Probiotics and Urogenital Infections: A protocol for an evidence and gap map

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BACKGROUND

The urogenital system, comprising the urinary and genital organs, is susceptible to infections from various sources due to its exposure to the external environment (1). Urogenital infections, particularly bacterial vaginosis (BV), vulvovaginal candidiasis (VVC) and urinary tract infections (UTI), are routinely treated with antibiotics (2). However, there are mounting concerns about the need for alternative therapies due to increasing antimicrobial resistance (3). Antimicrobial resistance (AMR) is a serious global health threat, causing 1.27 million deaths directly attributable to AMR in 2019 (4), and it is estimated to become the leading cause of death by 2050 (5).

One notable therapy that has garnered significant interest both in the scientific community and the public as alternative or adjuvant therapy is probiotics. Probiotics are live microorganisms, such as *Lactobacillus acidophilus* and *Bifidobacterium adolescentis,* which when administered in sufficient quantities confer health benefits to the host (6). These organisms compete with pathogenic microorganisms, hindering their colonization and contributing to host defence mechanisms (6, 7).

Despite the volume of research conducted on the use of probiotics in the management of urogenital infections, their effectiveness in clinical and primary care settings have been inconsistent. On one hand, clinical studies have provided evidence supporting the efficacy of probiotics as supplementary treatments alongside antibiotics for urogenital infections - BV (8, 9), VVC (10, 11), and UTI (12, 13) whether administered vaginally or orally. On the other hand, studies like (14) (15) (16) have reported the non- effectiveness of probiotics in these infections.

Similarly, outcomes of SRs and meta-analyses have also varied. (17) carried out a systematic review focusing on the application of probiotics in the management of urogenital infections. Their findings provided evidence that probiotic interventions were effective in both the treatment and prevention of BV and the prevention of recurrent candidiasis and UTIs. In another meta-analysis of six randomized controlled trials, (18) demonstrated that treatment with probiotics was significantly more effective compared to a placebo in terms of reducing recurrence rates of VVC. However, therapeutic effect of probiotics against BV diminished

after analysis of heterogeneity in (19) meta-analysis of antibiotics alone or the use of probiotics or probiotics in combination with antibiotics.

The difference in outcomes in these studies may be attributed to variations in probiotics employed. The mode of action of probiotics are often multidirectional, can vary among different genera, species, and strains (6) and is an area of ongoing research. This underscores the need for an evidence and gap map (EGM) to offer comprehensive and clearer overviews of probiotics in relation to urogenital infection management. This method ensures an unbiased evaluation of the present body of evidence on probiotic use, consolidating the existing knowledge and identify the knowledge gaps which can inform research, clinical decision-making and healthcare practice policy development.

Aim:

This EGM aims to identify systematic reviews and impact assessments regarding the clinical effectiveness and cost-effectiveness of probiotics in managing urogenital infections, with a summarized overview in a report. Specific objectives are:

- To create a database entry for the studies included, summarizing the type of probiotics used, method of administration, study design, and primary findings.
- To identify research gaps that necessitate both systematic reviews and primary research efforts.

METHODS

Stakeholder engagement

Early and continuing engagement with stakeholders is critical for EGMs to ensure relevance and actionable outputs. An advisory group will be created composed of patient and public Involvement groups (PPI) and primary care providers.

Meetings will be held separately between the two groups to co-ordinate stakeholder engagement in the EGM. Alongside providing training to members as necessary, meetings will focus on the scope of the review, feeding into the methods of the EGM (e.g. data extraction) and defining the EGM framework (types of probiotics and relevant outcomes). The EGM will

be piloted with the advisory group in the initial stage and findings of the EGM will be presented to the advisory group to discuss the implications for different audience.

Search strategy and screening

The review will be registered on PROSPERO. To identify relevant reviews and impact evaluation studies, the following databases will be searched: MEDLINE, EMBASE (via Ovid); CINAHL Ultimate, Allied and Complementary Medicine Database (AMED), (via EBSCO); Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (via the Cochrane Library); Campbell Collaboration, 3ie Development Evidence Portal and Epistemonikos.

To identify studies not accessible via bibliographic databases, the following supplementary searches would be carried out: Citation tracking, Reference snowballing, Google Scholar searching and Google searching.

Records that are retrieved will be imported into Endnote software for deduplication. The screening of studies will then be conducted using the Rayyan free online tool. Two reviewers will independently screen the studies, and any disagreements will be resolved through discussion or arbitration with a third reviewer. The complete preliminary list of search terms, abbreviations and Boolean connectors used on Medline OVID can be found in the appendix.

Eligibility criteria

We defined our research question following the PICOTS (Population, Intervention, Comparator, Outcome, Time, and Study settings) framework.

Population

Include: females 16 years of age and older who have tested probiotics to prevent or treat BV, HPV, VVC, or UTI. Studies with multiple populations will be included if information regarding the population of interest can be extracted.

Exclude: studies on people below 16 years and males; mixed population without disaggregated data for target population; in vitro and animal studies.

