

**VAGINAL MICROBIOME DYSBIOSIS AND RECURRENT BACTERIAL
VAGINOSIS: BIOFILM ECOLOGY, CLINICAL EVIDENCE, REAL-
WORLD ANALYTICS AND PRECISION PREVENTION****Xolboyeva Mashhura Yoqutjon qizi**Email – yoqutjonovnam@gmail.com**Termez University of Economics and Service****Faculty of Medicine****Abstract**

Background: Recurrent bacterial vaginosis (BV) constitutes a persistent clinical challenge in which temporary symptom resolution after antimicrobial therapy frequently fails to produce durable microbial recovery. Its pathobiology involves loss of protective lactic-acid-producing vaginal communities, expansion of diverse anaerobic organisms, surface-associated polymicrobial structures, host–microbe interactions, and sexual exchange of BV-associated bacteria. Objective: To critically synthesize microbiological and clinical evidence explaining recurrence, compare conventional and emerging prevention strategies, and assess the role of real-world evidence (RWE) and computational methods. Methods: This structured critical narrative review integrated identifiable clinical trials, peer-reviewed syntheses, public guidance, and regulatory sources available through October 2026. The manuscript does not claim a prospectively registered systematic search, individual-patient access, or de novo meta-analysis. Evidence quality, definitions of recurrence, selection processes, and transportability were evaluated qualitatively. Results: In a randomized phase 2b trial involving 228 women, vaginal *Lactobacillus crispatus* CTV-05 after metronidazole was associated with recurrence by week 12 in 30% versus 45% receiving placebo (risk ratio 0.66; 95% confidence interval 0.44–0.87). A 2025 randomized partner-treatment trial added substantive evidence that sexual-partner reservoirs can contribute to recurrence in selected heterosexual couples. Established CDC treatment guidance supports nitroimidazole- or clindamycin-based regimens and recognizes options for multiple recurrences, while emerging microbiome restoration and antibiofilm interventions require context-specific appraisal of regulatory status and evidence strength. Real-world data from electronic clinical records, prescriptions, laboratories, microbiome profiles and longitudinal patient reports may reveal heterogeneous treatment response, adherence barriers and safety patterns.

However, incomplete symptom ascertainment, confounding and compositional sequencing artifacts can strongly bias estimates. Conclusions: Recurrent BV is better understood as an ecological and relational syndrome than an isolated episode of growth by a single bacterial species. Durable prevention requires accurate diagnostic phenotyping, attention to biofilm persistence, evidence-based therapy, selected partner-related strategies and rigorous study of microbiome restoration. AI-enabled prediction and precision interventions should not displace validated clinical assessment before prospective and external validation.

Keywords

bacterial vaginosis; recurrent bacterial vaginosis; vaginal dysbiosis; vaginal microbiome; Gardnerella; Fannyhessea vaginae; Lactobacillus crispatus; polymicrobial biofilm; metronidazole; Lactin-V; partner treatment; real-world evidence; machine learning; antimicrobial stewardship

Abstract (English: complementary clinical summary)

Clinical framing: Recurrence of bacterial vaginosis after antimicrobial therapy is not necessarily evidence of individual nonadherence or failure by one specific antibiotic. A subset of women experience persistent ecological vulnerability characterized by reduced protective lactobacilli, complex anaerobic populations and microbial exchanges that may occur within intimate partnerships. Existing diagnostic methods remain essential to distinguish symptomatic BV from other causes of discharge. Evidence framing: The 2020 randomized Lactin-V trial provides intervention-specific proof of principle for restoration with a defined Lactobacillus crispatus strain, while a 2025 randomized trial supports a role for male-partner treatment in a selected clinical population. Both require attention to treatment eligibility and implementation constraints. Data-science framing: Observational data and predictive models can aid understanding of repeated clinical episodes but are vulnerable to confounding, misdiagnosis, technical batch effects, informative follow-up and overfitting. Implementation framing: Reliable episode tracking, diagnostic verification, patient-reported outcomes and appropriate antimicrobial stewardship should precede any deployment of artificial-intelligence-guided decisions. The conclusions are based on source-level critical synthesis, not on newly collected clinical data. No unreported sample, effect estimate, or statistically significant finding is created in this manuscript.

Keywords (English)

The preceding keyword set is presented in English.

1. Introduction

The healthy vaginal environment is not microbiologically sterile. In many reproductive-age women it is characterized by communities enriched for lactic-acid-producing lactobacilli, yet there is substantial biological variation across individuals, menstrual phases, hormonal states and populations. A composition dominated by *Lactobacillus crispatus* is frequently associated with a comparatively stable, low-pH environment, whereas communities with greater anaerobic diversity are linked to bacterial vaginosis (BV) and other reproductive-health outcomes. The causal significance of any single detected organism, however, must be judged within its broader ecological and clinical setting. DNA detection is not synonymous with microbial viability, metabolic activity or disease.

BV is a clinical syndrome defined by characteristic vaginal discharge, odor and microbiological changes rather than a disease caused by one universally sufficient pathogen. In recurrent disease, the principal challenge is not only the initial suppression of associated anaerobes, but also restoration of a resilient microbial community and reduction of processes that repeatedly destabilize it. *Gardnerella* species, *Fannyhessea vaginae* (formerly *Atopobium vaginae*), *Prevotella* species and other BV-associated bacteria often coexist in surface-associated communities. Their ecological interactions may influence adherence to epithelium, production of enzymes, metabolite exchange, immune recognition and treatment failure. The field has therefore shifted from the simplistic concept of an infection 'eradicated' by one antibiotic course toward longitudinal microbial ecology.

Recurrence has operational definitions that vary substantially across trials and clinical services. A commonly used research definition is three or more symptomatic episodes requiring treatment in twelve months, while refractory BV describes failure to achieve satisfactory clinical or microbiological resolution following a standard course. These entities should not be treated as interchangeable. Clinical recurrence after an apparently successful regimen may arise from residual organisms protected in an adherent community, re-expansion of anaerobes following failure to re-establish lactobacilli, renewed microbial exchange between sexual partners, or a combination of these processes. Accordingly, cross-study comparison requires common definitions

for baseline cure, time to recurrence, microbiological thresholds and symptom-based endpoints [1,2].

Real-world data (RWD) are information routinely collected during delivery of healthcare or through related sources, such as electronic records, prescription dispensing, laboratory information systems, registries and patient-generated digital reports. Real-world evidence (RWE) consists of clinically interpretable evidence about use, benefits or harms derived from the analysis of such data. RWD are the raw materials; RWE is an inferential product whose trustworthiness depends on data provenance, explicit clinical questions, valid designs and bias control. Longitudinal recurrence is particularly suited to thoughtful RWD research because repeated episodes, discontinuation, follow-up losses and care across institutions are often insufficiently captured in traditional efficacy trials [7,8].

Randomized controlled trials (RCTs) reduce baseline confounding through assignment of interventions, enabling a more defensible interpretation of efficacy under a defined protocol. Routine clinical care yields effectiveness information under real adherence, access, co-medication and patient-preference constraints. The two types of evidence are complementary rather than competing hierarchies: an RCT may establish a treatment effect for eligible participants, and a carefully designed real-world study may characterize transportability, uncommon adverse events or durability in the broader population. Yet observational comparisons cannot automatically be interpreted causally. Severity-driven prescribing, recurrent exposure, unmeasured sexual practices and differential follow-up can generate very convincing but misleading associations.

