Combined (Tota) BV/VC 0.725 0.303 1.734 -0.722 0.470 0.01 0.1 1 10 100 Favors probletic group Favors control group B Cure/remission B Cure/remission C Cure Later Cure/R Cu	Davar (2016)	VVC	0.141	0.028	0.706	-2.384	0.017	│ ──┼╋───┤ │ │ │	19.03
Enistrom (2010) BV/VVC 1.076 0.463 2.500 0.171 0.864 deterogeneity test: outil: Q-value=5.59, df=2, p-value=0.061, l-squared=64.29% 3 Cure/remission 3 Cure/remission 5 Udy name Diagnosis Odds ratio Lower Upper Z-value p-value 0 Odds ratio (95%CI) Provide 0 Odds ra	Bradshaw (2012)	BV	1.057	0.617	1.810	0.202	0.840		44.97
Combined (Total) 0.725 0.303 1.734 -0.722 0.470 0 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1	Ehrström (2010)	BV/VVC	1.076	0.463	2.500	0.171	0.864		36.00
Heterogeneity test: 0.01 0.1 1 100 100 Grant Covalue=5.599, dt=2, p-value=0.061, I-squared=64.28% 1 1 100 Favors control group Grant Covalue=5.599, dt=2, p-value=0.061, I-squared=64.28% 0.01 0.1 1 100 Favors control group Grant Covalue=5.599, dt=2, p-value=0.061, I-squared=64.28% 0.01 0.1 1 100 Favors control group Grant Covalue=1.1000 BV 10.884 0.552 3.752 0.762 0.446 Martinez (2008) BV 10.884 0.552 3.752 0.762 0.446 Martinez (2008) BV 1.010 28.728 0.806 0.033 0.000 1.44 Marcone (2008) BV 2.374 0.180 2.837 0.303 1.829 0.000 Mai (2007) VVC 3.857 1.989 3.132 1.399 0.322 1.11 0.56 0.563 Eriksson (2008) BV 0.486 0.559 0.562 0.012 0.01 1 10 100 Combined (F0x) 2.580 0.758 8.848 <td>Combined (Total)</td> <td></td> <td>0.725</td> <td>0.303</td> <td>1.734</td> <td>-0.722</td> <td>0.470</td> <td></td> <td></td>	Combined (Total)		0.725	0.303	1.734	-0.722	0.470		
Idencement test: Total: Q-value=0.061, I-squared=64.28% Favors problotic group Sudy name Diagnosis Odds ratio Lower Upper Z-value p-value Odds ratio Codds ratio Private colspan="2">Private colspan="2">Private colspan="2">Private colspan="2">Private colspan="2" Study name Diagnosis Odds ratio Codes ratio Codes ratio Private colspan="2" Private colspan="2" Codes ratio Code								0.01 0.1 1 10 100	
Otable O-value=-5.599, df=2, p-value=0.061, I-squared=64.28% Favors probiotic group Favors control group 3 Cure/remission Diagnosis disease Odds ratio Lower Upper limit Value p-value Odds ratio (95%Cl) Private control group 4 Cure/remission Diagnosis Odds ratio Lower Upper limit Codds ratio (95%Cl) Private control group 5 Clue-vig time=1 month Lawe (2018) BV 10.984 0.542 222.634 1.561 0.119 4 Marinez (2009) VVC 1.44 0.559 3.752 0.762 0.446 Marinez (2009) VVC 2.602 0.638 10.608 1.333 0.182 Hua (2008) VVC 1.41 0.656 1.983 0.467 0.641 Lin (2006) BV 9.667 4.099 0.322 1.373 0.303 Han (2006) BV 0.897 0.491 1.847 5.939 0.001 Combined (BV) 2.280 0.175 0.799 0.322 1.62 0.011 1 10 10 Combined (BV) 2.280 0.290 0.119 1 <t< td=""><td>leterogeneity test:</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>	leterogeneity test:								
3 Cure/remission Study name Diagnosis disease Odds ratio Lower Upper limit Value P-value Odds ratio (95%Cl) Privation (95%Cl) Follow-up time=1 month Disease Disease Odds ratio (95%Cl) Privation (95%Cl) Privors probiotic group Privors	fotal: Q-value=5.599,	df=2, p-valu	ue=0.061, I-s	quared=	64.28%			Favors probiotic group Favors control group	
Currentmission Diagnosis disease Odds ratio Lower limit Upper limit Z-value P-value Odds ratio (95%Cl) FR w Study name Diagnosis disease Odds ratio 0.984 0.542 222.634 1.561 0.119 Laue (2018) BV 10.984 0.559 3.752 0.762 0.446 Marinez (2009) VVC 1.441 0.656 1.833 0.682 Varinez (2008) BV 2.1474 0.169 1.333 0.162 Haa (2006) VVC 3.197 1.098 9.313 2.131 0.033 Marcone (2008) BV 2.179 1.098 9.313 2.131 0.033 Markan (2006) VVC 3.197 1.098 9.313 2.131 0.033 Lin (2006) VVC 3.179 0.292 3.137 0.037 0.162 Lin (2006) VVC 3.179 0.292 3.370 0.017 0.37 Combined (BV) 2.2590 0.758 8.484<									
Study name Diagnosis disease Odds ratio Lower Upper timit Z-value Odds ratio Opper (95%Cl) Fr Follow-up time=1 month Laue (2018) BV 10.984 0.559 3.752 0.762 0.446 Laue (2018) BV 10.984 0.559 3.752 0.762 0.446 Martinez (2009) V/C 2.6681 10.608 1.333 0.102 Yang (2008) V/C 2.6681 0.661 1.333 0.162 Hua (2006) V/C 2.667 5.993 5.000 0.611 Marcone (2006) BV 9.057 4.409 18.67 5.993 0.012 In (2006) V/C 3.197 0.392 2.511 0.393 0.162 Lm (2006) BV 0.899 0.223 2.531 0.011 1 0 10 Combined (CVC) 1.724 1.125 2.643 2.500 0.012 1 Favors control group Favors probiotic group PC-value=5452	Cure/remission								
