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Vaginal ring acceptability: A systematic review and meta-analysis of vaginal ring experiences from around the world

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Abstract

Objective: The vaginal ring (ring) is a female-initiated, long-acting drug delivery system for different indications, including HIV prevention. Our aim was to provide evidence for acceptability of the vaginal ring across indications to support dapivirine and multipurpose prevention technology ring introduction and roll out.

Study design: This systematic review and meta-analysis followed PRISMA guidelines. We searched PubMed, Web of Science, Embase, and grey literature for publications reporting favorable ring acceptability and secondary outcomes involving actual ring use (comfort, ease of ring use, ring comfort during sex, expulsions, and vaginal symptoms) or hypothetical acceptability for any indication published January 1, 1970–June 15, 2021. We estimated random-effects pooled prevalence, assessing between-study variation using meta-regression.

Results: Of 2,234 records, we included 123 studies with 40,434 actual and hypothetical ring users. The primary outcome assessment included 50 studies with 60 ring subgroups totaling 19,271 ring users. The favorable acceptability pooled prevalence was 85.6% (95%CI 81.3, 89.0), while hypothetical acceptability among non-ring users was 27.6% (95%CI 17.5, 40.5). In meta-regression, acceptability was higher in menopause (95.4%; 95%CI 88.4, 98.2) compared to contraceptive rings (83.7%; 95%CI 75.6, 89.5). Acceptability was lower in pharmacokinetic

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Supplementary materials

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studies (50%; 95%CI 22.1, 77.9) compared to RCTs (89.5%; 95%CI 85.8.92.4) and in studies assessing acceptability at ≥12 months (78.5%; 95%CI 66.5, 87.1) versus studies assessing acceptability at <3 months (91.9%; 95%CI 83.7, 96.1). European (90.6%; 95%CI 83.9, 94.7), Asian (97.1%; 95%CI 92.0, 99.0), and multi-region studies (93.5%; 95%CI 84.6, 97.4) reported more favorable acceptability compared to African studies (59.4%; 95%CI 38.3, 77.5). Secondary outcomes were similarly favorable, including ring comfort (92.9%; 95%CI 89.2, 95.4), ease of use (90.9%; 95%CI 86.5, 94.0), and comfort during sex (82.7%; 95%CI 76.4, 87.6). Limitations include inconsistent outcome definitions and unmeasured factors affecting acceptability.

Conclusions: Women who used vaginal rings reported they were acceptable across indications geographic regions and indications. Policy makers should consider the ring as an important option for pregnancy and HIV prevention drug development.

Implications: This review found favorable acceptability among vaginal ring users across indications and geographic areas, in contrast to low hypothetical acceptability among non-users. Vaginal rings are an important drug delivery system for pregnancy and HIV preventions, and scale-up should plan to address initial hesitancy among new users.

Keywords

Acceptability; Contraception; HIV prevention; Meta-analysis; Systematic review; Vaginal ring

1. Introduction

The vaginal ring (ring) is a drug delivery system providing long-acting, controlled release of an active pharmaceutical ingredient (API) for systemic or localized effects [1]. Rings can be used for various indications, including prevention of unintended pregnancy [2] and treatment of menopausal symptoms [3]. In March 2021, the World Health Organization released guidance on the dapivirine ring for HIV prevention, after including the dapivirine ring on the prequalification list of medicines in November 2020 [4] and recommending the dapivirine ring as an additional HIV prevention option for women at substantial risk of HIV in January 2021 [5, 6]. The European Medicines Agency announced a positive opinion on the dapivirine ring under Article 58 in July 2020 [7]. As of August 2021, the dapivirine ring has been approved for use in Zimbabwe [8] and is under regulatory review in the United States [9] and multiple countries in sub-Saharan Africa [10, 11]. Rings are also in clinical trials as multipurpose prevention technologies (MPTs), protecting against multiple sexual and reproductive health risks, such as unintended pregnancy and HIV [12].

Globally, women's sexual and reproductive health burden remains high, with 44% of pregnancies unintended [13], 870,000 annual cases of HIV infection in women and girls [14], and 295,000 maternal deaths each year [15]. Interest in rings has grown as research has demonstrated increased contraceptive options and access to longer-acting methods are associated with improved sexual and reproductive health outcomes [16]. Novel, woman-controlled technologies, including rings, provide options for long-acting protection from sexual and reproductive health risks and, unlike implants or intrauterine devices (IUDs), allow women to initiate or discontinue use without involving a healthcare provider.

Ring users have expressed preferences for long-acting, partner-approved methods preventing both HIV and pregnancy, with few side effects, and the potential for use without partner knowledge [17]. Qualitative systematic reviews suggest most women are satisfied with rings, find them easy to use, and report infrequent expulsions and other adverse events [17, 18]. Most women also report they disclose use to partners and do not feel the ring during sex [17].

Given the importance of providing options for women to protect themselves against multiple sexual and reproductive health risks, we conducted a meta-analysis to summarize current knowledge about acceptability of the vaginal ring as a drug-delivery system, agnostic of the API. We estimated the proportion of women finding the ring acceptable and examined related acceptability constructs such as ease of use, comfort, and ring expulsions [19]. Our approach expands on previous systematic reviews focusing on qualitative acceptability of contraceptive rings; [18] rings used in low- and middle-income countries; [17] and, discontinuation of contraceptive rings [20]. We examine rings used globally and for all indications; address the need for quantitative estimates of ring acceptability; and, investigate the association of study and ring characteristics with primary and secondary acceptability outcomes via meta-regression. Our aim is to examine vaginal ring acceptability across indications to provide evidence for the potential acceptability of the dapivirine ring and other rings under development as multipurpose prevention technologies.

2. Material and methods

This systematic review and meta-analysis follows PRISMA guidelines; the protocol is available online through PROS-PERO (ID: 150229; found at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=150229) (S1 File) [21]. We included studies reporting primary quantitative data on relevant acceptability outcomes; with women of any age; assessing active, placebo, or hypothetical rings for any indication; and, published in English between January 1, 1970 and June 15, 2021. The review was completed July 5, 2021. Due to our interest in ring acceptability as a drug-delivery platform, we excluded references only reporting effectiveness or API-related complications.

We searched PubMed, Web of Science, and Embase using a predetermined search strategy and searched grey literature including conference proceedings and reports. We identified additional references via a hand-search of bibliographies, a web search, and through a predetermined list of experts. We developed a search strategy with an RTI International librarian and can be found in the appendix (S2 File). Two authors (KR and JG) conducted screening and data extraction independently in Covidence. The same authors (KR and JG) resolved disagreements via consensus and contacting publication authors where necessary. This review utilized summary estimates.

One primary (KR) and one secondary reviewer (JG) assessed risk of bias for all studies, using a 10-item risk of bias tool; [22] each item was scored as “low” or “high” risk (1 or 0 points, respectively). We summed the four items pertaining to internal validity and six items pertaining to external validity; and, due to little variation in the internal validity score, combined them to create a single continuous score with higher values indicating greater

validity. We did not exclude studies based on risk of bias and included the validity score as a covariate in meta-regression models. Due to the wide variety of study designs and the assessment of multiple outcomes, we did not judge the overall body of evidence using an approach such as GRADE.

We extracted descriptive data (proportions, means, and standard deviations) for our primary acceptability outcome, "general acceptability"; for secondary acceptability outcomes, including study completion, ease of use, comfort, comfort during sex; and, for secondary unfavorable ring outcomes likely to be associated with lack of acceptability including ring expulsions and vaginal symptoms. Acceptability outcome measures are summarized below. We extracted study-level data, including country, study design, population and setting, and sample size, ring indication, and ring attributes. We classified progestogen-only rings for postpartum contraception separately from other contraception rings, given their unique indication and population. To account for within-study variation in ring characteristics, the unit of analysis is unique ring groups within studies.