Regulatory science increasingly recognizes the qualified use of RWE. FDA guidance specifies issues in using clinical-care data for regulatory decisions, while the European Medicines Agency has developed network-based evidence generation, including DARWIN EU. Neither agency asserts that routine databases are inherently reliable, nor that predictive AI creates causal evidence. The World Health Organization emphasizes governance, equity, evaluation and accountability in health AI. In a sensitive domain such as vaginal symptoms and sexual health, stigma, intimate information, consent, representativeness and cybersecurity are not peripheral design issues but determine whether an intervention is ethical and useful.

AI has potential roles in reading microscopy images, integrating molecular profiles with clinical symptoms, detecting misclassification in documentation, forecasting recurrence and identifying possible adverse reactions after antimicrobial use. However, models trained at high-prevalence referral clinics can overestimate risk in primary care, and sequencing models can learn laboratory batch signatures instead of biology. A clinically meaningful AI tool requires calibration, external validation, explainability appropriate to the clinical task, prospective workflow evaluation and explicit testing for unequal error rates. The scientific question addressed in this review is thus both biological and translational: what causes recurrent dysbiosis, what treatments have credible evidence, and what data infrastructure can evaluate outcomes without mistaking statistical association for mechanistic proof?

2. Materials and Methods

Study design and scope. The present article is a structured critical integrative narrative review, not a new prospective cohort study and not a PRISMA-certified systematic review. It synthesizes trial findings, guidance documents, microbiological studies and methodological literature relevant to recurrent BV and vaginal dysbiosis. Sources were investigated through publicly accessible PubMed-indexed records, PMC full texts, CDC and FDA resources, and primary publications in journals including the New England Journal of Medicine and Journal of Infectious Diseases. Scopus, Web of Science, Embase and Cochrane were treated as recommended verification and comprehensive-search sources; access to their complete subscriber indexes was not independently established, so exhaustive screening counts, registration numbers and false claims of having interrogated every platform are intentionally omitted.

Search concepts and eligibility. Core search concepts included 'bacterial vaginosis', 'recurrent', 'vaginal microbiome', 'Gardnerella', 'Fannyhessea', 'Lactobacillus crispatus', 'polymicrobial biofilm', 'partner treatment', 'metronidazole', 'probiotic', 'vaginal microbiota transplantation', 'real-world evidence' and 'machine learning'. Peer-reviewed human studies and syntheses, authoritative clinical guidance, microbiology experiments with translational relevance, and methodological or regulatory sources were eligible. Publications during 2020–2026 received priority; older foundational studies were included only where they defined microbiome community states, diagnosis or laboratory methods. Editorials and early mechanistic research were distinguished from controlled clinical efficacy evidence.

Critical extraction and synthesis. Data elements prioritized were study design, setting, eligibility, microbiological diagnostic criterion, whether recurrent or first-episode BV was enrolled, baseline treatment, randomized unit, intervention, comparator, follow-up, recurrence definition, effect estimate, adverse events, and funding or implementation limitations. No independent effect pooling was attempted because a reproducible complete study inventory and patient-level data were not available. Trial estimates are quoted only where identifiable publications allow direct source verification. Evidence tables distinguish established clinical practice from investigational approaches and avoid fabricating pooled statistics or claims of local cohort recruitment.

Propensity score matching (PSM) may compare similar patients receiving different recurrent-BV therapies in observational datasets by estimating the probability of treatment from baseline covariates. Appropriate predictors include previous recurrences, symptoms, age, pregnancy status, concurrent sexually transmitted infections, hormonal contraception, sexual exposure indicators if ethically collected, access to care and antibiotic history. Balance diagnostics are essential; a propensity score does not correct for unknown or poorly measured confounders. Matching may reduce sample size and alter the target population. Inverse probability weighting (IPW) instead uses treatment probabilities to create a weighted pseudopopulation; extreme weights, lack of overlap and misspecified models can destabilize inference and must be inspected.

Target trial emulation explicitly specifies eligibility, treatment strategies, treatment assignment, time zero, follow-up, outcomes, causal contrast and analysis before examining observational records. For recurrent BV, an illustrative comparison might begin on the day of a documented recurrent episode and compare an eligible suppressive regimen with a clinically appropriate alternative, with recurrence-free time assessed over a prespecified follow-up period. Immortal-time bias arises if patients must survive symptom-free until a later prescription to enter a treatment arm. Baseline and postbaseline factors must be separated, especially because subsequent symptoms influence treatment switches. Sequential trial emulation may be preferable for recurrent episodes, provided within-person correlation is considered.

Kaplan–Meier survival curves can represent time to first symptomatic recurrence while treating censoring transparently. Cox proportional-hazards regression can estimate adjusted hazard ratios if proportional-hazards assumptions are plausible; clinically interpretable absolute recurrence risks should accompany relative measures. Recurrent-event approaches, including counting-process models or frailty models, may be more informative than first-event models where episodes recur repeatedly. Competing events, changes in reproductive status or loss to follow-up can alter the risk set. Survival analysis estimates from a database require real event times; they cannot be reconstructed faithfully from descriptive publications or generated as illustrations and presented as observed findings.

Machine learning may include penalized regression, random forests and gradient boosting for nonlinear interactions between longitudinal symptoms, microbiome measurements and exposure history. Deep learning is potentially suited to microscopy images and high-dimensional sequence data, though small cohorts and batch effects create a high risk of overfitting. Natural language processing (NLP) may identify episodic symptoms and treatment failure from free-text notes, but false negation interpretation and multilingual documentation require clinician review. Reinforcement learning is sometimes proposed for dynamic treatment policies; its offline reward functions, action-space constraints, distribution shifts and safety requirements make routine deployment premature. Large language models should serve controlled abstraction and drafting tasks rather than independent diagnosis or unsupervised treatment decisions.

Missingness and bias. Missing laboratory tests may reflect a clinician's degree of suspicion; absent follow-up often differs between symptom-free and symptomatic patients; missing sexual-practice data may correlate with privacy concerns. These are not necessarily missing-at-random mechanisms. Multiple imputation should be evaluated against plausible mechanisms, and prespecified sensitivity analyses may explore informative dropout. Selection bias can arise when sequencing is preferentially ordered for severe recurrent cases. Microbiome relative abundance is compositional: one organism's proportion may rise merely because another falls. Absolute quantification, negative controls, strain-level methods and batch harmonization are important complements to routine sequencing outputs.

3. Results: Critical Evidence Synthesis

3.1 Vaginal ecological stability and community state patterns

A vaginal community should be interpreted through its function and temporal stability rather than taxonomic composition alone. Lactic acid, epithelial glycogen metabolism, hormone-related substrate availability and local inflammation interact across the menstrual cycle. *Lactobacillus crispatus* frequently defines a low-diversity ecological state; *Lactobacillus iners* can occur in both apparently stable and transitional states and may not afford equivalent resilience. Anaerobe-rich states are heterogeneous, so a single community-state category can conceal clinically relevant differences in bacterial metabolic potential. Stable microbiome recovery is therefore a better research target than a solitary posttreatment swab with a reduced Nugent score.

Repeated sampling can distinguish short-lived fluctuations from persistent dysbiosis. A snapshot taken during menstruation, recent sexual exposure or shortly after medication may reflect a transient perturbation rather than sustained recovery or failure. This distinction is critical when evaluating probiotic products and molecular diagnostics. Cross-sectional correlations between vaginal pH and particular taxa cannot determine whether acidification selected for the community or the community produced acidification; longitudinal mechanistic designs and controlled perturbation studies are needed.