Follow-up time=1 month Laue (2010) BV/VVC 10.984 0.542 222.634 1.561 0.119 Ehrstrom (2010) BV/VVC 1.448 0.559 3.752 0.762 0.446 Martinez (2009a) BV 7.000 1.993 24.581 3.036 0.000 Martinez (2008) BV 7.000 1.993 24.581 3.036 0.000 Martinez (2008) BV 2.670 0.503 0.617 0.503 Petriceivic (2008) BV 0.365 1.056 1.2926 2.046 0.041 In (2006) VVC 3.197 0.322 31.370 0.990 0.322 Eriksson (2005) BV 0.869 0.466 1.566 -0.472 0.637 Combined (ICtal) 2.283 1.205 4.325 2.531 0.011 1 10 100 Combined (ICtal) 2.590 0.758 8.484 1.519 0.129 1 Favors control group Favors probiotic group VC: Q-value=47.02, d1=6, p-value=0.01, I-squared=77.22% BV 0.01 0.1 1 1	Study name	Diagnosis disease	Odds ratio	Lower limit	Upper limit	Z-value	p-value	Odds ratio (95%CI)	Relativ weight
Laue (2018) BV 10.984 0.542 222.634 1.561 0.119 Enstration (2010) BV/VC 1.448 0.559 3.752 0.762 0.446 Martinez (2009a) BV 7.000 1.993 24.581 3.036 0.002 Yung (2009) VVC 2.602 0.638 10.608 1.333 0.182 Hua (2007) VVC 1.141 0.656 1.983 0.467 0.641 Marcone (2008) BV 9.067 4.409 18.647 5.993 0.000 Mai (2007) VVC 3.197 1.088 9.312 2.131 0.033 Han (2006) VVC 3.197 1.088 9.312 2.131 0.033 Lin (2006) BV 4.892 0.529 45.194 1.399 0.162 Lin (2006) BV 4.892 0.529 45.194 1.399 0.162 Lin (2006) BV 0.869 0.486 1.556 0.047 0.641 Marcone (2008) BV 0.869 0.486 1.556 0.047 0.637 Anukan (2006a) BV 0.280 0.115 0.753 -2.627 0.009 Combined (Total) 2.283 1.205 4.325 2.531 0.011 Combined (RV) 1.724 1.125 2.643 2.500 0.012 Combined (RV) 2.550 0.758 8.484 1.519 0.129 WC: Q-value=5.463, df=12, p-value<.001, I-squared=77.22% BV: Q-value=5.269, df=12, p-value<.001, I-squared=77.22% BV: Q-value=5.263, df=12, p-value<.001, I-squared=77.42% WC: Q-value=1.679, df=1, p-value=0.195, I-squared=47.84% WC: Q-value=1.679, df=1, p-value=0.195, I-squared=40.45% Cabined (BV) 2.576 1.066 6.225 2.101 0.036 Deltargonsis Odds ratio Marcone (2008) BV 17.216 0.852 347.786 1.856 0.063 Combined (BV) 2.576 1.066 6.225 2.101 0.036 Deltargonsis Odds ratio Marcone (2008) BV 5.721 1.938 16.892 3.157 0.002 Marcone (2008) BV 5.721 1.938 16.892 3.157 0.002 Marcone (2008) BV 5.721 1.938 16.892 3.157 0.002 Marcone (2008) BV 5.524 4.398 18.630 5.982 0.000 Anukam (20068) BV 9.0552 4.398 18.630 5.982 0.000 Anukam (20068) BV 9.0552 4.398 18.630 5.982 0.000 Combined (BV) 4.546 1.440 14.357 2.581 0.010	Follow-up time=1	month							
Eriston (2010) BV/VC 1.448 0.559 3.722 0.446 Martinez (2009) VVC 2.6602 0.638 10.608 1.333 0.002 Yang (2009) VVC 2.6602 0.638 10.608 1.333 0.182 Hua (2008) VVC 2.6602 0.638 10.608 1.333 0.182 Hua (2008) VVC 2.602 0.638 10.608 1.333 0.182 Hua (2008) VVC 2.602 0.638 10.608 1.333 0.182 Hua (2008) EV 2.374 0.190 29.726 0.670 0.503 Mai (2007) VVC 3.695 1.066 12.926 2.046 0.041 Lin (2006) EV 4.892 0.529 45.194 1.399 0.162 Lin (2006) EV 12.559 0.758 8.848 1.519 0.129 Combined (Total) 2.283 1.205 4.325 2.531 0.011 Combined (Total) 2.283 1.205 4.325 2.531 0.011 Heterogeneity test: Total: 0-value=5.452, df=4, p-value<0.01, l-squared=87.24% VVC: 0-value=5.452, df=4, p-value<0.01, l-squared=77.22% BV: 0-value=5.452, df=4, p-value<0.01, l-squared=77.22% EV: 0-value=5.452, df=4, p-value<0.01, l-squared=77.22% EV: 0-value=5.452, df=4, p-value<0.01, l-squared=77.22% EV: 0-value=5.452, df=4, p-value<0.01, l-squared=77.22% EV: 0-value=5.452, df=4, p-value=0.195, l-squared=77.22% EV: 0-value=1.679, df=1, p-value=0.195, l-squared=40.45% Eollow-up time=1 month BV: 0-value=1.679, df=1, p-value=0.195, l-squared=40.45% Eollow-up time=1 month Martinez (2008) BV 5.721 1.938 16.892 3.157 0.002 Marcone (2008) BV 5.721 1.938 16.892 3.157 0.0002 Combined (EV) 4.546 1.440 14.357 2.581 0.010	Laue (2018)	BV	10.984	0.542	222.63	4 1.561	0.119		3.26
India line 2 (2003a) BV 7,000 1.993 247.561 333 0.002 Yang (2006) VVC 1.141 0.656 1.983 0.467 0.641 Marcone (2008) BV 2.374 0.190 29.726 0.670 0.503 Petricelvic (2008) BV 2.374 0.190 29.726 0.677 0.503 Marcone (2008) BV 2.374 0.190 29.726 0.677 0.503 Marcone (2008) BV 9.067 4.409 18.647 5.993 0.003 Marcone (2006) BV 3.997 0.999 0.322 1.370 0.990 0.322 Lin (2006) VVC 3.175 0.292 31.370 0.990 0.322 Combined (BV) 2.590 0.115 0.730 472 0.637 Combined (BV) 2.590 0.758 8.481 1.519 0.129 Combined (BV) 2.590 0.758 8.481 1.519 0.129 VC: Q-value=5.452, df=4, p-value<.001, I-squared=77.22%	Enrstrom (2010) Martinez (2009a)	BV/VVC	1.448	0.559	3.752	0.762	0.446		9.33
