High Global Burden and Costs of Bacterial Vaginosis: A Systematic Review and Meta-Analysis

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Background: Bacterial vaginosis (BV) is the most common vaginal infection among women of reproductive age and is associated with important adverse health outcomes. Estimates of the burden of BV and associated costs are needed to inform research priorities.

Methods: We conducted a systematic review and meta-analysis of global BV prevalence among reproductive-aged women in the general population. We searched PubMed and Embase and used random effects models to estimate BV prevalence by global regions. We estimated the direct medical costs of treating symptomatic BV. Assuming a causal relationship, we also estimated the potential costs of BV-associated preterm births and human immunodeficiency virus cases in the United States.

Results: General population prevalence of BV is high globally, ranging from 23% to 29% across regions (Europe and Central Asia, 23%; East Asia and Pacific, 24%; Latin America and Caribbean, 24%; Middle East and North Africa, 25%; sub-Saharan Africa, 25%; North America, 27%; South Asia, 29%). Within North America, black and Hispanic women have significantly higher (33% and 31%, respectively) prevalence compared with other racial groups (white, 23%; Asian, 11%; $P < 0.01$). The estimated annual global economic burden of treating symptomatic BV is US $4.8 (95% confidence interval, $3.7–$6.1) billion. The US economic burden of BV is nearly tripled when including costs of BV-associated preterm births and human immunodeficiency virus cases.

Conclusions: The BV prevalence is high globally, with a concomitant high economic burden and marked racial disparities in prevalence. Research to determine the etiology of BV and corresponding prevention and sustainable treatment strategies are urgently needed to reduce the burden of BV among women. Additionally, the exceptionally high cost of BV-associated sequelae highlights the need for research to understand potential causal linkages between BV and adverse health outcomes.

Bacterial vaginosis (BV) is the most common vaginal infection among women of reproductive age, causing considerable physical and psychosocial discomfort.[1] BV is additionally associated with an increased risk of multiple adverse outcomes, including preterm birth, pelvic inflammatory disease, endometritis, and transmission and acquisition of human immunodeficiency virus type 1 (HIV-1) and sexually transmitted infections (STIs).[1]

Metronidazole has been the standard treatment for BV for more than 25 years,[2] with 4-week cure rates as high as 85%.[3] However, 58% of successfully treated cases recur within 1 year.[4] Additionally, evidence that existing BV treatments prevent adverse sequelae is limited. Randomized trials of BV treatment have shown a reduction in risk of vaginal cuff infections after hysterectomy and reduced risk of preterm delivery among high-risk pregnant women, but have failed to reduce the incidence of preterm birth among asymptomatic women of heterogeneous risk.[5] Efforts to improve BV treatment include antimicrobials with a lower dosing burden,[6] antimicrobials plus a probiotic adjuvant to reduce recurrence rates via recolonization of a healthy vaginal microbiome, and partner treatment.[1]

An understanding of the global burden of BV and associated costs is needed to highlight the potential benefits of improved prevention and treatment of BV and its sequelae and to prioritize distribution of such treatment. A previous systematic review described prevalence among diverse populations of women, including both low- and high-risk subsets of the general population, reporting widely heterogeneous estimates of prevalence globally, ranging from 5% among pregnant European women to 58% among South African women living in informal housing.[7] However, approximately one fifth of included estimates were obtained from samples of women selected on the basis of symptomatology or a BV-associated condition,[123s–140s], thereby inducing considerable risk of bias in estiamtes and introducing variability in estimates that would preclude meaningful pooled prevalence estimates.

Prevalence among intraregional subpopulations also varies, with higher prevalence of BV among women who have sex with women (WSW)[8] and black and Hispanic women in the United States.[9] Estimates also vary widely among pregnant women, a group of particular interest given the high number of BV-associated adverse obstetric outcomes, ranging from 8%[10] to 51%.[11]

The wide range of prevalence estimates in general and pregnant populations indicates a similarly wide range of potential cost burdens of BV, with the cost of BV treatment alone likely amplified by the costs incurred for treatment of BV-associated sequelae. A comprehensive inventory of the costs of treatment of BV and its sequelae is necessary to assess the potential benefits of improved treatment and prevention of BV and the possible subsequent prevention of adverse outcomes.

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In this systematic review and meta-analysis, we describe the prevalence of BV among reproductive-aged women of the general population in global regions using pooled estimates, and evaluate race- and ethnicity-specific prevalence within the United States. We furthermore estimate the direct cost burden of treating BV and its sequelae.