3.2 *Gardnerella*, *Fannyhessea* and polymicrobial organization

Gardnerella is a species-rich group with variable virulence-associated characteristics, making older laboratory reports of a single species inadequate for strain-specific causal claims. Some organisms adhere to vaginal epithelial surfaces, facilitate polymicrobial assembly and participate in enzymatic pathways associated with mucus and epithelial disruption. *Fannyhessea vaginae*, *Prevotella* and other anaerobes can coexist with *Gardnerella* in adherent communities. The biological behavior of these consortia cannot be accurately extrapolated from monoculture antibiotic susceptibility studies because interspecies cooperation changes the environment and can influence microbial tolerance [3,4].

Polymicrobial detection itself is not proof of an organized biofilm. Fluorescence in situ hybridization and other microscopy support extensive epithelial-associated microbial layers, but the precise extracellular matrix architecture and in vivo interactions

remain active research subjects. Biofilm terminology should therefore be used mechanistically rather than as an explanation invoked automatically for every recurrence. Tests that distinguish attached structures from free-living organisms might clarify whether targeted antibiofilm therapy has a useful biological target. Without standardization, investigators risk comparing unrelated substrates, laboratory media and endpoint definitions [3,4].

3.3 Biochemical pathways: acidity, metabolites, enzymes and inflammation

Changes in lactic-acid isomers, amines, short-chain fatty acids and other metabolites provide a functional bridge between dysbiosis and symptoms. Metabolites can influence mucosal pH, epithelial barrier function, inflammatory signaling and microbial competitiveness. Amines are clinically associated with characteristic odor, but a chemical readout is not equivalent to a validated clinical recurrence endpoint. Lactobacillus-mediated acid production may constrain the expansion of anaerobes, whereas enzyme-producing organisms may reshape the environment in ways that favor their own persistence.

The vaginal epithelial response is not uniform across all women with BV. Some present prominent discharge and odor with little tissue inflammation, whereas others have coexisting sexually transmitted infections or mucosal irritation. Inflammatory cytokines may signal disrupted barrier homeostasis, but their diagnostic usefulness requires specificity relative to concurrent pathogens and reproductive states. A mechanistic study should link strain-level composition, absolute microbial loads, metabolites and host markers in the same individuals over time to distinguish disease drivers from secondary consequences.

3.4 Defining recurrence, persistence, relapse and reinfection

Clinical and microbiological recurrence are distinct outcomes. A woman may be symptom-free while a molecular assay still detects BV-associated bacteria; another may experience symptoms due to candidiasis, trichomoniasis, cervicitis or noninfectious irritation despite an apparent shift in vaginal microbial composition. For trials, the time origin should be a documented remission following initial therapy, not an arbitrary date after enrollment. Misclassifying refractory cases as true recurrence inflates apparent relapse rates and undermines comparisons across therapies [2].

Strain-resolution data and concordant partner samples may help distinguish persistence from microbial reintroduction, although demonstrating shared strains does not establish exact direction of transmission. The patient's lived symptom burden is also critical: laboratory-defined disease without discomfort or reproductive implications is not necessarily equivalent to clinically troublesome recurrent BV. Patient-reported outcomes, treatment disruption and sexual-health impact should be recorded separately from Nugent or molecular outcomes. Combining these dimensions is more informative than asserting a universal numerical cure rate.

3.5 Conventional diagnosis: Amsel, Nugent and point-of-care approaches

Amsel clinical criteria combine discharge characteristics, vaginal pH, amine odor after potassium hydroxide and clue cells; a standard diagnosis typically requires at least three of four components. Nugent scoring examines bacterial morphotypes on Gram stain and provides a different, microscopy-based construct. These methods should not be regarded as interchangeable with sequencing-defined community types. Point-of-care tests and nucleic-acid amplification assays may be useful in selected symptomatic patients, but interpretation must respect the platform's intended use and the possibility of mixed vaginitis [1].

In recurrent cases, the first diagnostic priority is often to verify what actually recurred. A prior prescription or patient-reported odor alone does not establish repeated BV episodes. Testing for alternative or concomitant causes can prevent serial empirical antibiotic courses that are unlikely to help. Molecular assays detect targets, not clinical necessity for treatment; positive results require symptom correlation and awareness of the specific assay's validation population. Standardizing case ascertainment would markedly improve the clinical interpretability of retrospective recurrent-BV datasets.

3.6 Molecular diagnostics and 16S rRNA sequencing

16S rRNA sequencing profiles bacterial communities through amplified marker regions, but taxonomic resolution depends on the selected region, primer performance, pipeline and reference database. Whole-metagenome approaches can offer finer strain and functional resolution at greater cost and with more complex bioinformatic demands. Quantitative PCR can provide targeted absolute or semi-absolute measures for clinically specified organisms. No single technique is sufficient for all ecological and diagnostic questions: assays optimized to identify high-risk

dysbiosis are not necessarily optimized to monitor a transplanted strain or infer drug resistance.

Measurement reproducibility requires details of swab location, collection timing, transport, storage, extraction procedures, sequencing depth and contamination controls. Studies comparing pre- and posttreatment microbiomes should batch or randomize specimens to minimize artifactual time trends. Relative-abundance data require compositional methods and, when feasible, companion absolute-load measurements. An apparently large numerical shift in a rare organism may be biologically trivial if the baseline biomass is small. Clinical classification should remain anchored to validated thresholds rather than unsupervised taxonomic clusters alone.

3.7 Conventional antimicrobial treatment and its ecological limitations

CDC guidance recognizes oral metronidazole, intravaginal metronidazole and intravaginal clindamycin as recommended therapies for symptomatic BV, with specified alternative regimens [1]. These drugs can relieve symptoms, but biological remission is vulnerable if an anaerobe-rich community reconstitutes after treatment or protective lactobacilli fail to regain dominance. Antibiotic effectiveness is influenced by exposure, tolerability, administration route, concurrent infections, adherence and species-specific susceptibility. Short-term improvement should not be mistaken for prevention of later recurrence.

For multiple recurrences, CDC describes prolonged suppressive intravaginal metronidazole approaches and certain sequential regimens based on limited evidence [1]. The qualifying phrase matters: suppression may reduce episodes during use without resolving the underlying vulnerability once therapy stops. Frequent empirical retreatment also creates burdens from adverse effects, candidiasis, cost and possible selection for less susceptible organisms. Decisions require individualized assessment, differential diagnosis and an explicit treatment goal, rather than indefinitely repeating the same intervention in the absence of response data.

3.8 Antimicrobial tolerance and emerging antibiofilm strategies

Resistance, tolerance and biofilm-mediated persistence are not identical phenomena. Resistance implies altered susceptibility under standardized antimicrobial testing; tolerance may permit transient survival without a large change in minimum inhibitory concentration; biofilm-associated physiological heterogeneity can shelter

subpopulations. A 2024 systematic narrative review screened 201 unique titles and included 35 relevant studies, most of which were preclinical. Its central conclusion was that human clinical validation and safety testing of experimental antibiofilm products remain essential [3].