Hua (2008) VVC 1.141 0.655 1.983 0.467 0.647 0.647 Marcone (2008) BV 2.374 0.190 29.726 0.6670 0.503 Petricevic (2008) BV 2.374 0.190 29.726 0.670 0.503 Marcone (2008) BV 2.374 0.190 29.726 0.040 0.041 Lin (2006) BV 3.892 0.522 4.370 0.900 0.322 Eriksson (2005) BV 3.892 0.522 4.370 0.900 0.322 Eriksson (2006a) BV 0.3825 1.566 -0.472 0.637 0.019 Combined (Fotal) 2.283 1.205 4.325 2.531 0.011 1 10 100 Combined (WC) 1.724 1.125 2.643 2.500 0.012 1 Favors control group Favors probiotic group Picovariue=54.52, df=4, p-value=0.244, I-squared=77.22% VC: Q-value=54.52, df=4, p-value=0.244, I-squared=77.82% 0.01 0.1 1 10 100 BV: Q-value=54.52, df=1, p-value=0.195, I-squared=42.45% 0.01	Yang (2009)	BV VVC	2.602	1.993	10.608	1.333	0.182		7.50
Marcone (2008) By 2:374 0.150 29.726 0.670 0.503 Petriceivic (2008) By 9.067 4.409 18.447 5.993 0.000 Marcone (2008) BV 9.067 4.409 18.447 5.993 0.003 Han (2006) VVC 3.197 1.098 9.313 2.131 0.033 Lin (2006) BV 0.529 45.194 1.399 0.162 Lin (2006) VVC 3.179 0.322 2.1370 0.990 0.322 Combined (Total) 2.283 1.205 4.325 2.531 0.011 0.11 1 10 100 Combined (Total) 2.283 1.205 4.325 2.500 0.012 0.01 1 1 10 100 Combined (Total) 2.283 1.205 4.325 2.500 0.012 0.11 1 10 100 Total: C-value=52.69, df=12, p-value=0.011, I-squared=77.22% BV: C-value=54.59, df=4, p-value=0.244, I-squared=26.63% 0.003 1 1 10 100 100 Marcone (2008)	Hua (2008)	vvč	1.141	0.656	1.983	0.467	0.641		10.81
Petricevic (2008) BV 9,067 4,409 18,647 5,993 0,000 Mai (2007) VVC 3,197 1,098 9,313 2,131 0,033 Han (2006) VVC 3,179 0,322 31.370 0,990 0,322 Eriksson (2005) BV 0,869 0,486 1,556 -0,472 0,637 Anukam (2006a) BV 0,2590 0,115 0,730 -2,627 0,009 Combined (Fotal) 2,283 1,205 4,325 2,531 0,011 Combined (BV) 2,590 0,758 8,484 1,519 0,129 Combined (VVC) 1,724 1,125 2,643 2,500 0,012 Heterogeneity test: Total: Q-value=54.569, df=12, p-value<.001, I-squared=77.22% BV: Q-value=54.569, df=12, p-value<.001, I-squared=77.24% VVC: Q-value=54.52, df=4, p-value<0,1, I-squared=87.24% VVC: Q-value=54.52, df=4, p-value<0,1, I-squared=87.24% VVC: Q-value=54.52, df=4, p-value=0.244, I-squared=26.63% Follow-up time=6 months Larsson (2008) BV 17.216 0.855 3,47.786 1,856 0.063 Combined (BV) 2,576 1,066 6,225 2,101 0,036 Heterogeneity test: Diagnosis Odds ratio Lower Upper Study name Diagnosis Odds ratio Lower Upper Study name Diagnosis Odds ratio Lower Upper Follow-up time=1 month Martinez (2008) BV 5.721 1,938 16,892 3,157 0,002 Marcone (2008) BV 0,581 0,174 1,947 -0.880 0,379 Petricevic (2008) BV 9,052 4,393 18,630 5,982 0,000 Anukam (2006a) BV 1,000 4,432 2,7302 5,170 0,000	Marcone (2008)	BV	2.374	0.190	29.726	0.670	0.503		4.14
Mal (2007) VVC 3.197 1.098 9.313 2.131 0.033 Han (2006) VVC 3.197 1.098 9.313 2.131 0.033 Lin (2006) BV 4.892 0.529 45.194 1.399 0.162 Lin (2006) VVC 3.179 0.322 31.370 0.990 0.322 Eriksson (2005) BV 0.869 0.486 1.556 -0.472 0.637 Anukam (2006a) BV 0.290 0.115 0.730 -2.627 0.009 Combined (BV) 2.290 0.758 8.848 1.519 0.129 Heterogeneity test: Di Corvalue=52.69, df=12, p-value<.001, I-squared=77.22% BV C-value=52.69, df=12, p-value<.001, I-squared=87.24% VVC: Q-value=5.452, df=4, p-value<.001, I-squared=87.24% VVC: Q-value=5.452, df=4, p-value=0.244, I-squared=87.24% VVC: Q-value=5.452, df=4, p-value=0.244, I-squared=87.24% VVC: Q-value=5.452, df=1, p-value=0.195, I-squared=40.45% Follow-up time=6 months Larsson (2008) BV 17.216 0.852 347.786 1.856 0.063 Marcone (2008) BV 17.216 0.852 347.786 1.856 0.063 Combined (BV) 2.576 1.066 6.225 2.101 0.036 Heterogeneity test: BV: Q-value=1.679, df=1, p-value=0.195, I-squared=40.45% C Restoration of normal flora Study name Diagnosis Odds ratio Lower Upper Imit limit Follow-up time=1 month Martinez (2008) BV 5.721 1.938 16.892 3.157 0.002 Marcone (2008) BV 5.721 1.938 16.892 3.157 0.002 Marcone (2008) BV 0.581 0.174 1.947 -0.880 0.379 Petricevic (2008) BV 11.000 4.332 27.302 5.170 0.000 Combined (BV) 4.546 1.440 14.357 2.581 0.010	Petriceivic (2008)	BV	9.067	4.409	18.647	5.993	0.000		10.23
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mai (2007) Han (2006)	VVC	3.197	1.098	9.313	2.131	0.033		0.85