Intervention

Include: probiotics regardless of form (food, supplement, etc), route of administration, single or mixed strain, probiotics in combination of conventional antibiotics treatment matched with antibiotics or placebo as control; studies that examined probiotic treatment vs. non-probiotics treatment (control) with or without antibiotics.

Exclude: supplements that are not probiotics

Comparator(s)/Control: Any comparator

Outcomes

All outcomes relating to effectiveness and cost effectiveness including antibiotic prescription/use, consultations in primary care, antibiotic/probiotic side effects rates, failure rate, patient reported outcomes, infection recurrence rates, economic evaluation outcomes, and adverse events (length of hospital stay, intensive care unit admission, mortality).

Time limit: None

Setting: Any healthcare setting (e.g. community, primary care, secondary care, tertiary care) from any geographic location as defined by the World Health Organization regions (WHO, African Region, Regions of the Americas, South-East Asian Region, European Region, Eastern Mediterranean Region, Western Pacific Region). Primary studies and systematic reviews that do not report the countries or settings will not be excluded.

Study design

Include: systematic reviews

Systematic reviews of effectiveness and safety studies, whether randomised, non-randomised, or observational; Mixed-methods systematic reviews; scoping review; meta-analysis; Systematic reviews of reviews Rapid reviews, which include a synthesis of effectiveness; Cost-effectiveness reviews. For reviews to be eligible for inclusion, they need to meet the minimum quality criteria for the Database of Abstracts of Reviews of Effects (20) i.e., satisfy all of the following:

- Report adequate inclusion and exclusion criteria.
- Report an adequate search strategy (at least 3 database searches).
- Perform a synthesis of the included studies.

- Assess the quality of the included studies.
- Provide sufficient details about the individual included studies.

Exclude: reviews that are not undertaken systematically; literature reviews; qualitative evidence syntheses and systematic reviews of materials that are not original research (e.g., systematic reviews of guidelines); and protocols for ongoing reviews.

Include: Impact evaluations with a treatment and control group

Impact evaluation studies, regardless of their inclusion in a systematic review, would be included. If they are (a) randomised or non-randomized controlled trials; (b) quasi-experimental studies; (c) regression discontinuities; (d) controlled before and after studies; (e) interrupted time series - with at least three data points before and three after the intervention as per Cochrane Effective Practice and Organisation of Care recommendations.

Exclude: observational studies (e.g. case studies cross-sectional studies), opinion pieces, editorials, solely qualitative study design, protocols for ongoing impact evaluation studies.

Language: No restriction.

Data extraction

A standardised data extraction set will be developed in EPPI-Reviewer. It will be used to collect the following information from each included full text are listed in the table below.

Study details	**Population**	**Intervention and outcome**
First author	Participants' group (pregnant, non-pregnant, menopausal, etc)	Strain or probiotic organism Probiotic & comparator description
Year of publication	Health condition (UTI, BV, VVC)	Form of probiotic (food, drink, supplement, etc) & comparator
Publication type (journal, thesis, etc)	Demographics: Place of residence, Race, Ethnicity, Socioeconomic status	Dosage and duration of use
Title	Age group	Route of administration (oral or vaginal)
Country of data collection as defined by the WHO regions	Healthcare setting (Community care, Primary care, secondary care, etc)	Effect sizes, statistical significance of effect
Study aim		Economic evaluation outcome (e.g., Cost)
Study design (e.g., RCT, non RCT, SR)		Any other outcomes (adverse effect, mortality, etc)

Data extraction will be performed by one reviewer and checked by a second, with disagreements being settled through discussion, recruiting a third person as arbiter, if required.

Quality appraisal

Two reviewers would assess the quality of the included reviews using a modified AMSTAR-2 (21) quality appraisal tool for systematic reviews of primary studies of randomised and non-randomised study designs within eleven domains: Each domain would be given a score of 1 if it clearly addressed the question and 0 if not addressed or unable to robustly assess it due to inadequate reporting with a total possible score of 11. The reviews would be categorized as low quality if the total AMSTAR score was ≤3, moderate quality if the total AMSTAR score was between 4 and 7, and high quality if the total AMSTAR score was ≥8.

Data analysis and presentation

The EPPI-Mapper software, powered by EPPI-Reviewer will be used to generate an online, interactive map. This EGM will consist of two primary dimensions: rows listing intervention categories, and columns listing disease outcome, and each cell of the matrix will show studies containing evidence on that combination of intervention and disease outcome. The number of primary studies or included studies in a review will be shown by the size of the bubble on the map and the critical appraisal rating shown by colour of the bubble - green, orange and red corresponding to high, medium and low. The map will also contain filters, such as type of publication of included studies, year category, study design, population group and WHO regions focusing on a subset of studies meeting certain criteria. The proposed intervention-outcome framework would be developed through a consultative process with stakeholders.