MATERIALS AND METHODS

Search Strategy and Study Selection Criteria

Our review protocol is registered in the International Prospective Register of Systematic Reviews database with registration number CRD42017073625.

We searched the PubMed and Embase databases for studies of BV prevalence, incidence, and sequelae, and costs of treatment for BV and its sequelae. A full description of our search terms is included in Text S1 in Supplemental Digital Content (SDC) 1, http://links.lww.com/OLQ/A335. We did not impose date restrictions in the search, and included studies in English, Spanish, Italian, French, Portuguese, and Chinese. A single reviewer screened all titles and abstracts (or title alone if the abstract was unavailable) for identification of potentially relevant articles. A randomly selected 10% of these articles were then assessed by 2 reviewers for inclusion decisions and data extraction. A single reviewer made inclusion decisions and extracted data of remaining articles.

We included studies in which participants are of reproductive age, defined as ages 15 to 49 years or indication that participants are postmenarchal and premenopausal. To limit the potential for selection bias, we excluded studies in which participants were selected on the basis of symptomatology or a BV-associated condition (including pelvic inflammatory disease, female infertility, women with or at risk of preterm birth or miscarriage, preterm premature rupture of membranes, premature rupture of membranes, diabetes, women engaging in intravaginal practices, and women with an intrauterine device). We also excluded estimates from study populations with BV risk that differs from the general population, including sex workers and STI clinic attendees, and from study populations that are not representative of the general population, such as incarcerated women. In countries with high HIV-1 prevalence (defined as >5%), we excluded studies of exclusively HIV-1-negative women; given the association between BV and HIV-1,[12] the distribution of BV among HIV-1-negative women likely differs from the general population.

We included measures of prevalence and incidence in which estimates were obtained by Nugent score.[13] Due to the wide range in published estimates of sensitivity and specificity of Amsel's criteria relative to Nugent score,[14,15] we include estimates obtained by Amsel's criteria only for sub-populations for which Nugent score estimates were unavailable.

Estimation of BV Prevalence and Incidence

We estimated BV prevalence separately for each World Bank region[16] and study population. Estimates from the United States were excluded from these region-specific estimates if their study populations differed meaningfully in racial and ethnic composition from the general US population (>10% difference). However, these studies were included in race- and ethnicity-specific BV prevalence estimates in the United States.

We estimated pooled prevalence with a random effects model with inverse variance weights calculated with the Tukey-Freeman double arcsine transformation.[142s] We adjusted estimates of prevalence obtained by Amsel's criteria using the formula $\text{prevalence}_{\text{adjusted}} = \frac{\text{prevalence}_{\text{unadjusted}} + \text{specificity} - 1}{\text{sensitivity} + \text{specificity} - 1}$ and estimates of sensitivity and specificity relative to Nugent score.[14] Differences in population and region across studies reporting BV incidence preclude estimation of a pooled incidence rate. We therefore present each incidence estimate separately.

Estimation of Cost Burden of BV

We converted all currencies to US dollars and adjusted costs to 2017 US dollars. We present each cost estimate separately with a description of the components included in the cost estimate. We selected the most comprehensive estimate of direct costs for standard treatment in each region for use in subsequent cost analyses. The cost estimates for the regions of North America[100s] and Europe and Central Asia[101s] include the cost of the diagnostic test, medication, and an office visit, whereas the cost estimate used for remaining regions[106s] includes the cost of the office visit and medication, under the assumption that the syndromic management commonly employed in these regions would preclude the cost of a diagnostic test.

We estimated the annual global economic burden of treated BV cases as the product of the region-specific cost of treatment per BV case [100s,101s,106s]; Table S6 in SDC 3, http://links.lww.com/OLQ/A337), the annual number of incident cases per region, and the proportion of cases that are symptomatic (as a proxy for healthcare seeking behavior that would result in treatment). We estimated the number of incident cases per region as the product of region-specific prevalence, the size of region-specific female population ages 15 to 49 years,[17] and the proportion of cases that are expected to recur within 1 year after treatment.[4] We used a random-effects model with inverse variance weights calculated with the Tukey-Freeman double arcsine transformation to obtain a pooled estimate of the proportion of cases that are symptomatic from population-based samples of reproductive-aged women. Using the race-specific number of incident cases,[18,19] we also estimated the race-specific annual economic burden of BV in the United States. We repeated both the global- and US-specific economic analyses, irrespective of symptomatology, to estimate the cost of treating all BV cases.