Lin (2006) VVC 3.179 0.322 31.370 0.990 0.322 Eriksson (2005) BV 0.869 0.486 1.556 -0.472 0.637 Anukam (2006a) BV 0.290 0.115 0.730 -2.627 0.009 Combined (Total) 2.283 1.205 4.325 2.531 0.011 Combined (Total) 2.283 1.205 4.325 2.531 0.011 Combined (IVVC) 1.724 1.125 2.643 2.500 0.012 Heterogeneity test: Total: Q-value=52.69, df=12, p-value<.001, I-squared=77.22% BV: Q-value=52.69, df=12, p-value<.001, I-squared=77.22% BV: Q-value=52.69, df=4, p-value<.001, I-squared=77.22% BV: Q-value=54.52, df=4, p-value<.001, I-squared=77.22% BV: Q-value=54.52, df=4, p-value=0.244, I-squared=77.22% BV: Q-value=54.52, df=4, p-value=0.244, I-squared=87.24% VVC: Q-value=54.52, df=4, p-value=0.244, I-squared=87.24% VVC: Q-value=54.52, df=4, p-value=0.244, I-squared=87.24% VVC: Q-value=54.52, df=4, p-value=0.244, I-squared=26.63% Follow-up time=6 months Larsson (2008) BV 2.153 0.855 5.420 1.628 0.103 Marcone (2008) BV 2.576 1.066 6.225 2.101 0.036 Heterogeneity test: BV: Q-value=1.679, df=1, p-value=0.195, I-squared=40.45% C Restoration of normal flora Study name Diagnosis Odds ratio Lower Upper Z-value p-value Odds ratio (95%CI) Reverse probiotic group C Restoration of normal flora Study name Diagnosis Odds ratio Lower Upper Z-value p-value Martinez (2009a) BV 5.721 1.938 16.892 3.157 0.002 Marcone (2008) BV 9.052 4.398 18.630 5.982 0.000 Anukam (2006a) BV 1.10.00 4.432 2.7302 5.170 0.000 Combined (BV) 4.546 1.440 14.357 2.581 0.010	Lin (2006)	BV	3.695	1.056	45.194	1.399	0.162		8.10
Eriksson (2005) BV 0.869 0.486 1.556 -0.472 0.637 Anukam (2006a) BV 0.290 0.115 0.730 -2.627 0.009 Combined (Total) 2.283 1.205 4.325 2.531 0.011 Combined (BV) 2.590 0.758 8.848 1.519 0.129 Combined (VVC) 1.724 1.125 2.643 2.500 0.012 Heterogeneity test: Total: Q-value=52.69, df=12, p-value<.001, I-squared=77.22% BV: Q-value=54.52, df=4, p-value<.001, I-squared=87.24% VVC: Q-value=54.52, df=4, p-value<.001, I-squared=87.24% VVC: Q-value=54.52, df=4, p-value<.001, I-squared=87.24% VVC: Q-value=64.52, df=4, p-value<0.01, I-squared=87.24% VVC: Q-value=64.52, df=4, p-value<0.01, I-squared=87.24% VVC: Q-value=64.52, df=4, p-value<0.01, I-squared=87.24% VVC: Q-value=64.52, df=4, p-value<0.01, I-squared=87.24% VVC: Q-value=64.52, df=4, p-value=0.244, I-squared=26.63% Follow-up time=6 months Larsson (2008) BV 2.153 0.855 5.420 1.628 0.103 Marcone (2008) BV 17.216 0.852 347.786 1.856 0.063 Combined (BV) 2.576 1.066 6.225 2.101 0.036 Heterogeneity test: BV: Q-value=1.679, df=1, p-value=0.195, I-squared=40.45% C Restoration of normal flora Study name Diagnosis Odds ratio Lower Upper Z-value p-value Odds ratio (95%CI) Reverse probiotic group Martinez (2009a) BV 5.721 1.938 16.892 3.157 0.002 Marcone (2008) BV 9.052 4.398 18.630 5.982 0.000 Anukam (2006a) BV 11.000 4.432 27.302 5.170 0.000 Combined (BV) 4.546 1.440 14.357 2.581 0.010	Lin (2006)	vvc	3.179	0.322	31.370	0.990	0.322		4.85
Anukam (2006a) BV 0.290 0.115 0.730 -2.627 0.009 Combined (Total) 2.283 1.205 4.325 2.531 0.011 Combined (BV) 2.590 0.758 8.848 1.519 0.129 Combined (VVC) 1.724 1.125 2.643 2.500 0.012 Heterogeneity test: Total: Q-value=52.69, df=12, p-value<.001, I-squared=77.22% BV: Q-value=47.02, df=6, p-value<.001, I-squared=77.24% VVC: Q-value=5452, df=4, p-value=0.244, I-squared=26.63% Follow-up time=6 months Larsson (2008) BV 17.216 0.852 347.786 1.856 0.063 Combined (BV) 2.576 1.066 6.225 2.101 0.036 Heterogeneity test: BV: Q-value=1.679, df=1, p-value=0.195, I-squared=40.45% C Restoration of normal flora Study name Diagnosis Odds ratio Lower Upper Imit Imit Imit Follow-up time=1 month Martinez (2009a) BV 5.721 1.938 16.892 3.157 0.002 Marcone (2008) BV 0.581 0.174 1.947 -0.880 0.379 Petricevic (2008) BV 11.000 4.432 27.302 5.170 0.000 Combined (BV) 4.546 1.440 14.357 2.581 0.010	Eriksson (2005)	BV	0.869	0.486	1.556	-0.472	0.637		4.69
Combined (10tal) 2.283 1.205 4.325 2.531 0.011 Combined (VVC) 2.590 0.758 8.848 1.519 0.129 Combined (VVC) 1.724 1.125 2.643 2.500 0.012 Heterogeneity test: Total: Q-value=52.69, df=12, p-value<.001, I-squared=87.22% BV: Q-value=5.452, df=4, p-value=0.244, I-squared=87.24% VVC: Q-value=5.452, df=4, p-value=0.244, I-squared=87.24% VVC: Q-value=6 months Larsson (2008) BV 2.153 0.855 5.420 1.628 0.103 Marcone (2008) BV 17.216 0.852 347.786 1.856 0.063 Combined (BV) 2.576 1.066 6.225 2.101 0.036 Heterogeneity test: BV: Q-value=1.679, df=1, p-value=0.195, I-squared=40.45% Carbon of normal flora Study name Diagnosis Odds ratio Lower Upper Z-value p-value Odds ratio (95%CI) Follow-up time=1 month Martinez (2009a) BV 5.721 1.938 16.892 3.157 0.002 Marcone (2008) BV 0.581 0.174 1.947 -0.880 0.379 Petricevic (2008) BV 11.000 4.432 27.302 5.170 0.000 Anukam (2006a) BV 11.000 4.432 27.302 5.170 0.000 Anukam (2006a) BV 11.000 4.432 27.302 5.170 0.000 Combined (BV) 4.546 1.440 14.357 2.581 0.010	Anukam (2006a)	BV	0.290	0.115	0.730	-2.627	0.009		10.72