If multiple reports exist for the same study, for example, both working papers and journal articles, the latest or most complete version will be used in the map. If different papers report different analyses, for example on different outcomes or for different subgroups, each paper will be included. In a publication with multiple studies, each eligible study will be shown in the map separately, meaning that a study with multiple interventions or outcomes will be shown multiple times on the map. Systematic reviews will be mapped based on question defined in the systematic review. Primary studies included will be mapped as well regardless of whether they are included in one or more systematic reviews.

The number of sources screened, assessed for eligibility, included and excluded will be presented in a PRISMA flow diagram. A descriptive report will also be provided which will depict the interventions and outcomes of systematic reviews and impact evaluations, as well as outline the key characteristics of the population for interventions. The synthesis will also report on 'evidence gaps' (i.e., instances with no studies for a particular intervention) and 'synthesis gaps' (referring to situations with several impact evaluation literature but lacking systematic review) which will enhance our understanding of the research landscape and identify areas warranting further exploration.

Dissemination

The Evidence and Gap Map (EGM) and its corresponding report will be published in a peer-reviewed journal. Additionally, we plan to create plain language summaries in collaboration with our Patient and Public Involvement (PPI) group. These summaries will serve as a foundation for various dissemination materials and methods, such as a briefing paper, and posters, to be developed based on input from the research and stakeholder team.

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APPENDIX 1: OVID MEDLINE SEARCH STRATEGY

	Ovid MEDLINE(R) ALL <1946 to December 01, 2023>	
1	probiotics/ or synbiotics/	25106
2	(Probiotic* or Lactobacill* or "Lactic Acid Bacteria" or Bifidobacteri* or Saccharomyces or Enterococc* or Lactococc*).ti,ab.	199668
3	(Yakult or Actimel or ProViva or Cultura or Verum or Activia or Canesflor or yoghurt).ti,ab.	3820
4	(miso or sauerkraut or kefir or kimchi or tempeh or kombucha or sourdough).ti,ab.	3545
5	or/1-4	207525
6	Urogenital infection*.ti,ab.	1002
7	urogenital diseases/ or female urogenital diseases/	2257
8	("bacterial vaginosis" or colpitis or vaginitides or vaginosis or vaginitis or "vagina* infection" or "vagina* inflammation" or "Vaginosis Bacterial" or "Gardnerella vaginitis" or dysbacteriosis or BV or Gardnerella).ti,ab.	23473
9	Vaginosis, Bacterial/	3589
10	("vulvovaginal candidiasis" or vulvovaginiti* or vaginos?s or candidiasis or candida or candidosis or yeast or "vaginal yeast infection" or "candida* vaginitis" or "vaginal candidosis" or VVC or thrush).ti,ab.	268980
11	Candidiasis, Vulvovaginal/	3867
12	("urinary tract infection*" or "vaginal discharge" or urethritis or UTI or bacteriuria or cystitis or pyelonephritis or glomerulonephritis or "Anti-Infective Agents Urinary" or genitourinary or bacteremia or urogenic or pyuri*).ti,ab.	157234
13	Urinary tract infections/	43111
14	or/6-13	458878
15	5 and 14	61963
16	systematic review.pt.	246383
17	((cochrane or cost or effectiveness or implementation or rapid or systematic or "state of the art" or umbrella or evidence) adj2 (overview* or review* or synthes*)).ti,ab.	379328
18	meta-analysis.pt.	190927
19	(meta-analysis or metaanalysis or "meta analysis" or metaanaly?e or meta-analy?e or "meta analy?e").ti,ab.	248566
20	or/16-19	521580
21	(randomis* or randomiz* or randomly).ti,ab.	1156256
22	(trial* or controlled or "control group*" or "intervention group*").ti,ab.	2387082
23	rct.ti,ab.	32828
24	randomized controlled trial.pt.	604235
25	controlled clinical trial.pt.	95474
26	("treatment group" and ("usual care" or placebo)).ab.	7395
27	((single or doubl* or tripl* or treb*) and (blind* or mask*)).ti,ab.	228870
28	("4 arm" or "four arm").ti,ab.	1611
29	(("quasi experiment*" or quasiexperiment* or "quasi random*" or quasirandom* or "quasi control*" or quasicontrol*) adj3 (method* or stud* or design*)).ti,ab.	19664
30	((before adj4 after) or "BA stud*" or "CBA stud*").ti,ab.	435560
31	(interrupt* adj2 "time series").ti,ab.	6029
32	("time points" adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month* or hour* or day* or "more than")).ti,ab.	27016
33	("Quasi experiment*" or quasiexperiment* or "regression adjustment estimate*" or "regression discontinuity" or "instrumental variable* estimate*" or "time series" or timeseries or "before$after" or before-after or "pre post").ti,ab.	91648

34	or/21-33	3387190
35	20 or 34	3713498
36	15 and 35	4324
37	animal experiment/ not (human experiment/ or human/)	2505
38	exp "Animals"/ not "Humans"/	5175557
39	37 or 38	5175642
40	36 not 39	3832