Promising laboratory mechanisms include enzymes, peptides, antiseptics, probiotics and surface-active compounds, but an in vitro reduction in biofilm signal does not by itself establish vaginal safety, durable remission or preservation of beneficial organisms. Exposure concentrations achievable on mucosa, effects on epithelial cells and reproductive compatibility require special evaluation. Future trials should distinguish disruption of adherent structures from direct antibacterial killing and from restoration of protective taxa. Comparative clinical trials must use patient-relevant recurrence endpoints rather than only staining intensity or early microscopy appearance.

3.9 *Lactobacillus crispatus* restoration: randomized evidence

The 2020 randomized phase 2b Lactin-V trial evaluated vaginal *Lactobacillus crispatus* CTV-05 after standard vaginal metronidazole among 228 randomized participants. Recurrence by week 12 occurred in 46 of 152 women assigned Lactin-V (30%) and 34 of 76 assigned placebo (45%). The trial reported a multiple-imputation risk ratio of 0.66 (95% CI 0.44–0.87), and found evidence of continued benefit through week 24. These figures are tied to a particular live biotherapeutic formulation, dosing sequence and study population; they do not imply that any over-the-counter probiotic has equivalent efficacy [5].

The biological hypothesis is that reinoculation with an adapted protective strain can create an ecological barrier against dysbiosis after antibiotic-induced perturbation. Yet colonization is conditional on the existing community, host mucosal environment, recent antimicrobial exposure and sexual or menstrual factors. Clinical performance therefore requires independent replication and careful assessment of manufacturing quality, strain identity, cold-chain requirements where applicable, acceptability and local regulatory authorization. Although mechanistically attractive, microbiome restoration should be evaluated as a specific intervention, not as a marketing category.

3.10 Sexual partners, bacterial exchange and the 2025 StepUp trial

The sexual exchange hypothesis has often been oversimplified as a dispute over whether BV is a classic sexually transmitted infection. The more precise question is whether microbial exchange within partnerships can maintain or reintroduce a BV-associated community despite effective treatment of an individual woman. The 2025 StepUp randomized trial evaluated concomitant treatment of male partners in selected couples and reported less BV recurrence than treatment of women alone. Its importance lies in testing a modifiable mechanism with clinical endpoints, not in proving that every case of BV originates in a male partner [6].

Partner treatment decisions depend on the regimen, population, adherence, safety and contemporaneous professional guidance. Prior routine recommendations generally did not advise treating male partners based on older evidence [1], while the later RCT changes the evidence landscape for a defined context. This difference must be acknowledged rather than silently projecting the 2025 result backward into 2021 guidance. Trials of partner-directed care require careful consent, avoidance of blame, attention to nonheterosexual partnerships and equitable access to sexual-health services. Biological plausibility alone does not justify universal treatment without clinical assessment.

3.11 Vaginal microbiota transplantation and experimental ecosystems

Vaginal microbiota transplantation has attracted interest because a complex donor-derived community might reconstitute functions that cannot be recreated by a single bacterial strain. It remains an investigational intervention with significant donor-screening, pathogen transmission, microbial ecology, quality-control and long-term safety concerns. A transient shift in sequencing composition after transplantation would not suffice to show a favorable benefit–risk balance. Trial registries, controlled follow-up and careful determination of clinical endpoints are necessary before any broad implementation claim.

Ethical issues are especially complex because a living microbiome is not a chemically homogeneous medicine. Donor variability, strain transfer, potential antimicrobial-resistance genes and undetected organisms can create poorly quantified risks. Regulatory classification varies across jurisdictions and may evolve with evidence. Research designs should prioritize serious adverse events and sustained symptomatic

remission, with independent monitoring and preplanned stopping rules. No locally improvised transfer procedure should be promoted as established care.

3.12 Environmental, behavioral and hormonal modifiers

Menstrual bleeding, contraceptive exposures, smoking, sexual practices, partner change, intravaginal products and antibiotic use can influence vaginal ecology, but associations vary across studies. The direction of causality is often difficult to separate from confounding by symptoms or care-seeking. For example, a product used in response to symptoms may appear associated with recurrence because it follows early disease manifestations. Ecological exposure models should respect time-ordering and capture both patient decisions and clinician recommendations.

Recommendations must avoid stigmatizing normal hygiene or sexuality and should distinguish biological evidence from speculation. Counseling can discourage douching based on clinical guidance while acknowledging that no behavioral modification guarantees freedom from recurrence. Hormonal and reproductive changes may alter glycogen availability, epithelial maturation and microbial composition, but causal effects should not be inferred from simple comparisons between users and nonusers of contraception. Repeated-measures cohorts offer a more appropriate design for investigating temporal influences.

3.13 Pregnancy, obstetric outcomes and special populations

BV is associated with several reproductive-health outcomes, yet an association does not mean that treating all asymptomatic women will necessarily reduce those outcomes. Pregnancy changes microbial ecology, immune signaling and the balance of treatment risks. Studies enrolling reproductive-age nonpregnant women should not be generalized to pregnant populations without specific evidence of safety and effectiveness. Clinical protocols must use locally applicable pregnancy guidance and document gestational status before medication selection.

Adolescents, immunocompromised patients and individuals with coexisting sexually transmitted infections may have different diagnostic and management needs. Differential access to testing and specialist referral creates additional inequalities in recurrence ascertainment. Research should disaggregate outcomes by clinically justified strata while protecting privacy. Researchers must not interpret microbiome differences across racial or geographic populations as intrinsic biological hierarchies;

social, environmental and methodological determinants often explain part of the observed variation.

3.14 Electronic health records and structured clinical episodes

Electronic health records can link symptoms, point-of-care findings, pregnancy status, laboratory tests and repeat treatment episodes. The central difficulty is defining a genuine episode: the same symptomatic event may generate multiple consultations, prescriptions or diagnostic codes. A reliable recurrence algorithm needs an episode-spacing rule, clinically corroborated diagnostic evidence and time to remission. Misclassification can be differential when patients with frequent symptoms are more often tested or referred.

Natural language processing may recover free-text details such as prior treatment failure or odor recurrence, but negation, hypothetical language and clinician shorthand require validation against manually reviewed notes. Abstraction should avoid unnecessary disclosure of sexual-history detail. An auditable common data model, with versioned code sets and explicit follow-up windows, makes results more comparable across institutions than a simple count of billing codes.

3.15 E-prescriptions, dispensing, exposure and adherence

Electronic prescribing supplies useful information about which antibiotic was recommended, when it was ordered and whether treatment was modified. It does not prove pharmacy dispensing, correct administration or completion of a prescribed course. A study classifying women as 'metronidazole exposed' based only on an order can substantially misestimate real clinical effectiveness. Linkage to dispensing and patient-reported adherence should be considered where feasible and legally permitted.

In recurrent BV, prescription records help characterize repeated antibiotic exposure and possible downstream adverse events. They can also identify switching patterns that are easily mistaken for treatment failure. For example, a clinician may switch medications because of intolerance or formulary barriers despite microbiological response. Analyses should identify treatment strategy and timing before outcomes and avoid defining adherence using future information that can introduce selection bias.

3.16 Laboratory systems, national registries and insurance claims

Laboratory databases store point-of-care readings, molecular assay results and microscopy scores, but different laboratories may use incompatible reference intervals or organisms panels. A negative result from one assay is not necessarily equivalent to negative findings on an expanded molecular panel. National or regional registries could facilitate longitudinal follow-up across settings if episode definitions, patient identifiers and data-use permissions are sufficiently robust.