We estimated the US economic burden of 2 BV-associated sequelae for which there is consistent evidence of an independent relationship: preterm birth and HIV acquisition.[12,20] Due to limitations in the availability of detailed data in all regions, we limited estimates of the economic burden of BV-associated sequelae to the United States. We estimated the race-specific annual cost of BV-associated preterm births in the United States as the products of 2015 race-specific number of BV-associated preterm births[21,22] and the cost per low and normal birthweight preterm birth[107s], weighted by the proportion of preterm births that are low birthweight.[23] We also estimated the race-specific annual costs resulting from BV-associated prevalent HIV cases in 2016 as the product of the number of race- and age-specific BV-associated HIV cases[24] and the annual cost of HIV care.[110s] A detailed description of parameters and formulas used in these estimates is included in SDC 2, http://links.lww.com/OLQ/A336.

RESULTS

Literature Search

We identified 2361 potentially relevant records and include data from 122 publications (Fig. 1, Tables S1, S5, S6, S7, and S10 in SDC 3, http://links.lww.com/OLQ/A337).

Prevalence of BV

The majority of prevalence estimates among women of the general population were obtained from clinic-based populations or other convenience samples (21 of 36 and 7 of 36, respectively),

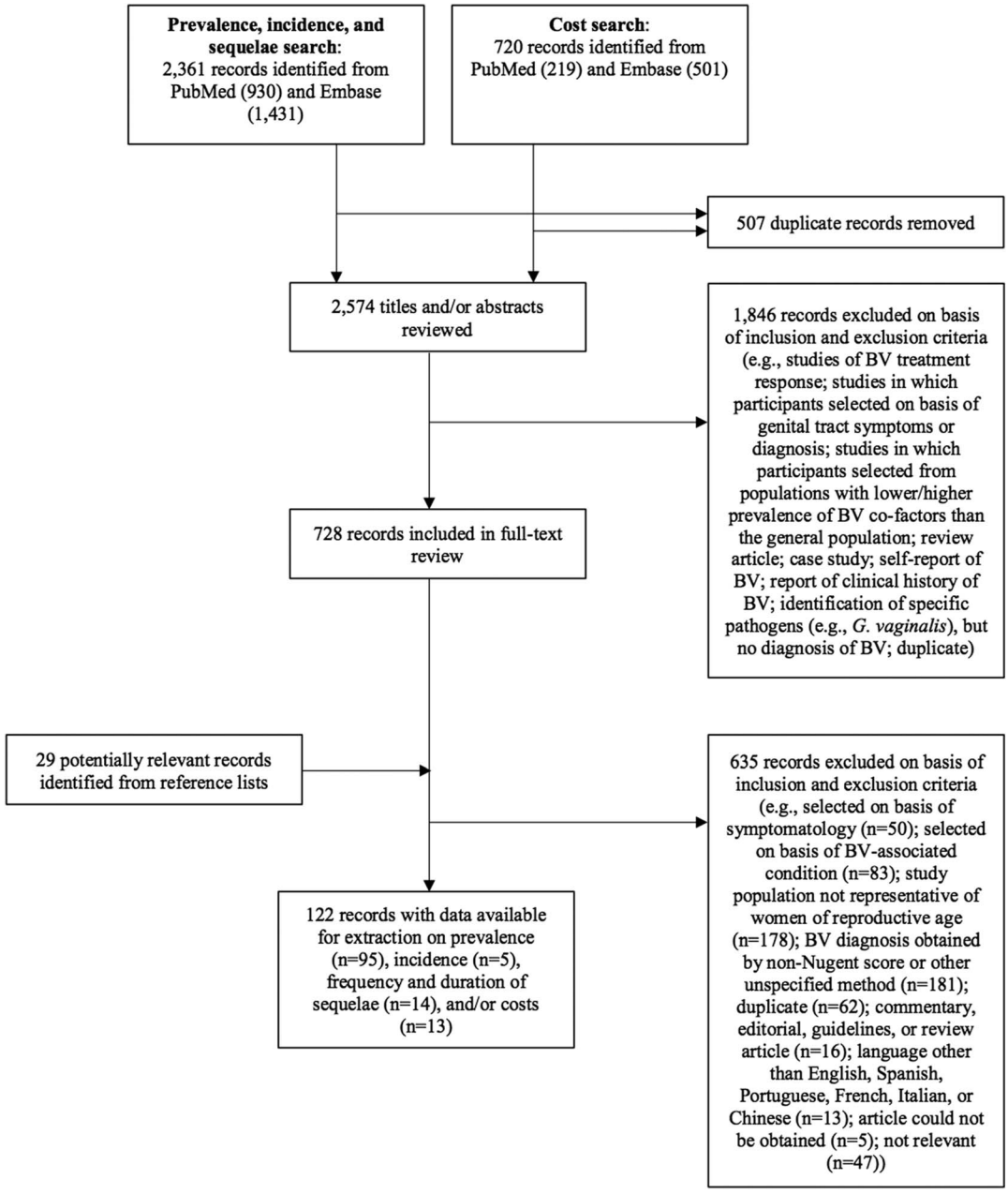

Figure 1. CONSORT diagram.