Combined (BV) 2.590 0.758 8.845 1.519 0.129 Heterogeneity test: 1.724 1.125 2.643 2.500 0.012 1 10 100 Heterogeneity test: 0.01 0.1 1 10 100 Favors control group 1 10 100 Follow-up time=6 months Earsson (2008) BV 2.153 0.855 5.420 1.628 0.103 1 1 10 100 Marcone (2008) BV 2.153 0.855 5.420 1.628 0.103 1 1 10 100 Marcone (2008) BV 17.216 0.852 347.786 1.856 0.063 1 1 10 100 100 Heterogeneity test: BV 2.576 1.066 6.225 2.101 0.036 1 1 10 100 100 Favors probiotic group 1 100 100 1 100 100 1 100 100 1 100 100 1 100 100 1 100 100 1	Combined (Total)		2.283	1.205	4.325	2.531	0.011		
Continued (VVC) 1,724 1,725 2,500 0,012 1 <td>Combined (BV)</td> <td></td> <td>2.590</td> <td>0.758</td> <td>8.848</td> <td>1.519</td> <td>0.129</td> <td></td> <td></td>	Combined (BV)		2.590	0.758	8.848	1.519	0.129		
Heterogeneity test: Total: Q-value=52.69, df=12, p-value<.001, I-squared=77.22% BV: Q-value=54.702, df=6, p-value<.001, I-squared=87.24% VVC: Q-value=5.452, df=4, p-value=0.244, I-squared=87.24% VVC: Q-value=6.70, df=1, p-value=0.195, I-squared=40.45% C Restoration of normal flora C Restoration of normal flora Study name Diagnosis Odds ratio Lower Upper Z-value p-value Odds ratio (95%CI) Ret disease Immit Immit Immit T-0.880 0.379 Petricevic (2008) BV 0.581 0.174 1.947 -0.880 0.379 Petricevic (2008) BV 11.000 4.432 27.302 5.170 0.000 Combined (BV) 4.546 1.440 14.357 2.581 0.010	Combined (VVC)		1.724	1.125	2.040	2.500	0.012		
Total: Q-value=52.69, df=12, p-value<.001, I-squared=77.22%	Heterogeneity tes	st:						0.01 0.1 1 10 100	
Follow-up time=6 months Larsson (2008) BV 2.153 0.855 5.420 1.628 0.103 9 Marcone (2008) BV 17.216 0.852 347.786 1.856 0.063 1 1 10 9 8 Combined (BV) 2.576 1.066 6.225 2.101 0.036 1 1 10 100 100 Heterogeneity test: BV: Q-value=1.679, df=1, p-value=0.195, I-squared=40.45% 0.01 0.1 1 10 100 100 Favors control group Favors probiotic group Marcone (2008) BV 5.721 1.938 16.892 3.157 0.002 Marcone (2008) BV 0.581 0.174 1.947 -0.880 0.379 Petricevic (2008) BV 0.52 4.398 18.630 5.982 0.000 Anukam (206a) BV 11.000 4.432 27.302 5.170 0.000 22 24 24 24 24 24 24 24 24	Total: Q-value=52 BV: Q-value=47.0 VVC: Q-value=5.4	2.69, df=12, 2, df=6, p- 452, df=4, p	p-value<.0 value<.001 p-value=0.2	001, I-sq , I-squa 244, I-sq	uared=7 red=87.2 uared=2	7.22% 4% 6.63%		Favors control group Favors probiotic group	
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Combined (BV) 2.576 1.066 6.225 2.101 0.036 Heterogeneity test: Diagnosis 0.01 0.1 1 10 100 BV: Q-value=1.679, df=1, p-value=0.195, I-squared=40.45% Favors control group Favors probiotic group 1 10 100 C Restoration of normal flora Diagnosis Odds ratio Lower Upper Z-value p-value Odds ratio (95%CI) Ref Follow-up time=1 month Imit Imit Imit 1.938 16.892 3.157 0.002 Marcone (2009a) BV 5.721 1.938 16.892 3.157 0.002 Petricevic (2008) BV 0.524 3.988 1.938 1.6392 3.157 0.002 Anukam (2006a) BV 11.000 4.432 27.302 5.170 0.000 22 Combined (BV) 4.546 1.440 14.357 2.581 0.010 22	Marcong (0000)	DV	17.040	0.000	247 700	1.020	0.000		0.00
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C Restoration of normal flora Study name Diagnosis disease Odds ratio Lower limit Upper limit Z-value p-value Odds ratio (95%Cl) Rd w Follow-up time=1 month Martinez (2009a) BV 5.721 1.938 16.892 3.157 0.002 Marcone (2008) BV 0.581 0.174 1.947 -0.880 0.379 Petricevic (2008) BV 9.052 4.398 18.630 5.982 0.000 Anukam (2006a) BV 11.000 4.432 27.302 5.170 0.000 Commend (BV) 4.546 1.440 14.357 2.581 0.010 Image: Commend (Commend)	BV: Q-value=1.67	9, df=1, p-	value=0.19	5, I-squ	ared=40.	45%		Favors control group Favors probiotic group	
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Marchine (2006) BV 0.581 0.174 1.947 -0.880 0.379 Petricevic (2008) BV 9.052 4.398 18.630 5.982 0.000 Anukam (2006a) BV 11.000 4.432 27.302 5.170 0.000 Combined (BV) 4.546 1.440 14.357 2.581 0.010	Marcone (2009a)	BV	5.721	1.938	16.892	3.157	0.002		24.09
Anukam (2006a) BV 3.052 4.396 10.630 5.962 0.000 Anukam (2006a) BV 11.000 4.432 27.302 5.170 0.000 Combined (BV) 4.546 1.440 14.357 2.581 0.010 Image: Combined (BV) Image: Combined (BV	Petricevic (2008)	BV	0.581	0.174	1.947	-0.880	0.379		22.88
Combined (BV) 4.546 1.440 14.357 2.581 0.010	Anukam (2006a)	BV	9.052	4.398	27 302	5 170	0.000		27.33
	Combined (BV)	0.	4,546	1.440	14.357	2.581	0.010		25.70
Heterogeneity test.	Heterogeneity too	t.	4.040	1.440	14.007	2.001	0.010		
BY Q-value=17.282, df=3, p-value=0.001, I-squared=82.64% 0.01 0.1 1 10 100	BV: Q-value=17.2	82. df=3. n	-value=0.00	0 1 . I-sa	Jared=82	2.64%		0.01 0.1 1 10 100	