We defined the primary outcome of general acceptability as "the extent to which people… receiving a healthcare intervention [vaginal ring] consider it to be appropriate, based on anticipated or experiential cognitive and emotional responses to the intervention" [19]. During data extraction, we recorded the proportion of users selecting a favorable response regarding acceptability ("very" or "somewhat acceptable"; "acceptable"); satisfaction ("extremely," "very," or "somewhat satisfied"; "satisfied"); would recommend ("would definitely" or "would probably recommend"; "would recommend"); would use in the future ("would like to" or "intended to" continue use after study); or, liked (liked "very much" or "somewhat"; "liked"). Secondary acceptability outcomes included: (1) hypothetical acceptability, defined as acceptability of a product described to potential users, lacking the context and preferences of real-life use [23]. The proportion of potential users selecting, following description of a hypothetical ring product, that they were "likely" or "very likely" to use; "wanted to use" or "were willing to use"; or "would be interested in using"; (2) comfort, defined as the proportion of users selecting a favorable response regarding comfort ("comfortable" or "very comfortable;" "agreeing" or "strongly agreeing" the ring was comfortable; "never" or "only occasionally" felt the ring was uncomfortable; no vaginal discomfort); and, not feeling the ring ("never" or "rarely" felt; did not feel; no foreign-body sensation); (3) ease of use, defined as the proportion of users selecting a favorable response regarding ease of insertion (insertion "easy," "always easy," or "mostly/fairly easy"; insertion was "not at all a problem"; no difficulty with insertion); and, ease of use (insertion and removal easy or unproblematic; "very easy to use"; no difficulty inserting and/or removing); (4) comfort during sex, defined as the proportion of users selecting a favorable response regarding not feeling during sex ("never" or "rarely" felt during sex); comfort during sex ("comfortable" during sex; no discomfort during sex); partner not feeling during sex (partner did not feel during sex; partner did not experience discomfort during sex); and, no interference with sex (did not interfere with sex; not bothersome during sex). Secondary unfavorable ring outcomes were defined as: (1) expulsions defined as the cumulative proportion of participants reporting a ring expulsion during the study period; and (2) vaginal symptoms defined as the proportion of participants reporting discharge (discharge; leukorrhea); vaginal irritation; and, vaginitis (vaginitis; colpitis).

We extracted data on cumulative product continuation and product-related discontinuation over the entire study period to assess the correlation of each outcome with general acceptability. Product continuation was defined as the proportion of users who initially agreed to participate continuing to use the study product at the last study assessment. Product-related discontinuation was defined as the proportion of users not completing the study due to discontinuations related to the ring (i.e. adverse events, discomfort) vs discontinuations due to change in need (i.e. pregnancy intention) or client situation (i.e. moved, personal reasons).

We used Stata v.15 metapreg package to conduct random-effects meta-analysis for primary and secondary acceptability outcomes [24]. Meta-analysis derives an overall mean score from individual studies (here, ring groups), weighting each group by its relative precision. The results for our primary outcome are summarized in a forest plot showing the reported proportions and 95% confidence intervals by group. For each outcome, heterogeneity between estimates was measured using the I^2 statistic, with 50% and 75% indicating substantial and considerable heterogeneity, respectively [25]. Studies with conceptually similar outcomes were combined for meta-analysis. If studies reported the same outcome over multiple timepoints (e.g. at 3 months, 6 months, and 12 months), we included the first timepoint after initiation of ring use, as results from multiple timepoints cannot be analyzed in standard meta-analysis; the earliest sample is the most representative as it captures ring users prior to discontinuation or loss to follow up; and, ring users have reported having the most difficulty with the ring early in use. For product continuation and product-related discontinuation, we reported cumulative continuation and discontinuation over the entire study period.

Between-study variation was investigated using random-effects meta-regression, which estimates the effects of ring group-level covariates on outcome proportions. The coefficients estimate the impact of a covariate on the logit of the outcome (S3 File). We conducted meta-regression of ring- and study-level covariates for all outcomes except for hypothetical acceptability (n=12 studies); as such, the pooled prevalence of hypothetical acceptability was compared descriptively to that of general acceptability among ring users. Analyses examined associations between ring group-specific outcomes and the study-level covariates (S6 File). As this research intends to inform research and implementation for the dapivirine ring and other rings for HIV prevention, we used North and sub-Saharan Africa, a high-priority setting, as the referent group for geographic region. We captured data on several physical attributes of rings and included ring diameter in our analyses since it was least frequently missing. We calculated the relative reduction in between-study variance using τ^2 in meta-regression with all covariates compared to τ^2 in a model with no covariates [26]. We assessed whether data collection method (face-to-face vs self-reported) influenced outcomes but excluded it from meta-regression due to lack of change in R^2 values. We gathered data on shore hardness (a measure of ring material resistance to indentation) and cross-sectional diameter but excluded these from meta-regression due to high correlations between both features and ring outer diameter. We assessed publication bias across studies using funnel plots and Egger's test for small-study effects (S8 File) [27].

3. Results

Our search identified 2,234 records, of which 90 were duplicates. Following title and abstract screening, we excluded 1,869 records; and, in full text screening, we excluded 133 records: 71 records were excluded due to reporting irrelevant outcome data, 16 for not reporting acceptability outcomes, 16 for reporting partial data captured fully elsewhere, and 30 for other reasons such as reporting only qualitative data. Following screening, 151 publications describing 123 studies with 34,740 ring users and 5,694 hypothetical users were included. Twenty-five studies were excluded from meta-analysis due to reporting product continuation without also reporting general acceptability [10, 28–47], reporting continuous rather than labelled categorical or dichotomous outcomes [48] and reporting preference data only [49, 50] (Fig. 1). Some secondary manuscripts of the included studies assessed acceptability across ring groups with different characteristics (e.g. active and placebo rings) and were not included in meta-analysis.

The studies included 51 countries, with 28 studies from Europe [33, 34, 37, 39, 40, 43, 49–71], 47 from North and South America and Australia [29–32, 36, 38, 42, 47, 48, 72–113], 18 from the Asia-Pacific [35, 114–129], 17 from North and sub-Saharan Africa [10, 28, 44, 46, 130–143], and 13 from multiple regions [41,45,144–154]. Sixty-three studies evaluated rings used for contraception, 21 for menopause, 21 for HIV prevention, and five for MPT; of the 123 studies, 58 were RCTs, 58 were observational studies, and 7 were pharmacokinetic studies. The median assessment time was 4 months (interquartile range [IQR]: 3, 12) (Table 1 and S4A and B File). The median internal threat to validity score was 6 (IQR: 6, 6); the median external validity score was 1 (IQR: 1, 2). Threats to external validity included lacking a sampling frame representative of the target population, not using random selection for recruitment, and having high non-response bias; threats to internal validity included not using validated measures (S4C File).

In meta-analysis, the crude pooled prevalence of general acceptability was 85.6% (95%CI 81.3, 89.0) from 50 studies (60 ring groups) with 19,271 ring users (Fig. 2). In contrast to the high general acceptability found among ring users, hypothetical studies not based on actual ring experience reported low acceptability (27.6%; 95%CI 17.5, 40.5) (S5A Figure). Secondary outcomes were similarly high, including ring comfort (92.9%; 95%CI 89.2, 95.4), ease of use (90.9%; 95%CI 86.5, 94.0), and comfort during sex (82.7%; 95%CI 76.4, 87.6) (S5B–F Figure).

Ring expulsions (9.1%; 95% CI 6.8, 12.3) and vaginal symptoms (11.3%; 95%CI 8.3, 15.1) were relatively infrequent. We observed substantial to considerable heterogeneity for all outcomes (I^2: 54.1%–94.5%). Adjusted estimates of pooled prevalence from meta-regression fell within the confidence limits of the unadjusted estimates for all outcomes (Table 2).

We conducted meta-regression to identify characteristics associated with the primary outcome, general acceptability (Table 3), secondary acceptability outcomes (Table 4), and unfavorable ring outcomes (Table 5). Full results for meta-regression models can be found in the appendix (S6 File) along with summary figures (S7 File). The proportion of total

between-study variance explained in the adjusted meta-regression model ranged from 52% to 75%.

3.1. General acceptability

In meta-regression, the primary outcome of general acceptability was associated with study and ring characteristics (Table 3). Outcome proportions varied by operationalization of general acceptability, with “would recommend” higher than “satisfaction.” General acceptability was higher in the Europe, Asia Pacific and multi-region studies compared to African studies; in menopausal rings compared to contraceptive rings; in API rings compared to placebo rings; in studies with earlier assessment of acceptability (<3 months) compared to later acceptability assessment (12 months or later); and, in larger rings (>55 mm) compared to smaller rings (≤55 mm). General acceptability was significantly lower in pharmacokinetic studies compared to RCTs.

3.2. Secondary acceptability outcomes

Secondary acceptability outcomes, including comfort, ease of use, and comfort during sex, were also associated with study and ring characteristics in meta-regression (Table 4). Outcome proportions varied by operationalization of comfort, ease of use, and comfort during sex. Secondary acceptability outcome proportions varied by region, with higher comfort in the Europe, Asia, and multi-region studies; lower ease of use in European, Asian and multi-region studies; and lower comfort during sex in the Americas/Australia and in multi-region studies, compared to African studies. Later assessment times were associated with higher ease of use and comfort during sex, but the relationship between comfort and assessment time was unclear. Compared to contraceptive rings, HIV/MPT rings had higher ease of use and menopause rings had higher comfort during sex and lower overall comfort. Rings with no API had higher comfort compared to rings with an API. Rings with a diameter >55 mm were less comfortable and more difficult to use compared rings with a diameter ≤55 mm.