whereas only 8 studies provided population-based estimates of BV prevalence (Table S1 in SDC 3, http://links.lww.com/OLQ/A337). Similarly, 34 of 50 prevalence estimates among pregnant women were obtained from antenatal care attendees, with an additional 11 estimates from other clinic-based settings, 4 convenience samples from other settings, and a single population-based estimate (Table S1 in SDC 3, http://links.lww.com/OLQ/A337). Among the 8 population-based samples of the general population, 5 provide an estimate of the proportion of women with symptomatic BV (Table S2 in SDC 3, http://links.lww.com/OLQ/A337).

Reported BV prevalence was high globally among reproductive-aged women of the general population, ranging from 23% to 29% (Europe and Central Asia: 22.8%, n = 5; East Asia and Pacific: 24.2%, n = 4; Latin America and Caribbean: 24.2%, n = 4; sub-Saharan Africa: 24.6%, n = 9; Middle East and North Africa: 25.1%, n = 2; North America: 27.4%, n = 3; and South Asia: 28.7%, n = 8) (Figs. 2 and 3). Within sub-Saharan Africa, BV prevalence was lower in Western and Central Africa (20.6%; 95% confidence interval [CI], 6.1–40.6) than in Southern and Eastern Africa (33.3%; 95% CI, 17.4–51.5), although this difference was not statistically significant ($P = 0.33$). Prevalence estimates across sampling strategies (population-based, clinic-based, or other convenience sampling method) followed a similar distribution (Fig. S1 in SDC 4, http://links.lww.com/OLQ/A338). Across 5 population-based samples, 34.9% (95% CI, 17.7–54.4) of those with BV were symptomatic (Table S2 in SDC 3, http://links.lww.com/OLQ/A337).

Within North America, black and Hispanic women of the general population had significantly higher (33.2% and 30.7%, respectively) BV prevalence than other racial and ethnic groups