Bradshaw (2012) Marcone (2010) Marcone (2008) BV 0.416 0.148 1.165 -1.669 0.095 25.67 Combined (BV) 0.986 0.203 4.801 -0.017 0.986 Heterogeneity test: BV: Q-value=47.86, df=3, p-value<.001, I-squared=93.73% 0.01 100 0.1 1 10 Favors control group Favors probiotic group

0.000

0.909

Follow-up time=6 months Recine (2016)

BV

BV BV

8.626

1.028 0.119

4.880

0.637

15.246

1.662 1.069

7.415

0.115

Favors control group

Favors probiotic group

27.76

28.06 18.51

Figure 2. Forest plots for antibiotic plus Lactobacillus vs. antibiotic plus placebo (type I study) in the treatment of bacterial vaginosis and vulvovaginal candidiasis: (A) 1-month and 6-month recurrence rate; (B) 1-month and 6-month cure or remission rate; (C) restoration of normal flora after 1 month of follow-up. BV, bacterial vaginosis; VVC, vulvovaginal candidiasis; df, degrees of freedom.



Figure 3. Quality assessment of included studies. Risk of bias summary of (A) randomized controlled trials and (B) non-randomized controlled trials. Risk of bias graph of (C) randomized controlled trials and (D) non-randomized controlled trials.

no significant difference in the cure rate at 1 month for BV (pooled OR=2.59; 95% CI: 0.76-8.85; P=0.129; Fig. 2B).

With respect to restoration of the normal flora, 4 studies (15,24,26,29) had complete quantitative data at 1 month and 4 studies (17,24,25,32) at 6 months after treatments for BV, and were included in the analysis. High heterogeneity existed among the studies on the restoration of normal flora at 1 month and 6 months after treatment (1 month: Q=17.28, I²=83%; 6 months: Q=47.86, I²=94%). The analysis indicated that patients in the probiotic group had a significantly higher rate of normal flora restoration at 1 month after treatment (pooled OR=4.55, 95% CI: 1.44-14.36, P=0.010). However, there were no differences in the normal flora restoration rate between the two groups at 6 months after treatment (Fig. 2C).

Additional analyses were performed for type II (19,21,27,33,34) or type III (16,28) studies that had at least one follow-up outcome. These studies all focused on BV and had varied heterogeneity (Recurrence: Q=7.98; I²=87%; Cure or remission: Q=1.94; I²=0%; Restored normal flora: Q=4.37; I²=54% for type II and Cure or remission: Q=2.58; I²=61%; for type III). Patients with BV given type II treatments in the probiotic group were indicated to have a higher cure or remission rate and normal flora restoration rate than those in the control group (cure/remission rate: Pooled OR=12.44, 95% CI: 4.86-31.89, P<0.001; normal flora restoration rate:

Pooled OR=3.32, 95% CI: 1.11-9.97, P=0.033). In BV patients given type III treatments, the probiotic group had a higher cure/remission rate than the control group (cure/remission rate: Pooled OR=8.39, 95% CI: 1.32-53.23, P=0.024; Table IV).

Quality assessment. The risk of bias assessment for individual studies is provided in Fig. 3, including the potential risk of individual studies (Fig. 3A and B) and the overall risk (Fig. 3C and D). Overall, the studies had a low risk of attrition bias and reporting bias, and low or unclear risk of selection bias and detection bias. Furthermore, 3 studies had a high risk of performance bias due to improper blinding of participants and researchers.