3.3. Secondary unfavorable ring outcomes

Unfavorable ring outcomes, including expulsions and vaginal symptoms, were associated with study and ring characteristics in meta-regression (Table 5). The validity score was negatively associated with expulsions. Vaginal symptoms were higher in Europe, the Americas and Australia, Asia, and in multi-region studies compared to Africa. Expulsions were higher for observational studies compared to RCTs. Observational studies and pharmacokinetic studies had lower vaginal symptoms compared to RCTs. HIV/MPT rings had higher vaginal symptoms, and other hormonal rings had lower vaginal symptoms compared to contraceptive rings. Rings with larger diameters had higher expulsions and vaginal symptoms compared to rings with smaller diameters.

3.4. Sensitivity analysis

Visual inspection and Egger’s tests demonstrated evidence of publication bias in the comfort during sex and expulsions models, which were explored in sensitivity analysis. Egger’s tests

remained statistically significant after excluding one outlier for comfort during sex, and 2 outliers for expulsions (S8 File).

4. Discussion

This study assessed global acceptability of the vaginal ring across indications, including general acceptability and related constructs, such as reported comfort, ease of use, and expulsions. A fundamental expression of acceptability among end-users is essential to the success of the ring for any health indication. This analysis comes in the context of the November 2020 inclusion of the dapivirine ring for HIV prevention on the prequalification list of medicines by the WHO [4] and recommendation for the ring as an HIV prevention option for women at substantial risk of HIV [5,6], as well as the positive opinion of the dapivirine ring by the European Medicines Agency under Article 58 [7], and recent approvals [8] and upcoming reviews by other regulatory agencies [9,11]. Our analysis offers several critical insights about ring acceptability and use that can inform future research and ring scale-up activities globally.

Most women who used the ring liked it, irrespective of geographic location, indication, or other factors. However, women who had not actually used the ring reported low hypothetical acceptability; and, it is likely that women with low hypothetical acceptability do not enter ring trials. Although the ring has been used as a drug delivery system for decades, it constitutes a novel technology for many due to limited global distribution. Lack of awareness, familiarity, and experience likely contribute to the lower hypothetical acceptability of the ring [17, 18]. We found increased duration of ring experience was associated with higher ease of use and comfort during sex. This is supported by studies indicating acceptability increases following ring use [155, 156], and the existence of a “learning curve”, where ring users were initially apprehensive and required peer and provider support to become more consistent and proficient users [157–163]. Consequently, scale up of the dapivirine or other rings must include recognition of, and planning for, hesitancy among women around uptake and initiation. Investments in overcoming initial hesitancy may result in greater adherence and persistence once initiated, a conclusion that is supported by recent positive findings of high continued use of the dapivirine vaginal ring in the DREAM and HOPE open-label extension studies and the REACH trial among adolescent girls and young women [28,141,164].

“General acceptability” is a complex concept incorporating several dimensions of a product’s appeal [19] and was operationalized differently across studies. In the models exploring overall acceptability, ease of use, and comfort during sex, there were different results depending on outcome operationalization. The measurement of acceptability constructs may have important implications for data consistency and interpretation [165]. It has been argued that acceptability is under-theorized, and that assessment is frequently measured via behavioral proxies [166]. We recommend that future assessments of vaginal ring acceptability adopt the recent theoretical work of authors such as Sekhon et al. [19] that use standardized, self-reported measures of acceptability and attitudes regarding the intervention across multiple acceptability domains and include both anticipated and experienced acceptability. Careful translation and cognitive pretesting are necessary to

ensure studies are adequately capturing acceptability constructs, particularly in multinational or multicultural studies [167].

There was some regional variation in key outcomes, as most regions had higher general acceptability compared to Africa. The Americas and Australia were associated with less favorable comfort during sex and vaginal symptoms, but less frequent expulsions. Studies conducted in Asia reported less favorable ease of use and more frequent vaginal symptoms. Multi-region studies were associated less favorable comfort during sex and more frequent vaginal symptoms. This variation could be related to the proportion of users with previous experiences with vaginal products [168], differences in normative behaviors around vaginal practices [169], and differences in norms around reporting socially desirable attitudes [170]. Ring acceptability across regions and cultures should continue to be assessed with ring scale-up, particularly as regulatory bodies in sub-Saharan Africa review the dapivirine ring and prepare for introduction and roll-out of the dapivirine ring and future multipurpose prevention technologies.

General acceptability and several other outcomes varied by indication. Indication-specific variations could be related to the purpose of the ring (e.g. whether it was for treatment or prevention), perceived risk, and/or the availability of alternative dosing forms. For example, general acceptability was highest for menopausal indications, where rings are used for symptom management and are indicative of a situation where dosing alternatives are limited compared to contraceptive indications. The interplay between the purpose of the ring, perceived risk, and the availability of alternative options, will change over time as new delivery forms are developed and approved for use.

Comfort was higher for placebo rings than for API rings, potentially indicating that API plays a role in user perceptions of ring comfort. While APIs may influence ring acceptability, and this review did not assess API-related adverse events, it is worth considering that vaginal insertion presents less systemic drug exposure to potent drugs like those for HIV PrEP, minimizing systemic side effects [171]. Of note, reported vaginal symptoms were not higher among the API subgroups, and the pooled prevalence of vaginal symptoms was relatively low (11.3%).

For some acceptability outcomes, the ring's API may favorably influence user perceptions of acceptability, making it challenging to separate the effects of the ring's API from the delivery system itself. For example, the finding that comfort during sex was more favorable for menopausal rings (vs contraceptive rings) may reflect these biases, as menopausal rings may be prescribed to treat menopause-related vaginal dryness which is largely evident during sex. Rings with an outer diameter >55mm were associated with higher general acceptability, but lower ease of use, lower comfort, and higher expulsions. This finding suggests physical properties of the ring matter, with the enhanced risk of expulsions suggesting a biophysical component. Ring properties are an important consideration for product developers, and this finding offers insight into an attribute that might still be optimized for rings under development. We found several ring characteristics were highly colinear, including outer diameter, cross-sectional diameter, and shore hardness; thus, in our analysis, we only included dichotomized outer diameter in meta-regression models. Further

research is needed to elucidate which ring characteristics influence acceptability and should consider features not included in this analysis such as tensile strength and shore hardness. To date there are limited studies reporting a comparison of acceptability and use experiences with rings having different properties in the same population [45, 52].

This analysis has several limitations. We prespecified covariates investigated as potential sources of statistical heterogeneity; however, factors not amenable to meta-regression such as user age, education level, and cultural norms could also be important predictors of acceptability. The small number of studies reporting hypothetical acceptability (n=12) precluded our ability to assess sources of between-study variation in meta-regression. There were issues with assessing fit statistics for two meta-regression models, limiting our ability to assess the extent to which heterogeneity was explained. Longitudinal studies of ring acceptability may be prone to bias as dissatisfied users drop out over time; however, we did not find statistically significant correlations either between acceptability and study completion among or between acceptability and product-related discontinuation among studies reporting both outcomes (S9 File). While we included unpublished material in our search strategy, we found evidence of publication bias for two outcomes. Meta-regression identifies factors associated with the outcome of interest but does not establish causality; therefore, these findings should be interpreted as hypothesis-generating.