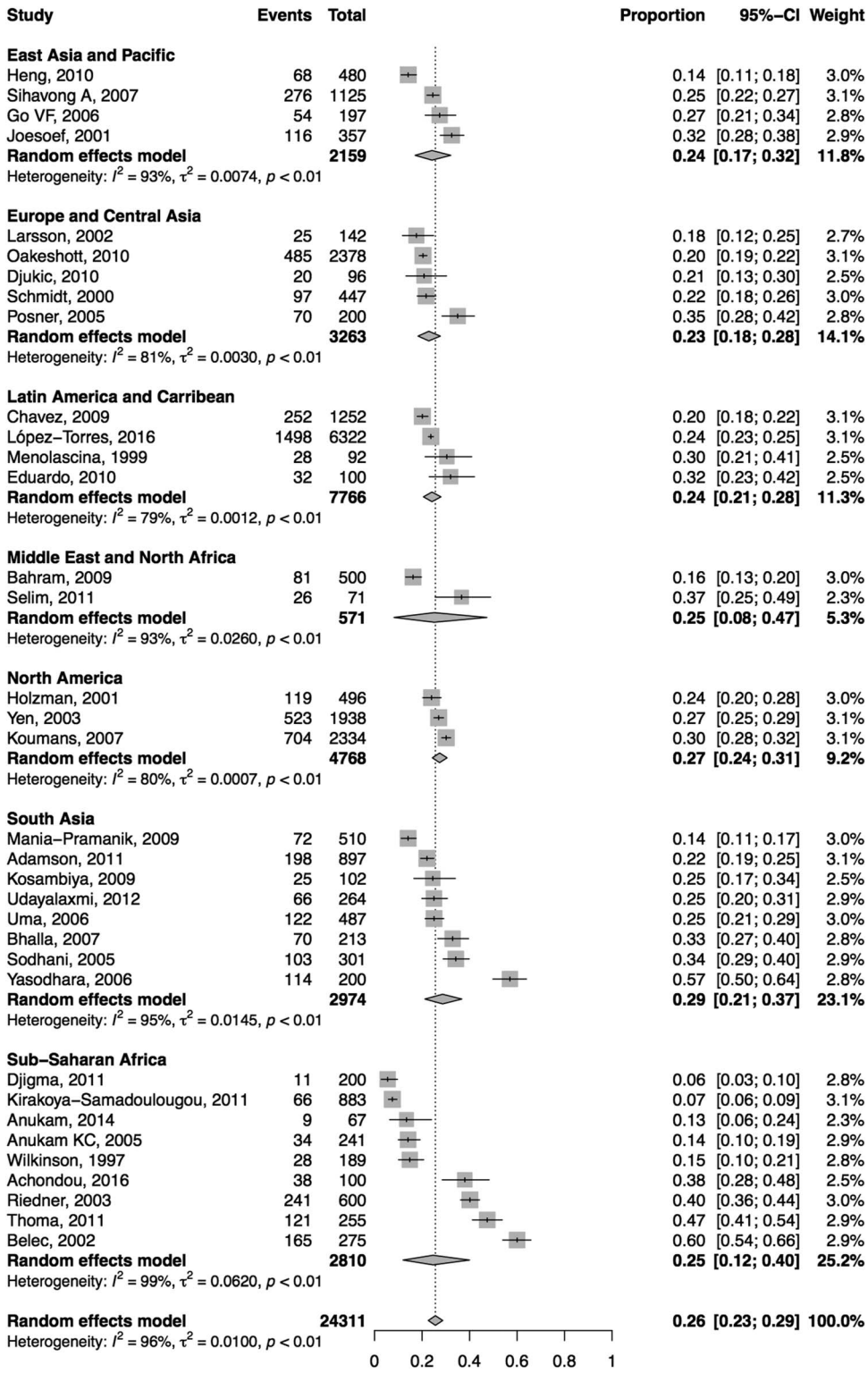

Figure 2. Forest plot of prevalence estimates obtained from samples of women of reproductive age of the general population, by World Bank region.

(white: 22.7%; Asian: 11.1%) (P = 0.001; Fig. 3). This disparity persisted when study populations were classified as majority (>50%) black women or majority non-black women, with approximately 2-fold higher prevalence among majority black study populations (46.5%; 95% CI, 37.5–55.6 vs. 21.3%; 95% CI, 16.7–26.3; P < 0.001).

Among pregnant women, BV prevalence ranged from 11.7% in South Asia (95% CI, 9.0–14.7) to 33.2% in Latin America and