Insurance claims describe utilization and costs but often lack symptom severity or confirmation of microbial remission. Claims-based recurrence therefore requires validation against clinical information. Registry studies can address long-term comparative effectiveness and equity, but linkage errors, differential attrition and selective inclusion can invalidate otherwise precise-looking estimates. Data linkage should use privacy-preserving governance and clearly state what individual-level information was not measured.

3.17 Pharmacovigilance and treatment-related harms

Pharmacovigilance should characterize suspected adverse drug reactions to nitroimidazoles, clindamycin and emerging microbiome-directed therapeutics, including gastrointestinal intolerance, hypersensitivity, treatment-associated candidiasis and adverse effects that prompt discontinuation. Spontaneous reporting systems can detect unusual safety signals, but the absence of a reliable denominator and selective reporting prevent direct calculation of incidence. Observational comparative safety studies need control for baseline health status, concurrent medication and clinical indication.

Drug safety signal detection may use disproportionality statistics, temporal sequencing and manual adjudication. Such signals are hypotheses rather than confirmed causal risks. Pharmacovigilance analytics can use NLP to group case narratives and screen duplicates, but explainable and human-reviewed adjudication remains necessary. In a reproductive-health population, pregnancy and fertility-related exposure windows should be specified with particular care. Safety measures must be integrated with symptom outcomes because a strategy that reduces short-term relapse but causes excessive harms may have negative net benefit.

3.18 Wearables, mobile symptom diaries and patient-generated data

Wearable sensors do not directly diagnose BV. Nonetheless, symptom diaries and consent-based mobile tools can describe odor, discharge, discomfort, menstruation, treatment adherence and quality-of-life fluctuations over time. These data may reveal clinically meaningful relapse earlier than scheduled clinic visits and help discriminate persistent symptoms from a new episode. Their subjective nature is not an inherent weakness if instruments are validated, timestamps are reliable and recall biases are minimized.

Digitally engaged participants may differ from the population receiving care, and frequent app reminders can themselves change reporting or health behavior. A mobile symptom signal should trigger appropriate evaluation rather than automatic antibiotic prescribing. Studies should report missing diary days, dropout, language accessibility and whether users can withdraw or delete their data. Combining high-frequency symptom data with occasional microbiological assays may be more realistic than demanding frequent invasive visits.

3.19 Machine learning and clinical recurrence prediction

Prediction models may estimate who is most likely to experience recurrence after an initial course of therapy by integrating baseline recurrence count, microbiome profile, concurrent infections, medication history, symptom severity and follow-up access. The prediction target must be explicit: 12-week symptomatic recurrence is not the same as detection of anaerobes at six weeks. Internal cross-validation is insufficient if every sample from one person is split across training and test sets; patient-level separation is mandatory.

Evaluation should include discrimination, calibration, decision-curve analysis and subgroup performance. An algorithm with high area under the curve can still be clinically harmful if a selected threshold misses severe recurrent cases or creates unnecessary retreatment. Rare species, changing assay panels and site-specific prescribing patterns create dataset shift. Appropriate reporting requires independent validation, a locked model version and a prespecified action tied to the risk score.

3.20 Deep learning, images, multiomics and batch effects

Deep learning can extract features from Gram-stain images or integrate microbiome sequences, host transcriptomic responses and metabolites. Its value depends on

sample size, technical reproducibility and a coherent biological endpoint. Imaging data can leak laboratory identity through color, microscope settings and slide preparation; sequence-based models may similarly classify extraction batches rather than pathology. Balanced multicenter design is more persuasive than a complex architecture trained on a small convenience cohort.

Multimodal fusion might eventually distinguish symptomatic from asymptomatic anaerobe-rich communities and identify mechanisms of refractory BV. However, clinical decisions require a model that is stable under missing modalities and differences in instrumentation. Explainability tools, such as feature attribution, should be interpreted as model diagnostics, not proof that an organism causes relapse. External laboratory validation and prospective comparative utility studies are prerequisites to clinical reliance.

3.21 NLP and large language models in reproductive-health records

Clinical NLP can convert narrative descriptions into a timeline of episodes, prior therapy and symptom response. Generative language models may help draft standardized summaries or extract prespecified variables with human validation. They can also hallucinate dates, confuse reported symptoms with clinician conclusions and inadvertently reveal sensitive information. No model should be allowed to diagnose recurrent BV or prescribe antimicrobials solely from unverified chat narratives.

Multilingual documentation presents particular challenges where Uzbek, Russian and Latinized terminology appear in the same clinical record. Models trained on English clinical notes may fail on local abbreviations or transliterated symptoms. Evaluation therefore needs local chart review, documented disagreement rates, clear data governance, opt-out provisions where required and clinician override. High apparent extraction accuracy in a benchmark dataset should not be confused with safety in production.

3.22 Reinforcement learning and adaptive treatment policies

Reinforcement learning proposes sequential decisions optimized against a reward that incorporates symptom-free time, adverse effects and treatment burden. Recurrent BV is an intuitively relevant test case because the best decision may depend on a series of previous responses rather than a single exposure. However, historical

prescribing records reflect clinician preferences and unmeasured indications, creating confounded action selection. Offline policy evaluation requires strong assumptions and robust off-policy methods, which are rarely verifiable in sparse outpatient data.

Direct autonomous policy learning is not appropriate for routine practice. A safer near-term approach would compare predefined, guideline-concordant treatment sequences in prospective pragmatic studies. Such designs can adapt evidence generation while maintaining human oversight and predefined stopping rules. Researchers must separately evaluate whether a treatment-selection algorithm improves clinical outcomes above a simple transparent protocol; algorithmic complexity is not itself a patient benefit.

3.23 Personalized medicine and biomarker classification

Precision management depends on distinguishing prognostic markers of recurrence from predictive markers that identify differential treatment benefit. A recurrent-BV risk marker does not automatically select the best antibiotic or live biotherapeutic. Candidate biomarkers include species-level profiles, lactate-related functional measures, epithelial inflammatory responses, strain persistence and broader host variables. Each needs analytical reproducibility, validation across populations and demonstration of clinical utility.

Pharmacogenetics may affect drug metabolism or intolerance for particular therapies, while pharmacogenomics uses broader genomic variation; neither currently provides a universally validated routine treatment-selection system for recurrent BV. Any personalized algorithm should compare risks and benefits against standard clinical assessment, not against the absence of care. Biomarkers should be considered only if their incremental information changes a decision that matters to patients and clinicians.

3.24 Treatment-response prediction across other disease domains

The requested cross-disease analogy is most valuable as a methodological comparison rather than as a claim that BV drug-response models are interchangeable with those developed for diabetes or cardiology. In diabetes, drug-response prediction may incorporate serial metabolic values and adherence; cardiovascular models often rely on competing outcomes and long-term event risk. These settings

highlight the need for consistent time zero, longitudinal measurements and risk calibration, all relevant to recurrent BV.

Oncology offers lessons on molecular subtyping and biomarker-driven treatment selection, infectious diseases on pathogen resistance and stewardship, and neurology on symptom trajectories that are imperfectly aligned with biological measurements. Yet transport of algorithms across disease areas is inappropriate because event definitions and treatment mechanisms differ. For BV specifically, a justified model must incorporate community-level ecology rather than assume that a single host laboratory value predicts outcome.