In conclusion, our review provides strong support for the acceptability and favorable use experience of rings used for diverse indications in women globally. Interventions with high acceptability are more likely to lead to persistent and adherent use [172], having the potential to have an important public health impact.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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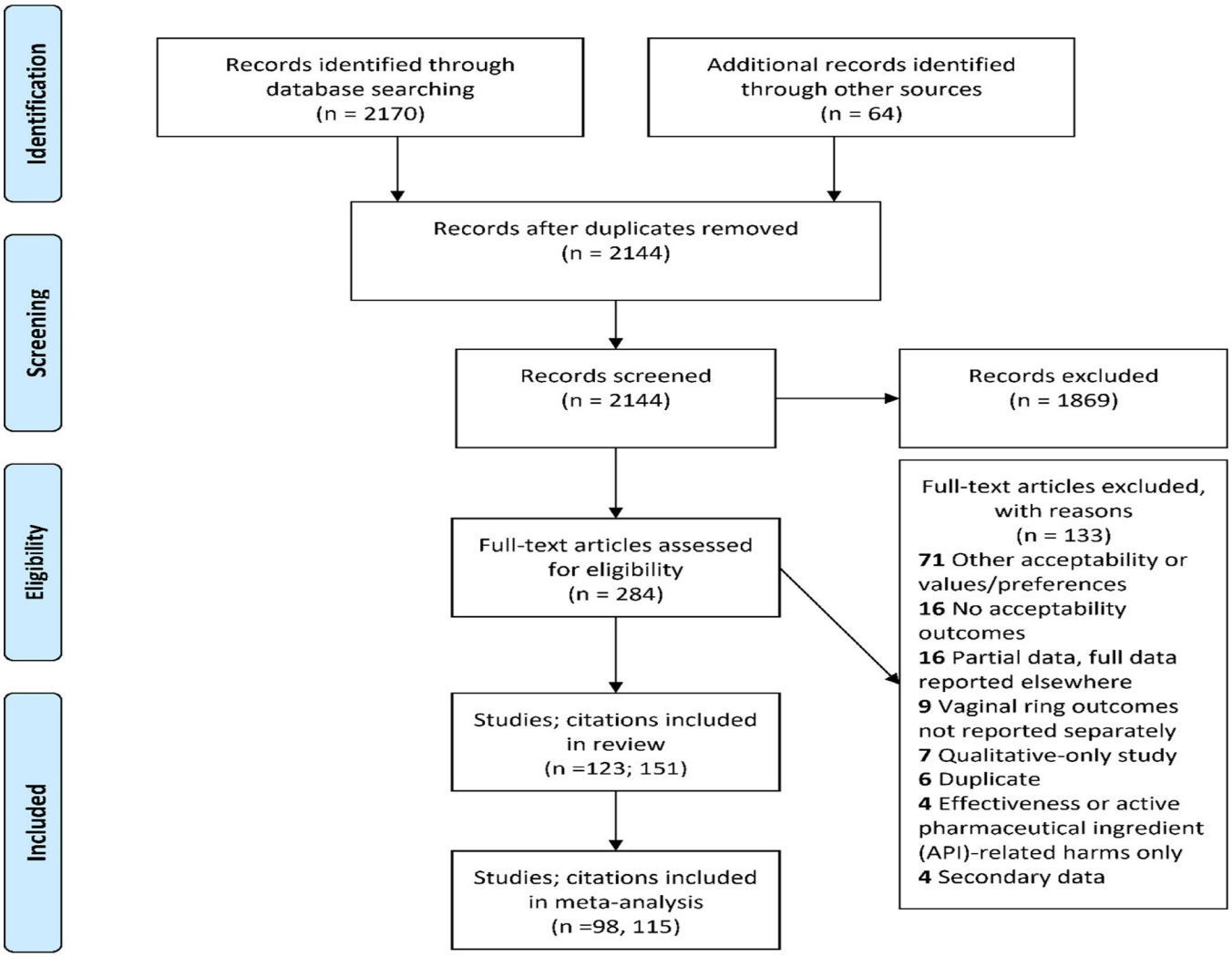

Fig 1.

PRISMA flowchart of publication screening and inclusion for systematic review and meta-analysis.

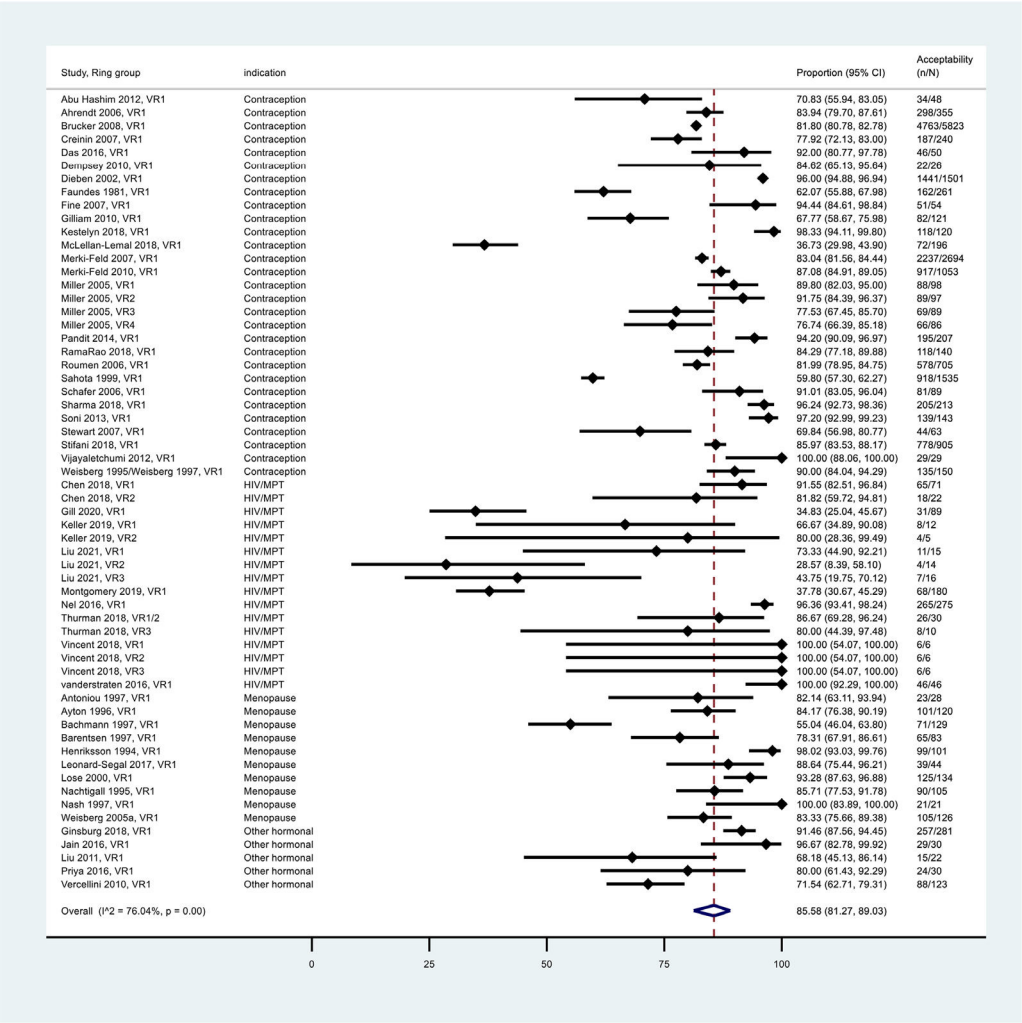

Fig 2.

Forest plot of vaginal ring acceptability from meta-analysis.

Table 1

Studies of vaginal ring acceptability included in meta-analysis

Author, year (Trial name)	Indication	Region	Study Design	Ring Brand	Ring Users	Non-Ring Comparator	Acceptability outcomes[a]						
							Accept.(%)	Hypoth. (%)	Comf. (%)	Use(%)	Sex(%)	Expul. (%)	Vagin. (%)
Abu Hashim 2012 [130]	Contraception	Africa	RCT	NuvaRing[b]	48	Oral norethisterone	70.8		95.8			0.0	
Kestelyn 2018 [132]; Kestelyn 2018a [173]	Contraception	Africa	RCT	NuvaRing	120	-	98.3			99.2	82.5	12.3	0.0
McLellan-Lemal 2018 [133]	Contraception	Africa	Obs.	NuvaRing	202	-	36.7						
Mohamed 2011 [134]	Contraception	Africa	RCT	NuvaRing	300	COC							3.7
RamaRao 2018 [137]; RamaRao 2015 [174]; Ishaku 2015 [175]	Contraception	Africa	Obs.	Unbranded	259	-	84.3				75.8	13.6	
Ahrendt 2006 [51]	Contraception	Europe	RCT	NuvaRing	499	COC	83.9			96.1			12.2
Brucker 2008 [55]	Contraception	Europe	Obs.	NuvaRing	5823	-	81.8			61.4		7.0	
Buhling 2014 [57]	Contraception	Europe	Obs.	NuvaRing/ Circlet	1235	COC, LNG-IUS, POP, contraceptive patch, progestin-only injectable		8.9					
Merki-Feld 2007 [61]	Contraception	Europe	Obs.	NuvaRing	2694	-	83.0			95.0	86.8		2.2
Merki-Feld 2010 [62]	Contraception	Europe	Obs.	NuvaRing	1053	-	87.1			94.0			2.1
Roumen 1990 [64]	Contraception	Europe	Obs.	Unbranded	140	-			100.0 (VR1), 80.0 (VR2), 80.0 (VR3)		94.7 (VR1), 75.0 (VR2), 95.0 (VR3)		20.0 (VR1), 20.0 (VR2), 10.0 (VR3)
Roumen 1999 [66]	Contraception	Europe	Obs.	Unbranded	10	-			76.2 (VR1), 81.8 (VR2),	89.5 (VR1), 90.0 (VR2),	63.2 (VR1), 65.0 (VR2),		23.8 (VR1), 4.5 (VR2),