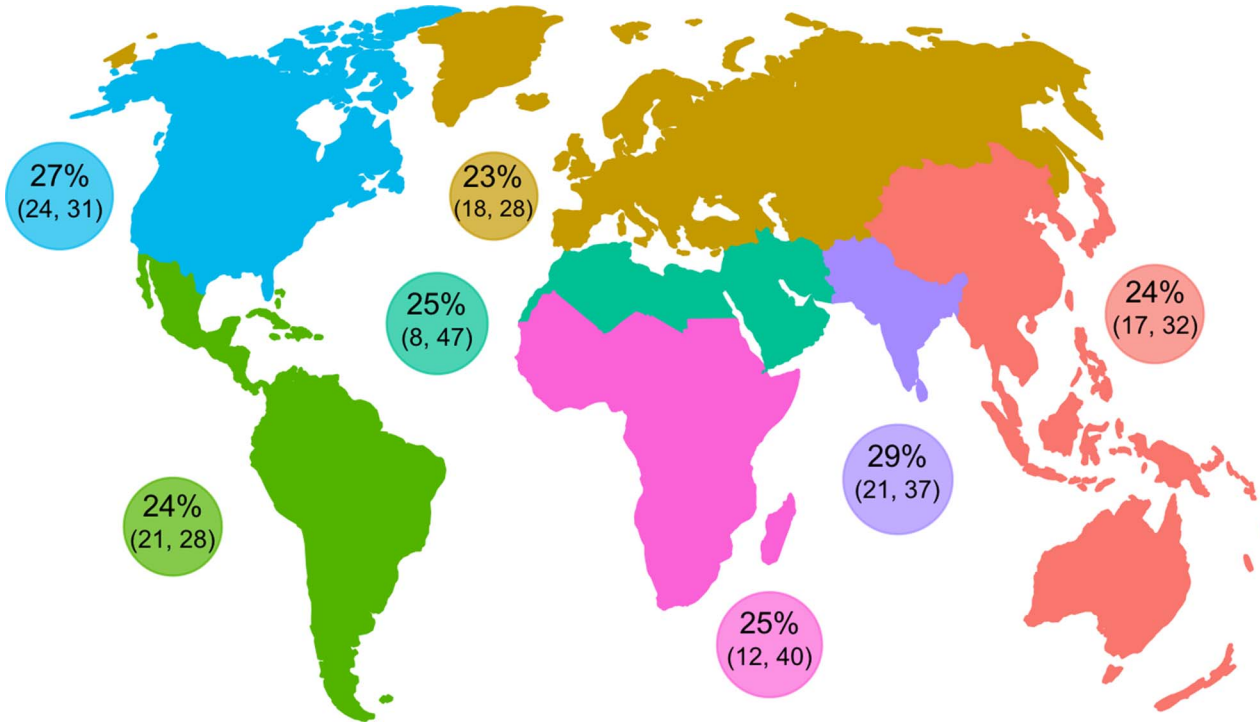

Figure 3. Global prevalence of BV by region. 95% CIs are presented in parentheses.

the Caribbean (95% CI, 14.8–54.7) (Table S3 in SDC 3, http://links.lww.com/OLQ/A337; Fig. S2 in SDC 4, http://links.lww.com/OLQ/A338). Within the United States, the prevalence of BV in pregnancy was highest among black (49.0%; 95% CI, 40.2–57.8) and Hispanic women (42.7%; 95% CI, 36.4–49.1) and lowest among Asian (20.3%; 95% CI, 5.4–41.2) and white women (19.9%; 95% CI, 8.0–35.5) (Fig. 4).

Six studies reported BV prevalence among women living with HIV in South Asia (n = 2) and sub-Saharan Africa (n = 4). Relative to women of the general population, BV prevalence was higher among women living with HIV (35.6%; 95% CI, 25.7–46.2 vs. 25.6; 95% CI, 22.6–28.7; $P = 0.054$) (Table S4 in SDC 3, http://links.lww.com/OLQ/A337).

The BV prevalence among WSW was not assessed by Nugent score in any studies, and was assessed by Amsel's criteria in a single study meeting our inclusion criteria. Prevalence was approximately 20% higher (33.5%, 95% CI: 30.5, 40.7) in WSW than in women of the general population ($P = 0.007$).

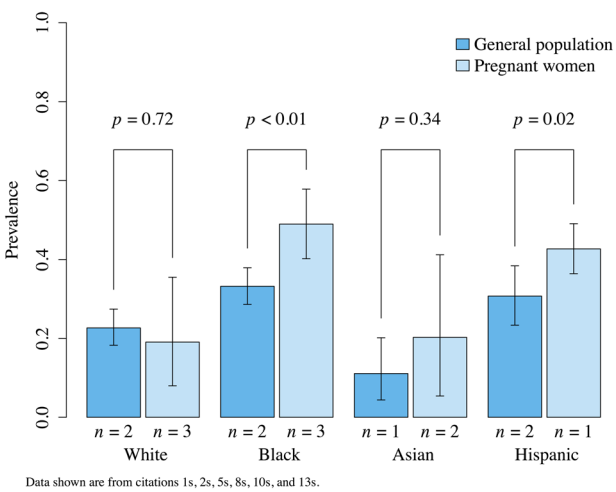

Figure 4. Prevalence of BV by race and ethnicity among women of the general population and pregnant women in the United States. *P* values were estimated in random effects models.

Incidence of BV

Of reviewed studies, only 5 provided estimates of BV incidence (Table S5 in SDC 3, http://links.lww.com/OLQ/A337), ranging from 1.6 per 100 woman-years among young Australian women[96s] to 74.2 per 100 woman-years among pregnant women in Anhui Province, China.[48s]

Cost Burden of BV and Associated Sequelae

The direct medical cost per treated case of BV is highest in North America ($90.47),[100s] followed by Europe and Central Asia ($27.13)[101s], and lowest in sub-Saharan Africa ($11.73)[106s] (Table S6 in SDC 3, http://links.lww.com/OLQ/A337). The cost associated with BV sequelae varied by region and sequelae. Reproductive sequelae of BV were relatively high-cost, ranging from US $4146.56 per premature rupture of membranes in North America[107s] to US $87,664.42 per preterm birth of a low birthweight infant in Europe and Central Asia[108s] (Table S7 in SDC 3, http://links.lww.com/OLQ/A337). The costs per case treated for curable STIs were comparatively low, and lower in low-resource settings (US $8.75–40.28 in sub-Saharan Africa[109s]) than high-resource settings (US $85.78–104.14 in Europe and Central Asia[101s]) (Table S7 in SDC 3, http://links.lww.com/OLQ/A337).