Sensitivity analysis. Sensitivity analyses were performed on the major results using the leave-one-out approach, in which the meta-analysis was performed with each study removed in turn (Table V). The direction of combined estimates on recurrence rates and cure/remission rates at 1 month and normal flora restoration rates at 6 months did not vary markedly with the removal of the studies, indicating that the meta-analysis had good reliability and supported that there was no or little inter-study heterogeneity. However, for normal flora restoration rates at 1 month, the study of Marcone *et al* (24) from 2008 may have had a disproportionate effect on the pooled OR, as the difference became more significant and greater

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Outcome/study [Author name (year) (Refs.)]	Treatment type	Time-point	Odds ratio	Lower limit	Upper limit	Z-value	P-value	Heterogeneity test
Recurrence								Q=7.977, df=1, P=0.005, I2=87.46%
Vicariotto (2014) (33)	BV-Type II	1 mon	0.023	0.003	0.189	-3.498	<0.001	
Hemalatha (2012) (21)	BV-Type II	9 d	0.757	0.230	2.492	-0.459	0.646	
Combined			0.147	0.005	4.529	-1.096	0.273	
Cure or remission								Q=1.939, df=2, P=0.379, I2=0%
Vicariotto (2014) (33)	BV-Type II	1 mon	44.019	5.280	366.956	3.498	<0.001	
Mastromarino (2009) (27)	BV-Type II	14 d	6.806	1.412	32.809	2.390	0.017	
Hallen (1992) (19)	BV-Type II	40 d	11.560	2.821	47.366	3.401	0.001	
Combined			12.444	4.856	31.888	5.251	<0.001	
Restored normal flora								Q=4.366, df=2, P=0.113, I2=54.19%
Vujic (2013) (34)	BV-Type II	3 mon	3.983	1.603	9.895	2.977	0.003	
Hemalatha (2012) (21)	BV-Type II	9 d	1.339	0.436	4.113	0.510	0.610	
Mastromarino (2009) (27)	BV-Type II	14 d	15.000	1.621	138.821	2.385	0.017	
Combined			3.319	1.105	9.974	2.137	0.033	
Restored normal flora								
Anukam (2006b) (16)	BV-Type III	1 mon	2.852	0.777	10.467	1.580	0.114	Not assessed
Recurrence								
Anukam (2006b) (16)	BV-Type III	1 mon	0.136	0.025	0.748	-2.294	0.022	Not assessed
Cure or remission								Q=2.577, df=1, P=0.108, I2=61.19%
Anukam (2006b) (16)	BV-Type III	1 mon	3.667	0.958	14.028	1.898	0.058	
Parent (1996) (28)	BV-Type III	28d	24.532	3.693	162.947	3.312	0.001	
Combined			8.393	1.323	53.227	2.257	0.024	
df, degrees of freedom; mon, months; d, days; E	3V, bacterial vaginosi	.s.						

normal flora for natients with BV given type II and type III treatment and restored mission è 0 5 đ Table IV. Extra meta-analveis for recurre 3761

Table V. Sensitivity analysis.

A, Recurrence at 1 month

		Statistics with study removed							
Author name (year)	Odds ratio	Lower limit	Upper limit	Z-value	P-value	(Refs.)			
Ehrström (2010)	0.214	0.135	0.342	-6.478	<0.001	(44)			
Martinez (2009a)	0.287	0.184	0.447	-5.516	< 0.001	(26)			
Martinez (2009b)	0.279	0.180	0.432	-5.720	< 0.001	(43)			
Yang (2009)	0.260	0.168	0.403	-6.023	< 0.001	(42)			
Hua (2008)	0.264	0.169	0.412	-5.848	< 0.001	(38)			
Mai (2007)	0.258	0.164	0.407	-5.848	< 0.001	(40)			
Anukam (2006a)	0.286	0.187	0.436	-5.809	< 0.001	(15)			
Han (2006)	0.269	0.173	0.420	-5.797	< 0.001	(37)			
Lin (2006)	0.288	0.188	0.441	-5.718	< 0.001	(31)			
Lin (2006)	0.288	0.186	0.444	-5.622	<0.001	(31)			

B, Cure or remission at 1 month

		Statisti	cs with study removed			
Author name (year)	Odds ratio	Lower limit	Upper limit	Z-value	P-value	(Refs.)
Laue (2018)	2.165	1.131	4.146	2.330	0.020	(23)
Ehrström (2010)	2.416	1.197	4.879	2.461	0.014	(44)
Martinez (2009a)	2.062	1.069	3.979	2.158	0.031	(26)
Yang (2009)	2.271	1.150	4.486	2.361	0.018	(42)
Hua (2008)	2.521	1.209	5.256	2.467	0.014	(38)
Marcone (2008)	2.286	1.179	4.431	2.447	0.014	(24)
Petricevic (2008)	1.818	1.047	3.155	2.123	0.034	(29)
Mai (2007)	2.224	1.117	4.427	2.275	0.023	(40)
Han (2006)	2.764	1.523	5.015	3.345	0.001	(37)
Lin (2006)	2.197	1.114	4.333	2.271	0.023	(31)
Lin (2006)	2.199	1.136	4.259	2.337	0.019	(31)
Eriksson (2005)	2.252	1.160	4.372	2.398	0.016	(18)
Anukam (2006a)	2.578	1.280	5.193	2.651	0.008	(15)

C, Restoration of normal flora at 1 month

		Statistics with study removed							
Author name (year)	Odds ratio	Lower limit	Upper limit	Z-value	P-value	(Refs.)			
Martinez (2009a)	4.121	0.853	19.905	1.762	0.078	(26)			
Marcone (2008)	8.705	5.274	14.368	8.464	< 0.001	(24)			
Petricevic (2008)	3.442	0.646	18.335	1.448	0.148	(29)			
Anukam (2006a)	3.284	0.692	15.591	1.496	0.135	(15)			

D, Restoration of normal flora at 6 months

	Statistics with study removed						
Author name (year)	Odds ratio	Lower limit	Upper limit	Z-value	P-value	(Refs.)	
Recine (2016)	0.536	0.195	1.477	-1.205	0.228	(32)	
Bradshaw (2012)	0.861	0.062	11.885	-0.112	0.911	(17)	

		Statisti	cs with study removed			
Author name (year)	Odds ratio	Lower limit	Upper limit	Z-value	P-value	(Refs.)
Marcone (2010)	1.599	0.293	8.737	0.542	0.588	(25)
Marcone (2008)	1.312	0.197	8.715	0.281	0.779	(24)

Table V. Continued.

when this study was not included in the meta-analysis, while the three other studies had no such effect.