Author, year (Trial name)	Indication	Region	Study Design	Ring Brand	Ring Users	Non-Ring Comparator	Acceptability outcomes[a]						
							Accept.(%)	Hypoth. (%)	Comf. (%)	Use(%)	Sex(%)	Expul. (%)	Vagin. (%)
									90.9 (VR3)	96.0 (VR3)	50.0 (VR3)		9.1 (VR3)
Roumen 2006 [65]	Contraception	Europe	Obs.	NuvaRing	22	-	82.0			96.0	84.9	6.0	1.1
Sahota 1999 [67]	Contraception	Europe	Obs.	Unbranded	94	-	59.8					28.8	
Say 2009 [68]	Contraception	Europe	Obs.	NA	39	Contraceptive patch, implant		11.8					
Algorta 2017 [72]	Contraception	Americas & Australia	RCT	NuvaRing (VR1), Ornibel[c] (VR2)	35	-							0.0 (VR1), 5.7 (VR2)
Carey 2007 [77]; Carey 2006 [76]	Contraception	Americas & Australia	Obs.	NuvaRing	164	-		45.7					
Creinin 2007 [79]; Creinin 2008 [176]	Contraception	Americas & Australia	RCT	NuvaRing	241	Contraceptive patch	77.9			89.2	75.4		72.6
de Jesus Antunes 2021 [107]	Contraception	Americas & Australia	PK	Unbranded	101								8.3 (VR1), 0.0 (VR2), 0.0 (VR3)
Dempsey 2010 [80]	Contraception	Americas & Australia	RCT	Unbranded	35	DMPA	84.6				69.2		
Faundes 1981 [81]; Hardy 1983 [177]	Contraception	Americas & Australia	Obs.	Unbranded	261	OCP	62.1			90.3		10.2	30.0
Fine 2007 [82]	Contraception	Americas & Australia	Obs.	NuvaRing	68	-	94.4			98.1	92.6		2.9
Gilliam 2007 [83]	Contraception	Americas & Australia	Obs.	NA	661	-		19.2					
Gilliam 2010 [84]	Contraception	Americas & Australia	RCT	NuvaRing	136	OCP	67.8						
Maheux-Lacroix 2011 [92]	Contraception	Americas & Australia	Obs.	Unbranded	59	-		16.9					
Ortiz Gonzalez 2014 [96]	Contraception	Americas & Australia	Obs.	NA	512	Male condom, OCP, contraceptive patch, DMPA, IUD, sponge, diaphragm, implant		4.5					

Author, year (Trial name)	Indication	Region	Study Design	Ring Brand	Ring Users	Non-Ring Comparator	Acceptability outcomes[a] Accept.(%)	Hypoth. (%)	Comf. (%)	Use(%)	Sex(%)	Expul. (%)	Vagin. (%)
Schafer 2006 [98]	Contraception	Americas & Australia	RCT	NuvaRing	127	OCP	91.0						
Stewart 2007 [99]	Contraception	Americas & Australia	RCT	NuvaRing	24	OCP	69.8				76.2		23.8
Terrell 2011 [100]	Contraception	Americas & Australia	Obs.	Unbranded	2265	-		36.0					
Veres 2004 [103]	Contraception	Americas & Australia	RCT	NuvaRing	123	OCP					28.2		
Weisberg 1995 [178]; Weisberg 1997 [179]	Contraception	Americas & Australia	RCT	Unbranded	6	-							27.0
Weisberg 1999a [106]	Contraception	Americas & Australia	RCT	Unbranded	61	-							4.9
Buckshee 1990 [115]	Contraception	Asia	Obs.	Unbranded	50	-							12.0
Das 2016 [117]	Contraception	Asia	Obs.	NuvaRing	50	-	92.0			98.0	70.0		4.0
Fan 2016 [118]	Contraception	Asia	RCT	NuvaRing	714	COC						2.2	
Gupta 1986 [119]	Contraception	Asia	Obs.	Unbranded	70	-			94.3			34.3	14.3
Madhavan Nair 1986 [122]	Contraception	Asia	Obs.	Unbranded	18	-						22.2	
Mehta 1981 [123]	Contraception	Asia	Obs.	Unbranded	39	-					97.4		
Pandit 2014 [124]	Contraception	Asia	Obs.	NuvaRing		-	94.2		86.3	69.1	81.4		2.4
Santibenchakul 2016 [127]	Contraception	Asia	Obs.	NuvaRing	1535	-				12.8			
Sharma 2018 [126]	Contraception	Asia	RCT	NuvaRing	103	COC	96.2		100.0				10.3
Soni 2013 [128]	Contraception	Asia	Obs.	NuvaRing	222	-	97.2			95.8			3.8
Vijayaletchumi 2012 [129]; Siraj 2015 [180]	Contraception	Asia	Obs.	Unbranded	39		100.0						
Dieben 2002 [144]; Roumen 2001 [2]; Roumen 2002 [181]	Contraception	Multi-region	Obs.	NuvaRing	2322	-	96.0		97.6	96.0	82.0		4.8
Koetsawang 1990 [145]; Elder 1991 [182]	Contraception	Multi-region	Obs.	Unbranded	1005	-						13.3	

Author, year (Trial name)	Indication	Region	Study Design	Ring Brand	Ring Users	Non-Ring Comparator	Acceptability outcomes[a]						
							Accept.(%)	Hypoth. (%)	Comf. (%)	Use(%)	Sex(%)	Expul. (%)	Vagin. (%)
Miller 2005 [146]	Contraception	Multi-region	RCT	Unbranded	109		89.8(VR1), 91.8 (VR2) 77.5 (VR3), 76.7 (VR4)						
Sivin 2005 [150]	Contraception	Multi-region	Obs.	Unbranded	802	-			96.0 (VR1), 100.0 (VR2), 98.0 (VR3)				36.0 (VR1), 36.0 (VR2), 36.0 (VR3)
Stifani 2018 [151]; Archer 2019 [183]	Contraception	Multi-region	Obs.	Unbranded	63	-	86.0		67.4	92.2	69.3	42.8	
Weisberg 1999 [153]	Contraception	Multi-region	Obs.	Unbranded	60	-	90.0					1.7	28.3
Weisberg 2005 [154]	Contraception	Multi-region	RCT	Unbranded	86	-						5.8 (VR1), 4.7 (VR2), (VR3)	29.1 (VR1), (VR2), 12.0 (VR3)
Gill 2020 [139] (UChoose)	HIV/MPT	Africa	RCT	NuvaRing	21	Injectable, COC	34.8						
Ipsos Healthcare 2014 [131]; Ipsos Healthcare NA [184]	HIV/MPT	Africa	Obs.	NA	1722	Injectable, implant, vaginal film		35.9					
Montgomery 2019 [185] (Quatro)	HIV/MPT	Africa	RCT	Unbranded	200	Vaginal film, vaginal tablet, vaginal gel	37.8						7.0
Nel 2016 [136] (IPM 015)	HIV/MPT	Africa	RCT	Ring-004[d]	275		96.4		96.4	94.9	84.7	7.1	14.3 (VR1), 15.0 (VR2)
Nel 2016a [140] (The Ring Study)	HIV/MPT	Africa	RCT	Ring-004	16	-							16.1 (VR1), 16.4 (VR2)
Nel 2021 [141] (IPM 032/DREAM)	HIV/MPT	Africa	Obs.	Ring-004	652	-							6.3
Tubert 2021 [142]	HIV/MPT	Africa	Obs.	Ring-004	10	Oral PrEP	42.9						
van der Straten 2012 [138]; Nel 2018 [186]; Montgomery 2012 [187] [186];	hiv/mpt	Africa	RCT	Unbranded	12	-			95.6	89.5		9.5	1.3