3.25 Comparative effectiveness: trial efficacy versus real-world performance

The benefit seen in a tightly controlled trial can diverge from effectiveness when real patients cannot obtain the product, discontinue it due to side effects, lack refrigeration or experience repeat exposures. Observational treatment comparisons should use active comparators and equivalent follow-up schedules whenever possible. A biased comparison between highly adherent specialist patients and less closely monitored routine patients cannot isolate the treatment effect. Absolute recurrence risk and patient-reported symptom burden are particularly useful for communicating clinical relevance.

RWD may uncover which patients fail to achieve durable benefit even when average efficacy is positive. However, effect modification is difficult to establish when subgroup selection occurs after looking at the data. Prespecified groups and interaction tests with appropriate uncertainty reporting are preferable to unsupported claims of personalized response. The regulatory acceptability of a dataset depends on fitness for purpose, traceability and validity, not on size alone [7,8].

3.26 Missing data, selection bias and clinical misclassification

Women who do not return for follow-up are not necessarily cured, and those who attend frequently may appear to have more recurrence simply because episodes are more likely to be detected. Informative observation creates bias that ordinary regression may not eliminate. Repeat microbiome measurements obtained only from refractory patients produce an enriched study population that does not represent all

individuals with BV. A future registry should capture contact attempts, test indication, care-seeking outside the main institution and loss-to-follow-up reasons.

Selection of antibiotic by disease severity creates confounding by indication; differential laboratory verification creates verification bias; classifying exposure using a future prescription creates immortal-time bias. Quantitative sensitivity analyses are useful, but cannot guarantee correction of missing causal variables. Reporting frameworks should disclose missingness patterns, censoring, assay version changes and all preplanned sensitivity comparisons. Transparent limitations are more valuable than artificially precise confidence intervals.

3.27 Explainable AI, fairness and clinical decision support

Explainability should be tailored to a clinician's decision. A list of microbiome features may help a researcher debug a model but may not explain why a specific patient should undergo further testing rather than empirical retreatment. Useful clinical decision support can prompt confirmation of symptoms, highlight pregnancy-specific safety restrictions, display a recurrence timeline and link to current guidelines. It must not convert uncertain model risk into a categorical disease label without an appropriate diagnostic standard.

Fairness means measuring whether predictive errors differ by age, geography, language, care setting and other clinically relevant groups, and examining whether disparities arise from unequal access to diagnostic testing. Privacy protection is particularly important because sexual-health records can cause substantial social harm if disclosed. WHO's ethics framework and evolving FDA/EMA approaches provide principles for accountability and lifecycle monitoring, but local governance must translate principles into responsible access controls, clinician escalation rules and patient explanations.

3.28 Uzbekistan: digital health, e-prescriptions and registry architecture

Uzbekistan has pursued staged digital-health and electronic-prescription implementation. A December 2025 official government notice describes the phased introduction of an e-prescription framework, including initial categories of systemic antibacterials and hormonal medicines [10]. This provides a potential building block for studying treatment episodes and antimicrobial stewardship, but its existence must not be mistaken for evidence that a national recurrent-BV registry or standardized

microbiome surveillance system is already operational. The Ministry of Health could support pilot definitions and interoperability rather than claiming comprehensive coverage without published audit data.

A practical multicenter pilot might begin with gynecology and primary-care clinics using standardized symptoms, Amsel or Nugent results where available, STI co-testing, medication and dispensing records, pregnancy status, repeat episodes and patient-reported outcomes. A laboratory subcohort could collect validated 16S or targeted PCR measurements at baseline, posttreatment and recurrence. Consent, pseudonymization, strict role-based access and an ethical review mechanism should precede data linkage. The pilot should collect data on who declines testing, who drops out and whether referral barriers change treatment effectiveness.

3.29 Uzbekistan: capacity, local validation and staged AI implementation

Clinical pharmacology and antimicrobial-stewardship services could evaluate repeated nitroimidazole exposure, adverse events and prescribing variation. A linked pilot should prioritize accurate episode identification before advanced machine learning: a simple validated rule-based algorithm may deliver more operational value than a poorly calibrated deep network. Laboratories would need harmonized specimen handling, standardized reporting of molecular assays, external quality assurance and transparent costs. Such conditions are proposed recommendations, not claims about currently functioning national infrastructure.

A phased policy evaluation should first document care pathways and data completeness, then pilot a registry with independent manual chart review, then assess the external validity of recurrence prediction and finally test whether decision support improves patient-important outcomes. RWE-based effectiveness comparisons can follow if enough well-characterized treatment strategies and confounders are available. The most defensible near-term measure of success is reliable access to diagnosis, appropriate therapy, safer repeat prescribing and a measurable reduction in avoidable symptomatic recurrence.

3.30 Integrated evidence assessment and clinical implications

Taken together, the evidence favors a multifactorial model of recurrence involving microbial community instability, surface-associated persistence, treatment and host context, and microbial exchange within some partnerships. The strongest

intervention evidence in this synthesis comes from identifiable randomized trials for a specific *L. crispatus* live biotherapeutic after initial antibiotic therapy and for selected male-partner treatment strategies. Evidence for generalized commercial probiotics, transplantation and novel antibiofilm products remains more heterogeneous or preliminary. Each proposed innovation must be judged against conventional, documented clinical care rather than against a simplistic absence-of-treatment comparator.

Clinical translation should privilege the person experiencing recurrence: confirm the diagnosis, distinguish refractory disease from a new event, evaluate alternative causes and concurrent infections, explain uncertainty and choose a guideline-consistent plan with follow-up criteria. Claims of universal cure, guaranteed probiotic replacement or autonomous AI prescription lack sufficient support. A successful translational program will measure repeated symptomatic events, time to recurrence, adverse effects, quality of life, treatment acceptability and equitable access, alongside microbiome changes.

3.31 Summary of directly verifiable clinical findings

Evidence	Design and population	Reported result	Interpretation
Lactin-V (Cohen et al., 2020)	Randomized phase 2b; 228 women	Week-12 recurrence versus 45%; RR 0.66 (95% CI 0.44–0.87)	BV 30% RR following metronidazole; not all probiotics [5]
Male-partner treatment (Vodstrcil et al., 2025)	Randomized partner-treatment trial	Significant improvement in recurrence prevention in eligible couples	Context-specific in partner strategy; assess local guidance and access [6]
Antibiofilm evidence (Gao et al., 2024)	Systematic narrative review; 35 included studies	Most preclinical; clinical validation limited	Avoid extrapolating laboratory efficacy to established therapy [3]

CDC clinical guidance (2021) Evidence-based national practice recommendations Standard oral and intravaginal treatment options; strategies for multiple recurrences Clinical depends on current local updates [1]

3.32 Proposed longitudinal data dictionary for recurrent BV

Domain	Variables	Collection period	Validation
Phenotype	Symptoms, Amsel, Nugent, alternative diagnoses	Baseline / each recurrence	Chart adjudication
Microbial ecology	Quantitative assays, taxonomy, assay batch	Baseline / post-treatment recurrence	QC controls, absolute loads
Treatment	Regimen, dose, route, dispensing, adherence	Each episode	Pharmacy reconciliation
Safety	Suspected adverse events, pregnancy status	During and after exposure	Causality review
Follow-up	New episode date, censoring, QOL	Standardized monthly interval	Contact ascertainment
Context	Partner strategy, healthcare access	Baseline and time varying	Consent and privacy controls

3.33 Analytical framework: causal questions and design choices

Question	Appropriate design	Principal threat	Recommended guardrail
Does a therapy reduce recurrence?	Randomized trial or target-trial emulation	Confounding by severity	Time-zero alignment, active comparator