The global annual cost burden of BV treatment is high, at an estimated US $4.8 billion to treat symptomatic BV cases (Table 1),

TABLE 1. Global Annual Economic Burden of BV Cases

Region	Cost per Treated Case of BV, US $	Annual Cost of Symptomatic Cases (95% CI) (Millions of 2017 US $)	Annual Cost of all Cases (95% CI) (Millions of 2017 US $)
All regions		4820 (3657–6130)	13,811 (10,479,–17,565)
North America	90.47	1298 (1151–1449)	3718 (3298–4152)
White	90.47	1022 (824–1234)	1851 (1492–2235)
Black	90.47	259 (223–295)	468 (403–535)
Europe and Central Asia	27.13	835 (670–1014)	2391 (1919–2905)
Latin America and Caribbean	11.73	291 (247–336)	833 (709–963)
East Asia and Pacific	11.73	1015 (717–1346)	2909 (2055–3858)
South Asia	11.73	914 (675–1172)	2619 (1935–3359)
Middle East and North Africa	11.73	197 (64–371)	564 (184–1064)
Sub-Saharan Africa	11.73	271 (132–441)	777 (379–1263)

with more than half of costs due to recurrent BV cases. The total annual cost of BV treatment is highest in North America (US $1.3 billion for symptomatic cases), due to both high prevalence and a high cost per treated case. In both South Asia and East Asia and Pacific regions, the relatively low cost per case treated nonetheless translates to a large cost burden (US $914 million and US $1.0 billion for symptomatic cases, respectively) due to high prevalence coupled with a large population size.

Within the United States, the cost burden of BV-associated sequelae is also high, with black women bearing a disproportionate burden of these costs, accounting for 39% of the US $2.7 billion annual burden of BV-associated preterm births and 83% of the US $916 million annual costs of BV-associated HIV cases among black and white women in the United States, despite making up only 15% of this same population (Tables S8 and S9, respectively, in SDC 3, http://links.lww.com/OLQ/A337).

DISCUSSION

In this systematic review and meta-analysis, we estimate that BV prevalence is high globally, with approximately a quarter of the women of the general population meeting the Nugent score criteria for BV. This high burden of BV carries a concomitantly high economic burden, despite the relatively low direct costs per case treated. Additionally, there are marked racial disparities in the prevalence of BV within the United States, with an accompanying disproportionate cost burden borne by black women.

In contrast to the region-specific variation in BV prevalence identified in a previous systematic review,[7] our meta-analysis showed similar BV prevalence across global regions. Kenyon et al. identified regions of low, moderate, and high BV prevalence according to the proportion of included studies with prevalence of >30%. By this metric, prevalence only in sub-Saharan Africa was classified as high, given that half of studies reported prevalence in excess of 30%. We also found that approximately half of estimates among reproductive-aged general population women in sub-Saharan Africa exceeded 30%. However, a pooled estimate of prevalence across these studies was similar to other global regions, indicating that categorization using the threshold indicator may reflect intraregional heterogeneity rather than a region-specific high prevalence. Previous meta-analyses of BV prevalence in sub-Saharan Africa among pregnant women[11] and HIV-negative women[25] have produced estimates higher than those presented here (30%[25]–51%[11]). However, both of these meta-analyses focused on populations other than the general population of women, and included in their estimates groups of women that may have higher BV prevalence than the general population (e.g., women living with HIV[11] and women at high risk of HIV acquisition[25]). Our estimates of BV prevalence in the general population are additionally strengthened by the exclusion of estimates of prevalence that were obtained from study populations selected on the basis of symptomatology or the presence of BV-associated conditions, limiting the potential for bias in our estimates. Nevertheless, population-based estimates of BV prevalence are needed to clarify the burden of BV in sub-Saharan Africa and to understand intraregional heterogeneity. Indeed, even among samples composed only of women of the general population, our meta-analysis results indicated considerable heterogeneity in BV prevalence within global regions (range I^2 79–99%; Fig. 2) that, given the similarity in distribution of prevalence estimates grouped by sampling strategy (Fig. S1 in SDC 4, http://links.lww.com/OLQ/A338), did not appear to be driven by methodological variation in sample recruitment. Further research is needed to elucidate the drivers of such intraregional variation.