Author, year (Trial name)	Indication	Region	Study Design	Ring Brand	Ring Users	Non-Ring Comparator	Acceptability outcomes[a]						
							Accept.(%)	Hypoth. (%)	Comf. (%)	Use(%)	Sex(%)	Expul. (%)	Vagin. (%)
Montgomery 2012 [187] (IPM 011)													
Nel 2014 [63] (IPM 024)	HIV/MPT	Europe	PK	Ring-004 (VR1); Unbranded (VR 2)	8	-			62.5 (VR1), 100.0 (VR2)				0.0 (VR1), 12.5 (VR2)
Chen 2018 [188]; van der Straten 2016 [101] (MTN-024/IPM 031)	HIV/MPT	Americas & Australia	RCT	Ring-004 (VR1); Unbranded (VR 2)	72	-		91.6 (VR1), 81.8 (VR2)	97.2 (VR1), 95.5 (VR2)	87.3 (VR1), 81.8 (VR2)			
Hardy 2007 [87]	HIV/MPT	Americas & Australia	RCT	NuvaRing	391	Diaphragm, vaginal gel				85.9			
Hynes 2019 [88]	HIV/MPT	Americas & Australia	Obs.	NA	835	Injectable, vaginal gel, diaphragm		26.0					
Keller 2019 [89]; Dobkin 2020 [112]	HIV/MPT	Americas & Australia	RCT	Unbranded	12	-	66.7 (VR1), 80.0 (VR2)				72.7 (VR1), 60.0 (VR2)		58.3 (VR1), 40.0 (VR2)
Liu 2019 [110] (MTN-028)	HIV/MPT	Americas & Australia	PK	MK-2048A[e]	45	-						15.4 (VR1), 0.0 (VR2)	0.0 (VR1), 16.7 (VR2)
Liu 2021 [109]; Liu 2021a [108] (MTN-036/IPM 047)	HIV/MPT	Americas & Australia	PK	Unbranded	6	-	73.3 (VR1), 28.6 (VR2) 43.8 (VR3)						
Noguchi 2019 [111] (MTN-029/IPM 039)	HIV/MPT	Americas & Australia	PK	Ring-004	27	-						6.3	6.3
Peitzmeier 2017 [97]	HIV/MPT	Americas & Australia	Obs.	NA	204	Oral PrEP		69.0					
Thurman 2018 [152], Tolley 2021 [113] [CONRAD A13–128)	HIV/MPT	Americas & Australia	RCT	Unbranded	200	-	86.67 (VR1/2), 80.0 (VR3)		95.0 (VR1), 100.0 (VR2), 100.0 (VR3)	89.5 (VR1), 100.0 (VR2), 100.0 (VR3)			
van der Straten 2016 [102] (MTN-013/IPM 026)	HIV/MPT	Americas & Australia	RCT	Unbranded	48	-		100.0	93.3	86.7		2.1	
Vincent 2018 [104]; Guthrie 2016 [189]; Guthrie 2018 [190]	HIV/MPT	Americas & Australia	PK	Unbranded	29	-	100.0 (VR1),		100.0 (VR1), 100.0	100.0 (VR1), 100.0			50.0 (VR1), 50.0

Author, year (Trial name)	Indication	Region	Study Design	Ring Brand	Ring Users	Non-Ring Comparator	Acceptability outcomes[a] Accept.(%)	Hypoth. (%)	Comf. (%)	Use(%)	Sex(%)	Expul. (%)	Vagin. (%)
							100.0 (VR2)		(VR2), 100.0 (VR3)	(VR2), 100.0 (VR3)			(VR2), 16.7 (VR3)
Plagianos 2018 [148]	HIV/MPT	Multi-region	Obs.	NA	58	Vaginal insert, peri-coital oral PrEP, vaginal gel, vaginal film, implant, daily oral PrEP, injection		56.8					
Al-Azzawi 2005 [25]	Menopause	Europe	RCT	Femring/ Menoring[f] (VR 1 & 2) Estring[g] (VR3)	58	-			93.6 (VR1), 91.5 (VR2), 93.9 (VR3)				
Antoniou 1997 [53]	Menopause	Europe	RCT	Unbranded	28	LNG-IUS	82.1		96.4		96.4	7.1	
Barentsen 1997 [54]	Menopause	Europe	RCT	Estring	83	Vaginal cream	78.3						
Buckler 2003 [56]	Menopause	Europe	RCT	Menoring	81	-			85.2				21.4
Henriksson 1994 [58]; Henriksson 1996 [59]	Menopause	Europe	RCT	Estring	101	Estriol vaginal pessary	98.0		92.1		97.0		13.2
Lose 2000 [60]	Menopause	Europe	RCT	Estring	134	Estriol vaginal pessary	93.3		95.5				5.2
Smith 1993 [69]	Menopause	Europe	Obs.	NA	50	-					98.6	8.1	
Spencer 1999 [70]	Menopause	Europe	Obs.	NuvaRing	184	-			45.8		70.8	50.0	
Ayton 1996 [73]	Menopause	Americas & Australia	RCT	Estring	120	Vaginal cream	84.2		64.2		90.0		7.6
Bachmann 1997 [74]	Menopause	Americas & Australia	RCT	Estring	129	Vaginal cream	55.0		65.9			4.4	2.3
Haney 2003 [86]	Menopause	Americas & Australia	Obs.	Unbranded	5768	-				86.2	92.8	15.6	
Leonard-Segal 2017 [90]	Menopause	Americas & Australia	RCT	Unbranded	32	-	88.6		97.7			3.1	11.4
Nachtigall 1995 [93]	Menopause	Americas & Australia	RCT	Unbranded	129	-	85.7		66.7	84.8			
Nash 1997 [94]	Menopause	Americas & Australia	Obs.	Unbranded	21	-	100.0		42.9			4.8	

Author, year (Trial name)	Indication	Region	Study Design	Ring Brand	Ring Users	Non-Ring Comparator	Acceptability outcomes[a]						
							Accept.(%)	Hypoth. (%)	Comf. (%)	Use(%)	Sex(%)	Expul. (%)	Vagin. (%)
Nelken 2011 [95]	Menopause	Americas & Australia	RCT	Estring	941	Oral oxybutynin							40.7
Weisberg 2005a [105]	Menopause	Americas & Australia	RCT	Estring	126	Vaginal tablet	83.3						
Hamada 2003 [120]	Menopause	Asia	RCT	Unbranded	8	-						12.5 (VR1), 16.7 (VR2)	100.0 (VR1), 63.6 (VR2)
Nash 1999 [147]	Menopause	Multi-region	RCT	Unbranded	65	-			92.3			10.8	33.8
Vercellini 2010 [71]	Other hormonal	Europe	Obs.	Unbranded	56	Contraceptive patch	71.5		94.3				
Ginsburg 2018 [85]	Other hormonal	Americas & Australia	RCT	Unbranded	281	Progesterone gel	91.5			80.9	66.9		
Liu 2011 [91]	Other hormonal	Americas & Australia	RCT	NuvaRing	22	COC	68.2						9.1
Agarwal 2016 [114]	Other hormonal	Asia	RCT	NuvaRing	25	COC						12.0	36.0
Dahiya 2016 [116]	Other hormonal	Asia	RCT	NuvaRing	25	COC							16.0
Jain 2016 [121]	Other hormonal	Asia	RCT	NuvaRing	30	COC	96.7					6.7	20.0
Priya 2016 [125]	Other hormonal	Asia	RCT	NuvaRing	533	COC	80.0					6.7	3.3
Roy 2020 [191]	Other hormonal	Asia	Obs.	Unbranded	854	Cu-IUD						15.7	5.0
Sivin 1997 [149]	Other hormonal	Multi-region	Obs.	Unbranded	556	Cu-IUD						6.0	9.1

Accept, Acceptability; Ac, acetate; API, active pharmaceutical ingredient; COC, combined oral contraceptives; Comf, Comfort; Cu, Copper; D, day; Dimen, dimension; DMPA, depot medroxyprogesterone acetate; DPV, Dapivirine; E2, estradiol; EE, estrodiol estrogen; ENG, etonogestrel; EVA, Ethylene-vinyl acetate; Expul, Expulsion; HIV, human immunodeficiency virus; Hypoth, Hypothetical acceptability; IVF, in-vitro fertilization; LNG, levonorgestrel; MVC, maraviroc; NET, norethisterone or norethindrone; NR, not reported; Obs, Observational; OC, oral contraceptives; PDMS, polydimethylsiloxane; PGN, progesterone; PK, Pharmacokinetic; PrEP, Pre-exposure prophylaxis; RTV, room-temperature vulcanized; Sex, Comfort during sex; TDF, tenofovir disoproxil fumarate; TNF, tenofovir; Use, Ease of use; Vagin,Vaginal symptoms; VCV, Vicriviroc; VR, vaginal ring; Yr, year.

[a]Outcomes for vaginal ring acceptability are reported as percentages. For studies reporting outcomes for more than one vaginal ring, the outcome percentages are reported separately for each vaginal ring (e.g. VR1, VR2, etc.).

[b]Nuvaring (Merck, USA) attributes: Ethylene vinyl acetate copolymers and magnesium stearate; 54 × 4mm; 0.120 mg/d etonogestrel and 0.015 mg/d ethinyl estradiol; continuous use for 21days., 7 ring-free day.