How long until recurrence?	Kaplan–Meier recurrent-event survival	/ Informative censoring	Report loss and sensitivity
Which microbiome predicts relapse?	Prospective external validation	Batch effects and leakage	Patient/site-level split
Can AI improve decision quality?	Prospective decision-impact trial	Automation bias	Human oversight, decision curves
Which adverse effects emerge?	Active cohort and safety review	Underreporting and signal	Verified outcomes and denominators

4. Discussion

The evidence synthesis challenges the tendency to assign BV recurrence to one failed antibiotic choice. A biologically plausible framework must accommodate microbial persistence, community reassembly, host conditions, antimicrobial tolerance, and potential exchange within partnerships. These mechanisms are not necessarily mutually exclusive. Their relative contribution may vary within the same individual over time. Consequently, a one-size-fits-all recurrence model is unlikely to capture the clinical heterogeneity observed across healthcare systems. Clinical studies that stratify by prior episodes, microbial state, partner exposure, and initial response can generate more actionable evidence than those reporting one average microbial diversity score.

The randomized Lactin-V trial and the more recent partner-treatment trial represent important advances because they directly intervene on distinct hypothesized drivers of recurrence. Still, they should not be amalgamated into a pooled 'microbiome therapy efficacy' estimate: interventions, eligibility and biological targets differ. The former supports the promise of selected strain restoration after antimicrobial therapy, whereas the latter supports addressing microbial exchange in defined relationships. Neither result validates unsupervised use of commercial products nor establishes an intervention for every patient subgroup. Pragmatic effectiveness research should examine whether these improvements persist under ordinary treatment adherence and diverse healthcare access.

The biofilm hypothesis is attractive partly because it makes recurrence understandable after apparent clearance of free-living bacteria. Nonetheless, current evidence is not uniform regarding structural criteria, assay interpretation or which biofilm-related endpoints reliably predict clinical relapse. Laboratory experiments often use surfaces and growth conditions poorly representative of the vaginal epithelium. It would be premature to describe every candidate biofilm disruptor as a practical option for patients. Reproducible human randomized studies, with adequate follow-up and adverse-event assessment, are required before routine guideline inclusion [3].

Real-world analytics can complement the sparse long-term follow-up of certain clinical trials. Their strength is population reach, not automatic validity. For instance, a dataset containing repeated antibiotic prescriptions may identify high-use patients, but without symptoms, adherence and test confirmation it cannot quantify genuine microbiological recurrence or drug resistance. The same data limitations can produce biased algorithmic predictions. External validation, prospective deployment trials and equity-focused implementation evaluation therefore belong to the scientific agenda, rather than being presented as administrative final steps.

Ethical AI is especially important for recurrent BV because sexual and reproductive-health histories are sensitive, some inputs are subjective, and a wrong prediction may invite stigmatizing advice or unnecessary antimicrobial therapy. Explainable algorithms cannot eliminate biased measurements; neither can a transparent decision tree compensate for absent clinical information. Governance must therefore address consent, retention, access rights, model monitoring, human override, and the ability to contest or correct an erroneous label. Large language models may be valuable for controlled administrative abstraction, but their fluency must not be mistaken for validated clinical reasoning.

Several limitations of this manuscript merit explicit acknowledgment. It is a critical narrative synthesis rather than a preregistered systematic review, and no exhaustive search ledger or formal risk-of-bias scoring is claimed. The concentration of evidence in identifiable guidelines, a small number of pivotal randomized trials and selected reviews means that publication bias and geographic transportability remain concerns. No local Uzbek patient-level dataset was provided, and therefore no Uzbekistan-specific recurrence rate, model accuracy, hazard ratio or effect-size estimate has been

created. Forward-looking implementation proposals are labeled as such. These choices prioritize verifiability over a false appearance of quantitative completeness.

Regulatory trends support controlled use of RWD and lifecycle evaluation of AI, not bypass of clinically established evidence standards. FDA guidance on RWE highlights fitness-for-purpose and data standards [7,8]; WHO ethics guidance emphasizes human autonomy and accountability, and EMA's DARWIN EU initiative illustrates a structured framework for observational evidence across systems. A recurrent-BV registry aligned with these principles would require explicit case definitions, provenance tracking, permitted data uses and a local accountability mechanism. Cross-border transfer of sensitive microbiome and sexual-health data would also require particular attention to legal and ethical constraints.

A high-value research agenda would first build a multicenter, longitudinal phenotype-rich cohort with scheduled follow-up and strain-level microbiome measures in a subcohort. It would then test mechanistic hypotheses within prospective studies, distinguish microbial remission from symptomatic remission, and conduct comparative trials of specific restoration or partner strategies. Long-term outcomes should include recurrence-free intervals, antimicrobial use, adverse events and quality of life. The principal scientific advance will not be the complexity of sequencing or computational models; it will be better alignment between measured ecology and decisions that actually improve durable patient outcomes.

[4.1 WHO, FDA, EMA and DARWIN EU: governance implications](#)

WHO guidance on ethical use of artificial intelligence in health emphasizes autonomy, safety, transparency, accountability, inclusiveness and sustainability. For recurrent-BV research these considerations translate into patient-controlled consent, responsible handling of sensitive reproductive-health data and disclosure of uncertainty. FDA recommendations for real-world evidence require study-specific assessment of reliability and relevance. EMA's DARWIN EU framework exemplifies networked observational analysis, but a large federated dataset is not inherently free from misclassification or unmeasured confounding. For AI-enabled clinical decision support, regulatory consideration depends on intended medical use, change management and evaluated clinical performance. None of these initiatives substitutes for context-specific clinical validation.

4.2 Reporting standards and limitations of this review

The paper uses IMRAD headings to organize published evidence and proposed analytical strategies. Its Results section comprises findings from published sources, not new statistical analyses. A true systematic review should preregister a protocol as appropriate, reproduce complete database-by-database search strategies, report screening counts with a PRISMA flow diagram, assess risk of bias using suitable tools and establish eligibility before screening. A real-world causal study would require an explicitly populated source cohort and a prespecified analysis plan consistent with STROBE/RECORD principles. Since those components were not supplied or executed, this article avoids simulated p-values, invented study counts, unsupported pooled estimates and unwarranted claims of systematic-review status.

4.3 Prioritization of unanswered research questions

The most pressing unresolved issue is whether microbial phenotypes can be used prospectively to assign therapies that improve durable remission compared with simple guideline-based care. Studies should prospectively separate initial clinical response, molecular community recovery and time to subsequent symptoms, because these outcomes are only partially aligned. A second priority is to quantify the relative roles of within-host microbial persistence, partner-associated exchange and environment-related destabilization using paired longitudinal specimens with adequately documented treatment and exposure timing. A third priority is to establish which candidate host or microbial markers offer incremental decision value beyond careful symptom-based diagnosis. Negative studies and unsuccessful strain colonization attempts should be published to limit selective dissemination of favorable findings.

Pragmatic trials can address how patient preference, dosing burden, medication cost, follow-up capability and access to partner care change observed effectiveness. Endpoints should include validated quality-of-life scales, avoidance of unnecessary antimicrobials and clinically verified recurrence intervals, rather than assuming sequencing-defined *Lactobacillus* dominance is sufficient. Studies involving microbiome-directed interventions should distinguish biological colonization, product safety and relief of patient-important symptoms. For algorithm evaluation, external-site testing should be followed by a prospective comparison of decisions with and

without the model; silent observational deployment is not an adequate substitute for impact assessment.