Our review confirms previous findings of racial and ethnic disparities in BV prevalence within the United States, and additionally highlights the resulting higher financial burden of treatment for BV and its sequelae among black women. Previous attempts to isolate race as an independent predictor of BV risk have had mixed conclusions,[26] with investigators noting that observed disparities may be the result of both structural factors, such as socioeconomic status, and biological factors, such as lower vaginal concentrations of protective *Lactobacillus* species among black women.[27] Further research is needed to elucidate the mechanisms underlying intraregional disparities in BV prevalence to most effectively target treatment and prevention.

In population-based estimates, the proportion of women with BV who were symptomatic varied considerably, from less than 10% in sub-Saharan Africa[72s] to greater than one third in North[2s] and South America[32s] (Table S2 in SDC 3, http://links.lww.com/OLQ/A337). Should symptomatic women be more likely to seek treatment for BV, treatment rates may be higher in some regions than others, and may differ among subpopulations within regions, as well. However, given that annual recurrence rates are as high as 58% with current treatments,[4] differences in care seeking are unlikely to result in considerable variation in prevalence estimates.

The global economic burden of treating BV cases is high, and this burden likely increases when including the cost of BV-associated sequelae. Indeed, in the United States, the cost burden of BV-associated sequelae is 3-fold the cost of treating symptomatic cases. Although we limited the estimates of the cost of BV-associated sequelae to preterm births and HIV cases in the United States, BV is associated with additional sequelae, so the total cost of BV-associated sequelae may be

higher than the estimates provided here. The high cost of BV-associated preterm births and HIV treatment highlights the need for research to understand potential causal linkages between BV and adverse health outcomes, and to determine whether treatment and prevention of BV can prevent these outcomes.[141s] This work also highlights disparities in the cost burden of BV among regional and sub-regional populations. Although our analysis considers only direct medical costs, disparities in prevalence in the United States would also result in a higher societal cost to black women incurred through the time burden and costs of transportation and childcare necessary to attend clinic visits for BV treatment.

Despite decades-long recognition of BV, the etiology of BV remains undefined.[122s] Etiological theories propose that incident BV is triggered by intravaginal practices and consequent disruption of vaginal microbiota, or that BV is a sexually transmitted infection in which *Gardnerella vaginalis* may operate synergistically with microorganisms normally present in low concentrations in the vagina to produce the dysbiosis characteristic of BV.[122s] Given the high burden of BV described here and high rates of recurrence with existing therapies,[4] research to determine the etiology of BV and corresponding prevention and sustainable, affordable treatment strategies are urgently needed to reduce the burden of BV among women.

There are several limitations in the work presented here. First, estimates of prevalence obtained from samples of general population women are more likely to exclude those who seek BV treatment shortly after the onset of BV symptoms; such length-biased sampling may result in lower prevalence estimates than would be observed otherwise. Additionally, the majority of prevalence estimates were obtained from clinic-based populations, with few studies providing population-based BV estimates, potentially limiting generalizability to populations of care-seeking women. Second, our estimates of the cost burden of BV-associated sequelae assume a causal relationship between BV and preterm birth and HIV acquisition. However, both causality and the impact of treatment to reduce these outcomes remain uncertain, and our estimates should be viewed in light of this uncertainty. Third, although previous studies have established declining BV prevalence as pregnancy progresses,[28–30] gestational age in studies included here was variable, and differences in how gestational age was reported across studies precluded assessment of how the distribution of gestational age may explain the regional variation in BV prevalence we observed among pregnant women. Finally, despite limiting included estimates to those of comparable study populations of reproductive-aged women of the general population, there is substantial unexplained heterogeneity across study estimates (all $I^2 > 75\%$). Nevertheless, the mean prevalence estimate produced by our random-effects meta-analysis provides an important summary of BV prevalence globally among this population.

In conclusion, BV prevalence is high globally, with a consequently high economic burden. Within the United States, there are striking racial disparities in BV prevalence. Treatment that results in effective and sustained resolution of BV is needed to reduce the burden of BV and potentially its associated sequelae.

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For further references, please see "Supplemental References," http://links.lww.com/OLQ/A348.