[c]Ornibel (Exeltis Healthcare, Spain) attributes: Ethylene vinyl acetate; 54 × 4mm; 0.120 mg/d. etonogestrel and 0.015 mg/d. ethinyl estradiol; continuous use for 21days, 7 ring-free days.

[d]Ring-004 (International Partnership for Microbicides, USA) attributes: Platinum-catalyzed silicone; 56 × 7.7mm; 25 mg DPV; continuous use for 1 month.

[e] MK-2048A (MTN-28) attributes: Ethylene vinyl acetate; 54 × 4mm; 182 mg of vicriviroc, 30 mg of MK-2048; continuous use for 28 days.

[f] Femring/Menoring (Galen Holdings, Northern Ireland) attributes: Silicone elastomer, 56 × 7.6mm, 5 or 10 mcg/d estradiol, continuous use for 90 days.

[g] Estring (Pfizer, USA) attributes: Silicone elastomer, 55 × 9mm, 7.5 mcg/d estradiol, continuous use for 90 days.

Table 2

Unadjusted and adjusted pooled prevalence estimates for each vaginal ring (ring) acceptability outcome

Outcome	Number of studies(number of ring subgroups)	Total ring users	I^2	Unadjusted[a] pooled prevalence (95% CI)	Adjusted[b] pooled prevalence (95% CI)
General acceptability	50 (60)	19,271	76.0	85.6% (81.3, 89.0)	85.7% (82.4, 88.4)
Hypothetical acceptability[c]	12 (12)	5,694	94.5	27.6% (17.5, 40.5)	NA
Comfort	29 (43)	4,627	54.1	92.9% (89.2, 95.4)	93.4% (91.4, 95.0)
Ease of use	26 (33)	22,294	76.1	90.9% (86.5, 94.0)	90.6% (87.8, 92.9)
Comfort during sex	25 (30)	14,295	77.0	82.7% (76.4, 87.6)	83.1% (80.7, 85.2)
Expulsions	33 (37)	19,253	62.6	9.1% (6.8, 12.3)	8.8% (7.2, 10.8)
Vaginal symptoms	52 (71)	15,854	66.7	11.3% (8.3, 15.1)	11.1% (8.8, 13.9)

CI.confidence interval; NA,not applicable; ring,vaginal ring

[a]Unadjusted pooled prevalence estimated from meta-analysis.

[b]Adjusted pooled prevalence from meta-regression model adjusting for region, outcome type (coding dependent on outcomes reported, see Methods section for details), validity score, study design, publication year, outcome measurement timepoint, ring indication, presence of an API, and ring diameter.

[c]Hypothetical ring users.

Table 3

Results of meta-regression models for the primary outcome of general vaginal ring (ring) acceptability, reporting values of the adjusted proportion, the 95% confidence interval of the adjusted proportion, the beta coefficient (β), the standard error (SE) of the beta coefficient, and the p-value for each study-level covariate

	Proportion (95% CI)	**β (SE)**	***p*-value**
Overall acceptability outcome type			
Satisfaction	85.7 (76.8, 91.6)	REF	REF
Acceptable	72.2 (52.6, 85.8)	−0.84 (0.57)	0.139
Recommend	**94.9 (89.6, 97.6)**	**1.14 (0.47)**	**0.016**
Would continue	84.6 (66.2, 93.9)	−0.09 (0.69)	0.892
Like	84.5 (61.3, 94.9)	−0.10 (0.79)	0.900
Region			
Africa	59.4 (38.3, 77.5)	REF	REF
Europe	**90.6 (83.9, 94.7)**	**1.89 (0.58)**	**0.001**
Americas and Australia	79.5 (71.4, 85.7)	0.98 (0.53)	0.067
Asia	**97.1 (92.0, 99.0)**	**3.13 (0.66)**	**< 0.001**
Multi-region	**93.5 (84.6, 97.4)**	**2.28 (0.67)**	**< 0.001**
Validity score	NA	0.15 (0.15)	0.308
Study design			
RCT	89.5 (85.8, 92.4)	REF	REF
Observational	83.9 (74.8, 90.1)	−0.50 (0.36)	0.169
Pharmacokinetic	**50.0 (22.1, 77.9)**	**−2.15 (0.69)**	**0.002**
Publication year	NA	0.04 (0.03)	0.145
Assessment time			
<3 mo	91.9 (83.7, 96.1)	REF	REF
3–11 mo	84.9 (79.8, 89.0)	−0.69 (0.47)	0.140
12 mo or more	**78.5 (66.5, 87.1)**	**−1.12 (0.56)**	**0.044**
Indication			
Contraception	83.7 (75.6, 89.5)	REF	REF
HIV/MPT	83.7 (65.6, 93.2)	−0.01 (0.68)	0.994
Menopause	**95.4 (88.4, 98.2)**	**1.38 (0.60)**	**0.020**

	Proportion (95% CI)	**β (SE)**	***p*-value**
Other hormonal	67.2 (44.6, 84.0)	−0.92 (0.52)	0.077
Ring API			
Ring with API	86.8 (83.5, 89.5)	REF	REF
Ring with no API	68.7 (42.1, 86.9)	−1.1 (0.60)	0.066
Ring diameter			
≤55mm	82.3 (77.3, 86.3)	REF	REF
>55 mm	**92.4 (86.6, 95.8)**	**0.96 (0.39)**	**0.015**
Reduction in R^2 Likelihood ratio X^2, *p*-value	0.523 404.98, $p < 0.01$		

API, active pharmaceutical ingredient; MPT, multipurpose prevention technology; RCT, randomized controlled trial; Ring, vaginal ring; REF, reference.

Significant associations (p < 0.05) are indicated in bold typeface

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Table 4

Results of meta-regression models for the secondary vaginal ring (ring) acceptability outcomes, reporting values of the adjusted proportion, the 95% confidence interval of the adjusted proportion, the beta coefficient (β), the standard error (SE) of the beta coefficient, and the p-value for each study-level covariate

	Comfort			**Ease of use**			**Comfort During Sex**		
	Proportion (95% CI)	**β (SE)**	***p*-value**	**Proportion (95% CI)**	**β (SE)**	***p*-value**	**Proportion (95% CI)**	**β (SE)**	***p*-value**
Outcome Type	Comfort: 96.7 (94.9, 97.8) **Not feeling ring: 73.6 (62.9, 82.1)**	Comfort: REF **Not feeling ring: −2.34 (0.40)**	Comfort: REF **Not feeling ring: <0.001**	Ease of insertion: 92.3 (89.6, 94.3) **Ease of use: 71.8 (51.3, 86.0)**	Ease of insertion: REF **Ease of use: −1.54 (0.49)**	Ease of insertion: REF **Ease of use: 0.002**	Did not feel: 87.1 (83.9, 89.6) Comfort: 87.8 (80.3, 92.7) No sex interference: 88.6 (85.8, 91.0) **Partner did not feel: 53.9 (43.4, 64.1)**	Did not feel: REF Comfort: 0.06 (0.32) No sex interference: 0.15 (0.18) **Partner did not feel: −1.75 (0.29)**	Did not feel: REF Comfort: 0.841 No sex interference: 0.415 **Partner did not feel: <0.001**
Region Africa	76.5 (59.1, 88.0)	REF	REF	97.9 (93.1, 99.4)	REF	REF	89.6 (85.1, 92.8)	REF	REF
Europe	**95.2 (92.8, 96.8)**	**1.80 (0.49)**	**<0.001**	**88.8 (80.5, 93.8)**	**−1.80 (0.78)**	**0.022**	86.8 (82.2, 90.3)	−0.27 (0.27)	0.31
Americas and Australia	80.1 (72.5, 85.9)	0.21 (0.47)	0.656	95.0 (88.4, 97.9)	−0.92 (0.62)	0.141	**82.1 (76.2, 86.9)**	**−0.63 (0.22)**	**0.005**
Asia	**98.1 (96.3, 99.0)**	**2.75 (0.54)**	**<0.001**	**71.9 (45.8, 88.5)**	**−2.92 (0.93)**	**0.002**	81.9 (71.4, 89.1)	−0.64 (0.38)	0.091
Multi-region	**97.5 (95.2, 98.7)**	**2.48 (0.59)**	**<0.001**	**79.7 (44.9, 95.0)**	**−2.50 (1.22)**	**0.041**	**37.6 (17.6, 63.0)**	**−2.66 (0.63)**	**<0.001**
Validity score Study design	NA	−0.10 (0.14)	0.503	NA	**0.75 (0.26)**	**0.004**	NA	0.01 (0.15)	0.962
RCT	96.9 (95.0, 98.1)	REF	REF	82.6 (67.8, 91.5)	REF	REF	80.2 (74.9, 84.7)	REF	REF
Observational	**78.4 (69.7, 85.1)**	**−2.15 (0.43)**	**<0.001**	93.7 (89.3, 96.4)	1.14 (0.63)	0.07	84.8 (82.0, 87.3)	0.32 (0.20)	0.114
Pharmacokinetic	97.2 (89.5, 99.3)	0.10 (0.77)	0.901	92.9 (56.6, 99.2)	1.01 (1.31)	0.441	NA	NA	NA
Publication year Assessment time	NA	0.01 (0.02)	0.772	NA	0.06 (0.04)	0.081	**NA**	**−0.03 (0.01)**	**0.001**
<3 mo	95.3 (92.7, 97.1)	REF	REF	79.4 (68.2, 87.4)	REF	REF	81.4 (75.2, 86.3)	REF	REF
3–11 mo	**89.2 (83.1, 93.2)**	**−0.91 (0.36)**	**0.012**	**91.6 (85.6, 95.2)**	**1.04 (0.44)**	**0.018**	74.7 (65.8, 82.0)	−0.39 (0.36)	0.278
12 mo or more	92.6 (88.6, 95.2)	−0.50 (0.35)	0.153	**99.4 (96.7, 99.9)**	**3.81 (1.09)**	**0.001**	**95.8 (88.5, 98.5)**	**1.64 (0.61)**	**0.007**
Indication Contraception	96.6 (92.9, 98.4)	REF	REF	83.0 (70.8, 90.8)	REF	REF	80.7 (76.5, 84.2)	REF	REF
HIV/MPT	96.8 (93.3, 98.5)	0.07 (0.69)	0.924	**97.7 (93.0, 99.3)**	**2.18 (0.90)**	**0.016**	82.6 (69.4, 90.8)	0.13 (0.42)	0.761
Menopause	**76.7 (66.6, 84.5)**	**−2.14 (0.43)**	**<0.001**	92.9 (79.2, 97.8)	0.98 (0.77)	0.201	**90.7 (87.2, 93.3)**	**0.84 (0.25)**	**0.001**
Other hormonal	96.3 (87.8, 98.9)	−0.08 (0.65)	0.901	63.3 (19.6, 92.4)	−1.04 (1.09)	0.339	71.7 (54.0, 84.6)	−0.50 (0.43)	0.248