Finally, geographic representation matters. A microbiome prediction rule trained in one region may fail in Uzbekistan because of laboratory methods, prescribing practices, disease ascertainment and structural healthcare differences rather than intrinsic properties of local patients. A transparent pilot with ethics approval, reproducible laboratory protocols and registered statistical questions would create a platform for testing transportability. The publication of missing-data summaries and protocol deviations should be treated as a scientific strength. These research priorities emphasize modest, verifiable improvements in care rather than promises of universal recurrence prevention.

5. Conclusion

Recurrent bacterial vaginosis is a dynamic syndrome arising from vaginal microbial dysbiosis, unstable recovery after antimicrobial therapy, adherent polymicrobial communities, host and environmental influences, and in some contexts microbial exchange within partnerships. Evidence-based clinical care should begin with verified diagnosis and a distinction between treatment-refractory disease and recurrent symptomatic episodes. Established antimicrobial regimens remain foundational; controlled evidence for particular *L. crispatus* restoration and partner-directed strategies broadens prevention options without justifying indiscriminate use of unvalidated products. Real-world data and computational models can improve longitudinal understanding and implementation only when case definition, causal design, data quality, privacy and external validation are robust. An Uzbekistan-focused pilot linking structured gynecologic care, laboratory diagnostics, medication exposure and longitudinal patient reports would be a defensible platform for future evaluation. The objective is durable patient benefit, not merely short-term removal of detectable anaerobic taxa.

Declaration of evidence and research integrity

No participants were recruited and no patient-level datasets were analyzed for this review. No novel recurrence rate, odds ratio, hazard ratio or meta-analytic pooled estimate is represented as newly calculated. Author contributions, conflicts of interest, funding, ethics declarations and institutional details must be supplied and

verified before submission. The UDC is provisional. Text originality and similarity index can only be assessed using the target journal's specified screening procedures.

References (Vancouver-style; primary URLs included for verification)

1. Centers for Disease Control and Prevention. Bacterial Vaginosis. Sexually Transmitted Infections Treatment Guidelines, 2021. <https://www.cdc.gov/std/treatment-guidelines/bv.htm>
2. Muzny CA, Sobel JD. Understanding and Preventing Recurring Bacterial Vaginosis: Important Considerations for Clinicians. *Int J Womens Health*. 2023. <https://pmc.ncbi.nlm.nih.gov/articles/PMC10423565/>
3. Gao M, Manos J, Whiteley G, et al. Antibiofilm Agents for the Treatment and Prevention of Bacterial Vaginosis: A Systematic Narrative Review. *J Infect Dis*. 2024;230:e508-e517. doi:10.1093/infdis/jiae134.
4. Bacterial Vaginosis—Vaginal Polymicrobial Biofilms and Dysbiosis. 2023. <https://pmc.ncbi.nlm.nih.gov/articles/PMC10412922/>
5. Cohen CR, Wierzbicki MR, French AL, et al. Randomized Trial of Lactin-V to Prevent Recurrence of Bacterial Vaginosis. *N Engl J Med*. 2020;382:1906-1915. doi:10.1056/NEJMoa1915254.
6. Vodstrcil LA, Plummer EL, Fairley CK, et al. Male-Partner Treatment to Prevent Recurrence of Bacterial Vaginosis. *N Engl J Med*. 2025;392:947-957. doi:10.1056/NEJMoa2405404.
7. Food and Drug Administration. Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products. Guidance for Industry. 2023. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug>
8. Food and Drug Administration. Data Standards for Drug and Biological Product Submissions Containing Real-World Data. Guidance for Industry. 2023. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-standards-drug-and-biological-product-submissions-containing-real-world-data>

9. Food and Drug Administration. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. Final Guidance. 2025.
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices>
10. Government of the Republic of Uzbekistan. Procedure for Phased Implementation of Electronic Prescriptions. 23 December 2025.
<https://digital.gov.uz/oz/advice/784/document/4462>
11. Ministry of Health of the Republic of Uzbekistan. Discussion of Implementation of Electronic Prescription System. 15 December 2025.
<https://gov.uz/ru/ssv/news/view/110849>
12. Workowski KA, Bachmann LH, Chan PA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187.
<https://www.cdc.gov/mmwr/volumes/70/rr/rr7004a1.htm>
13. Muzny CA, Sobel JD. Bacterial Vaginosis—Time to Treat Male Partners. N Engl J Med. 2025;392:1026-1027. doi:10.1056/NEJMe2500373.
14. Bacterial vaginosis: a review of approaches to treatment and prevention. 2023.
<https://pmc.ncbi.nlm.nih.gov/articles/PMC10264601/>
15. Bacterial vaginosis and biofilms: Therapeutic challenges and innovations—a narrative review. 2024. doi:10.25259/IJDVL_1322_2023.
16. World Health Organization. Ethics and Governance of Artificial Intelligence for Health: WHO Guidance. 2021.
<https://www.who.int/publications/i/item/9789240029200>
17. World Health Organization. Ethics and Governance of Artificial Intelligence for Health: Guidance on Large Multi-Modal Models. 2024.
<https://www.who.int/news/item/18-01-2024-who-releases-ai-ethics-and-governance-guidance-for-large-multi-modal-models>
18. European Medicines Agency. Data Analysis and Real World Interrogation Network (DARWIN EU). <https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu>

19. European Medicines Agency. Real-world evidence. <https://www.ema.europa.eu/en/human-regulatory-overview/research-development/real-world-evidence>
20. Food and Drug Administration. Artificial Intelligence-Enabled Medical Devices. <https://www.fda.gov/medical-devices/digital-health-center-excellence/artificial-intelligence-enabled-medical-devices>
21. Food and Drug Administration. Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence-Enabled Device Software Functions. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/marketing-submission-recommendations-predetermined-change-control-plan-artificial-intelligence>
22. World Health Organization. WHO releases AI ethics and governance guidance for large multi-modal models. 2024. <https://www.who.int/news/item/18-01-2024-who-releases-ai-ethics-and-governance-guidance-for-large-multi-modal-models>
23. Food and Drug Administration. Real-World Evidence. <https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence>
24. World Health Organization. WHO recommendations on interventions against sexually transmitted infections and associated conditions. <https://www.who.int/health-topics/sexually-transmitted-infections>
25. Food and Drug Administration. FDA Guidances with Digital Health Content. <https://www.fda.gov/medical-devices/digital-health-center-excellence/guidances-digital-health-content>
26. World Health Organization. Global strategy for health sector responses to sexually transmitted infections. <https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/stis/strategies>
27. Food and Drug Administration. Predetermined Change Control Plans for Machine Learning-Enabled Medical Devices: Guiding Principles. <https://www.fda.gov/medical-devices/software-medical-device-samd/predetermined-change-control-plans-machine-learning-enabled-medical-devices-guiding-principles>

28. European Medicines Agency. Big data. <https://www.ema.europa.eu/en/about-us/how-we-work/big-data>
29. World Health Organization. Sexual and reproductive health and research. <https://www.who.int/teams/sexual-and-reproductive-health-and-research>
30. European Medicines Agency. European medicines regulatory network data strategy. <https://www.ema.europa.eu/en/about-us/how-we-work/big-data>