Discussion

The overall summary of the qualitative analysis of the 30 studies suggests that probiotic treatments are useful for managing common vaginal infections, particularly BV and VVC. However, patient populations, treatment protocols, endpoints and follow-up time-points exhibited a marked variation. The results of the meta-analysis indicated that probiotics as a supplement of antibiotic/anti-fungal treatments (as observed in type I studies) reduced the recurrence rate and increased the cure/remission rate in non-pregnant adult females at 1 month after treatment. With less evident data, the normal bacterial flora restoration rate was also increased by probiotic-supplemented treatments in BV. The short-term benefits of probiotics were further supported by individual analysis of BV and VVC, although probiotics supplementary to standard treatments did not increase the cure/remission rate in BV and the post-treatment normal bacterial restoration rate in VVC was lacking. However, observations at 6 months post-treatment were less frequently reported. In line with the results demonstrated by probiotic-supplemented treatments, probiotics alone without antibiotics may have clinical benefits in promoting the cure/remission rate and normal flora restoration rates in BV.

To the best of our knowledge, the present meta-analysis was the first to review and analyze the effect of probiotics in common vaginal infections reported by RCTs or appropriately-controlled studies. Furthermore, only few studies have evaluated the benefits of probiotics in vaginal infection stratified by treatment regimen. The quantitative data of the present study are supported by conclusions from two published systemic reviews, which examined the overall effect of probiotics in females with urogenital infections qualitatively. In 2009, Abad and Safdar (6) identified 25 studies that used Lactobacillus-containing probiotics to either prevent or treat a urogenital infection [BV, VVC and urinary tract infections (UTI)]. Of the 25 studies, 18 used Lactobacillus preparations for the treatment or prevention of urogenital infections and 7 focused solely on vaginal colonization (6). Of the 18 studies, only 8 studies included patients with BV, 4 included patients with VVC, 5 included patients with UTI and 1 was on multiple infections (6). Overall, Lactobacilli were beneficial for the treatment of BV, while no clear benefit was observed for VVC or UTI (6). A more recent systematic review published in 2016 investigated probiotics for the treatment and prevention of urogenital infections in females (4). A total of 20 studies (published from 2008 to 2015) were identified, with 14 examining BV, 2 examining VCC, 3 examining UTI and 1 examining human papillomavirus (HPV) (4). While the studies reviewed by Hanson et al (4) in 2016 were heterogeneous with respect to study type, design, intervention and outcomes and varied in quality (4 of good quality, 9 of fair and 7 of poor quality), the authors still made to the conclusion that the use of probiotics may be effective for the treatment and prevention of BV, recurrent candidiasis or UTI, as well as HPV lesions. In the current review, an analysis of quantitative outcomes from a total of 1,788 patients with common vaginal infections was presented, with focus on BV and VVC that are most directly impacted by an imbalanced microflora/dysbiosis.

One prior meta-analysis examined the use of probiotics for treating BV. In a meta-analysis published in 2014, Huang et al (3) indicated that the use of probiotic supplementation significantly improved the cure rate in adult females with BV [risk ratio (RR)=1.53; 95% CI: 1.19-1.97]. When only 9 high-quality studies were included in the analysis, the RR increased slightly to 1.60 (95% CI: 1.16-2.22) (3). Of note, when a subgroup analysis was performed, a single treatment with probiotics may only be effective for short-term follow-up $(\leq 1 \text{ month})$ but not for long-term follow-up (>1 month) (3), which was consistent with the present result that no difference between two groups in recurrence rate and cure/remission rates was determined at 6 months after the treatment. In a meta-analysis by Huang et al (3) from 2014, the eligible articles were searched up to May 2013 and the studies included in the meta-analysis were also heterogeneous. In the present meta-analysis, the literature search was further updated to December 24th, 2018, and studies all except one RCT analyzed in the previous study by Huang et al (3) from 2014 were included. This particular RCT was excluded from the present study due to its study design for healthy females with a history of BV (45); furthermore, it had different follow-up time-points from other studies analyzed in the present study and was deemed unsuitable for analysis of post-treatment outcomes.

A recent meta-analysis study suggested that, although probiotics appeared effective in treating VVC, relevant studies were not sufficient in number (5-7 studies included for each analysis) or of comparable quality (7). In the present study, which focused on common vaginal infections as a whole, only studies with comparable treatment designs and study follow-up schedules were included in the meta-analysis. Furthermore, the major results of the present study were based on >10 RCTs or prospective studies with control arms. In 2006, Falagas et al (46) reported on several clinical trials on VVC that support the effectiveness of Lactobacilli administered either orally or intravaginally in decreasing colonization of C. albicans or preventing vaginal candidiasis. However, most of the relevant clinical trials had methodological problems, including small sample size, no control group (single-arm) and included females without confirmed recurrent VVC. All of the studies on VVC reviewed in the present meta-analysis were designed to compare Lactobacillus capsule-supplemented anti-fungal treatments (probiotic group) with anti-fungal agents alone (control group). Despite the follow-up period ranging from <1 week to 6 months among the studies included, only those with comparable follow-up schedules were included in the present meta-analysis. The outcome supports the effectiveness of Lactobacilli in decreasing the recurrence rate and improving the cure rate.

The primary limitation of the present study has already been mentioned-the large heterogeneity between studies with respect to the patient population, type of treatment, probiotic strains and outcome follow-ups. However, it was sought to overcome this by carefully-planned stratification based on treatment design and follow-up schedules. The major results on short-term benefits of combined therapy of antibiotics/anti-fungals with probiotics was further confirmed by the sensitivity test. By contrast, the limited sample size and heterogeneous study design prevented us from a reliable subgroup analysis of long-term benefits and of probiotics treatment alone without antibiotic/anti-fungal agents.

In conclusion, the results of the present study confirm the results of other reports in a quantitative manner, namely that probiotics as a supplement to conventional pharmacological treatments are effective in the short term for the treatment of common vaginal infections in non-pregnant adult females. However, high-quality evidence for the effectiveness of probiotics alone in recurrent or curative vaginal infections is limited. Further high-quality clinical trials are necessary to identify the most effective probiotic strains, the most effective treatment regimens (with or without antibiotics) and the subpopulations of females (e.g. pre-menopausal vs. post-menopausal) that may benefit the most from probiotics.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

HSJ conceived and designed the current study, defined the content of the research, conducted literature research, performed statistical analysis and prepared and edited the manuscript. TRY is the guarantor of study integrity, designed the current study, defined the content of the research and reviewed the manuscript. JYC conducted literature research, acquired data and performed statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that there are no competing interests.

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