	Comfort			Ease of use			Comfort During Sex		
	Proportion (95% CI)	**β (SE)**	***p*-value**	**Proportion (95% CI)**	**β (SE)**	***p*-value**	**Proportion (95% CI)**	**β (SE)**	***p*-value**
Ring API									
Ring with API	91.3 (88.9, 93.3)	REF	REF	91.0 (87.7, 93.4)	REF	REF	84.4 (80.8, 87.4)	REF	REF
Ring with no API	**96.9 (94.2, 98.3)**	**1.08 (0.34)**	**0.001**	89.5 (78.7, 95.2)	−0.17 (0.49)	0.735	79.7 (67.6, 88.1)	−0.32 (0.42)	0.442
Ring diameter									
≤55mm	95.0 (93.1, 96.4)	REF	REF	94.9 (92.3, 96.7)	REF	REF	83.9 (81.1, 86.4)	REF	REF
>55 mm	**91.9 (88.7, 94.3)**	**−0.51 (0.22)**	**0.020**	**52.8 (26.1, 78.0)**	**−2.82 (0.74)**	**<0.001**	81.2 (76.0, 85.5)	−0.19 (0.19)	0.333
Reduction in R^2	*a*			0.719			*a*		
Likelihood ratio X^2, *p*-value	*a*			127.50, $p<0.01$			*a*		

API, active pharmaceutical ingredient; MPT, multipurpose prevention technology; RCT, randomized controlled trial; Ring, vaginal ring; REF, reference.

Significant associations ($p< 0.05$) are indicated in bold typeface

[a]Reduction in R^2 and likelihood ratio X^2 unavailable due to error with τ^2 calculation in Stata metapreg output.

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Table 5

Results of meta-regression models for the unfavorable vaginal ring (ring) outcomes, reporting values of the adjusted proportion, the 95% confidence interval of the adjusted proportion, the beta coefficient (β), the standard error (SE) of the beta coefficient, and the p-value for each study-level covariate

	Expulsions			Vaginal Symptoms		
	Proportion (95% CI)	**β (SE)**	***p*-value**	**Proportion (95% CI)**	**β (SE)**	***p*-value**
Outcome type	NA	NA	NA	Discharge: 12.82 (9.78, 16.63) Vaginitis: 8.01 (3.38, 17.81) Irritation: 5.59 (2.30, 12.97)	Discharge: REF Vaginitis: −0.52 (0.50) Irritation: −0.91 (0.51)	Discharge: REF Vaginitis: 0.298 Irritation: 0.076
Region						
Africa	12.17 (6.61, 21.34)	REF	REF	1.35 (0.41, 4.39)	REF	REF
Europe	8.05 (4.56, 13.81)	−0.46 (0.46)	0.323	**8.11 (4.34, 14.65)**	**1.86 (0.76)**	**0.014**
Americas and Australia	4.91 (2.67, 8.88)	−0.99 (0.52)	0.058	**16.83 (10.35, 26.18)**	**2.69 (0.72)**	**<0.001**
Asia	14.59 (8.97, 22.84)	0.21 (0.45)	0.639	**18.00 (10.04, 30.18)**	**2.77 (0.74)**	**<0.001**
Multi-region	8.19 (5.10, 12.91)	−0.44 (0.42)	0.300	**18.43 (9.68, 32.27)**	**2.80 (0.75)**	**<0.001**
Validity score Study design	**NA**	**−0.36 (0.15)**	**0.014**	NA	−0.06 (0.18)	0.745
RCT	5.79 (4.01, 8.30)	REF	REF	22.94 (15.89, 31.93)	REF	REF
Observational	**12.14 (8.30, 17.43)**	**0.81 (0.34)**	**0.016**	**7.21 (4.32, 11.80)**	**−1.34 (0.36)**	**<0.001**
Pharmacokinetic	18.04 (3.61, 56.42)	1.28 (0.92)	0.167	**1.96 (0.39, 9.19)**	**−2.70 (0.95)**	**0.005**
Publication year	NA	0.01 (0.01)	0.460	NA	−0.01 (0.02)	0.513
Assessment time						
<3 mo.	7.34 (3.71, 14.01)	REF	REF	15.09 (8.02, 26.58)	REF	REF
3–11 mo	9.50 (6.61, 13.48)	0.28 (0.47)	0.551	7.33 (4.63, 11.43)	−0.81 (0.51)	0.113
12 mo. or more	9.14 (6.10, 13.47)	0.24 (0.48)	0.615	14.92 (8.43, 25.04)	−0.01 (0.56)	0.982
Indication						
Contraception	9.10 (6.30, 12.97)	REF	REF	8.66 (5.56, 13.23)	REF	REF
HIV/MPT	6.16 (2.30, 15.45)	−0.42 (0.64)	0.511	**28.81 (12.74, 52.87)**	**1.45 (0.68)**	**0.033**
Menopause	14.14 (8.74, 22.08)	0.50 (0.37)	0.173	8.20 (3.70, 17.18)	−0.06 (0.44)	0.893
Other hormonal Ring API	4.56 (2.06, 9.77)	−0.74 (0.39)	0.058	4.60 (1.88, 10.83)	−0.68 (0.50)	0.172
Ring with API	8.19 (6.52, 10.25)	REF	REF	11.02 (8.29, 14.52)	REF	REF
Ring with no API	15.91 (8.44, 27.96)	0.75 (0.40)	0.062	11.27 (4.92, 23.73)	0.02 (0.53)	0.963
Ring diameter						
≤55mm	4.97 (3.43, 7.16)	REF	REF	8.28 (5.74, 11.80)	REF	REF

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	Expulsions			Vaginal Symptoms		
	Proportion (95% CI)	**β (SE)**	***p*-value**	**Proportion (95% CI)**	**β (SE)**	***p*-value**
>55 mm	**13.39 (10.13, 17.51)**	**1.08 (0.28)**	**< 0.001**	**15.84 (10.64, 22.95)**	**0.74 (0.34)**	**0.032**
Reduction in R^2	0.753			0.555		
Likelihood ratio X^2, *p*-value	50.42, $p<0.01$			384.50, $p<0.01$		

API, active pharmaceutical ingredient; MPT, multipurpose prevention technology; RCT, randomized controlled trial; Ring, vaginal ring; REF, reference.

Significant associations ($p<0.05$) are indicated in bold.